

Prevalence trends of rhinoconjunctivitis, eczema, and atopic asthma in Greek schoolchildren: Four surveys during 1991–2008

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ABSTRACT

After a continuous increase of asthma, hay fever, and eczema during 1991–2003 among schoolchildren in Patras, Greece, the prevalence of current wheeze/asthma (diagnosed wheezing and/or asthma in the past 2 years) has reached a plateau (6.9%) during the period 2004–2008. Using methodology identical to the three previously conducted cross-sectional, parental questionnaire surveys (1991, n = 2417; 1998, n = 3076; 2003, n = 2725) we examined further trends in the prevalence of rhinoconjunctivitis and eczema in the same urban environment among third and fourth grade schoolchildren (8–9 years old) in 2008 (n = 2688). In the four surveys, respective prevalence rates of rhinoconjunctivitis were 2.1, 3.4, 4.6, and 5.1% (absolute prevalence increase: 1998 versus 1991, 61.9%; 2003 versus 1998, 35.5%; 2008 versus 2003, 10.9%) and those of eczema were 4.5, 6.3, 9.5, and 10.8% (absolute prevalence increase: 1998 versus 1991, 40.0%; 2003 versus 1998, 50.8%; 2008 versus 2003, 13.7%; sex-adjusted p for trend, <0.001). Among current wheezer/asthmatic patients there was an increase in lifetime rhinoconjunctivitis (sex-adjusted p for trend, <0.001) and lifetime eczema (sex-adjusted p for trend, <0.001) over the period 1991–2008. The proportion of atopic wheeze/asthma (current asthma with lifetime rhinoconjunctivitis and/or eczema) increased further during 2003–2008 (p < 0.05; p for trend during 1991–2008, <0.001). In conclusion, there is a continuous increase in the prevalence of allergic manifestations—rhinoconjunctivitis and eczema—among preadolescent children in Patras, Greece, during the period 1991–2008. After a steep rise during 1991–2003, the frequency of atopic wheeze/asthma continued to increase at a decelerating rate during 2003–2008, while wheeze/asthma prevalence remained unchanged during the same 5-year period.

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There is extensive evidence that childhood asthma and allergic disease such as rhinoconjunctivitis and eczema have witnessed a rapid rise in Westernized societies from the 1960s until the early 2000s.^{1–8} However, more recent data suggest that the prevalence of these conditions may have reached a plateau^{9–15} or may have actually declined, in certain parts of the world.^{13–19} Conversely, a continuing rise has been noted by others into the first 10 years of the new century.²⁰

Using identical methodology, in five consecutive surveys conducted in 1978, 1991, 1998, 2003, and 2008 we have shown a continuous increase in the prevalence of current asthma among 8- to 9-year-old schoolchil-

dren in Patras, Greece; this increase became nonsignificant over the period 1998–2003 and ceased during 2003 and 2008.^{6–8,12} On the other hand, the prevalence of current and lifetime rhinitis, rhinoconjunctivitis, and eczema continued to rise in the 1991–1998 and 1998–2003 periods; this rise occurred at a decelerating rate in the case of rhinitis and rhinoconjunctivitis but accelerated in the case of eczema.⁸ Based on these findings, we postulated that deceleration in prevalence would also eventually occur in eczema and would persist (or decelerate further) in rhinitis and rhinoconjunctivitis. In the present report we test this hypothesis using the data on current or chronic rhinitis, rhinoconjunctivitis, and eczema obtained in the 2008 survey. We also investigate the role of the secular trend of sex ratio as well as the impact of the presence of allergic diseases on changes in asthma prevalence.

MATERIALS AND METHODS

Questionnaire and Definitions

The standard parental questionnaire consisted of simple questions on current (within the last 2 years) and lifetime (“ever had”) symptoms of asthma, supplemented by questions on symptoms of other allergic diseases. The exact wording of the questions on

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wheeze/asthma, chronic or recurrent rhinitis (henceforth termed “rhinitis”), chronic or recurrent rhinoconjunctivitis (henceforth termed “rhinoconjunctivitis”), and eczema as well as the definitions of the terms used in the study have been presented previously; this is also the case for the definitions of current, lifetime, new-onset, and persistent wheeze/asthma as well as current and lifetime rhinitis, rhinoconjunctivitis, and eczema (Appendix 1, included as online supplement).^{6–8,12} The presence of lifetime rhinoconjunctivitis and/or lifetime eczema in children with diagnosed current wheeze/asthma was termed “atopic wheeze/asthma.”

Study Population and Design

A standard parental questionnaire was distributed in January and February 2008 to third and fourth grade schoolchildren (*i.e.*, 8- to 9-year-old children; outliers aged 7 and 10 years) of 46 primary public schools in the city of Patras, Greece; 42 schools were also included in the three previous surveys, all of which evaluated large population samples (1991, $n = 2417$, 1181 boys; 1998, $n = 3076$, 1507 boys; 2003, $n = 2725$, 1337 boys).^{6–8,12} Patras is a coastal city and the regional capital of western Greece. Its metropolitan area has ~22,000 inhabitants. Identical methodology regarding the wording of the questions, the months of the year conducted, the targeting, the distribution, and the collection of the parental questionnaire as well as the confirmation of responses was used in all four surveys; it is described in detail elsewhere.^{7–9,12} The study population represented >80% of the target population in all four surveys (National Statistical Services, census 1991 and 2001).

Formal approval was obtained from the University of Patras Ethics Committee and the Greek Ministry of Education. The Head Masters of the primary schools surveyed were approached by the researchers, and the parental questionnaire—along with an informative statement on asthma and allergic diseases—was distributed to and collected from the children in the classroom with the assistance of the teachers.

Statistical Analysis

Prevalence was calculated as the ratio of cases to total number of children surveyed and was expressed in absolute and relative numbers. Comparisons of prevalence of asthma between male and female subjects were performed using the Z test. The Mantel-Haenszel extension of the chi-square test for trend was used to evaluate tendency between time points. Multiple logistic regression analysis was used to assess the effect of sex on prevalence time trends as well as the risk of current (total), persistent, and new-onset wheeze/asthma in the presence of

rhinoconjunctivitis and/or eczema. Using sex-adjusted relative risk (RR), the population attributable risk ratio (proportion of asthma attributable to the presence of allergic disorders) was consequently estimated as $P \times (RR - 1) / (1 + P \times [RR \times 1])$, where P is the incidence of rhinoconjunctivitis and/or eczema in the surveyed population. A value of $p < 0.05$ for two-sided hypotheses was considered as statistically significant. All calculations were performed with the SPSS 17 (SPSS, Inc., Chicago, IL) statistical software.

RESULTS

The overall response rate in the 2008 survey ($n = 2688$, 1304 boys) was 84.7% (range among schools, 76.2–95.0%). Questionnaires with missing or inconsistent values (2.4%) were not included in the analysis. The population sample included 12.6% non-Greek ethnic origin groups, mostly Albanian.¹² Telephone confirmation of the responses was achieved in 82.4% of positive responders and in a random sample of 350 negative responders; none of the negative controls who were contacted changed their answer. Similar high consistency in responses were achieved in the 1991, 1998, and 2003 surveys.^{6–8}

Table 1 shows the evolution in the prevalence of asthma, rhinitis, rhinoconjunctivitis, and eczema in the four surveys. There is a statistically significant trend for increase in the prevalence of current wheeze/asthma throughout the surveillance period. However, its rate of rise decelerated, reached plateau in 2003, and remained unchanged in the 2008 survey.¹² The prevalence of rhinitis, rhinoconjunctivitis, and eczema increased throughout the 1991–2008 period. The increase in the prevalence of wheeze/asthma (with the exception of new onset) and that of allergic disorders was statistically significant for both boys and girls and was not influenced by changes in sex ratios. Boys contributed to the prevalence of these conditions more than girls throughout the surveillance period.

Table 2 presents the prevalence trends of rhinoconjunctivitis, eczema, and any of these two conditions (atopic wheeze/asthma) among children with current (total), persistent, and new-onset diagnosed wheeze/asthma. A statistically significant increase over time is evident in all cases. The between-surveys increases were statistically significant for current (total) and persistent atopic wheeze/asthma, with no apparent pattern in the case of new-onset disease.

The RR for current (total), persistent, and new-onset wheeze/asthma in the presence of rhinoconjunctivitis, eczema, or any of the two conditions in the four surveys is illustrated in Fig. 1. A gradual increase in the risk for

Table 1 Prevalence of wheeze/asthma, rhinitis, and allergic disorders (rhinoconjunctivitis and eczema) in the four surveys, and the influence of sex on prevalence time trends during the surveillance period

	1991	1998	2003	2008	Prevalence Change (%)			Male:Female Risk Ratio (95% CI)	p Value for the Effect of Sex on Time Trend
					1998 vs 1991	2003 vs 1998	2008 vs 2003		
Number surveyed	2417	3076	2725	2688					
Male/female	0.95:1	0.96:1	0.96:1	0.94:1					
Wheeze/asthma									
Current*	112 (4.6%)	184 (6.0%)	189 (6.9%)	185 (6.9%)	30.4#	15.0	0	1.41 (1.21–1.65)	<0.001
Male/female	1.15:1	1.16:1	1.22:1	1.23:1					
Lifetime*	194 (8.0%)	296 (9.6%)	338 (12.4%)	339 (12.6%)	20.0#	29.2\$	1.6	1.62 (1.43–1.83)	<0.001
Male/female	1.13:1	1.26:1	1.43:1	1.46:1					
Persistent*	61 (2.5%)	131 (4.3%)	159 (5.8%)	141 (5.2%)	72.0\$	34.9\$	–10.3	1.49 (1.24–1.79)	<0.001
Male/female	1.35:1	1.18:1	1.30:1	1.27:1					
New onset	51 (2.1%)	53 (1.7%)	30 (1.1%)	44 (1.6%)	–19.1	–35.5#	45.5	1.19 (0.89–1.60)	0.242
Male/female	0.96:1	1.12:1	0.88:1	1.10:1					
Rhinitis									
Current*	123 (5.1%)	201 (6.5%)	217 (8.0%)	236 (8.8%)	27.5#	23.1#	10.0	1.23 (1.07–1.43)	0.004
Male/female	1.08:1	0.93:1	1.09:1	1.15:1					
Lifetime*	145 (6.0%)	245 (8.0%)	267 (9.8%)	288 (10.7%)	33.3\$	22.5#	9.2	1.24 (1.08–1.42)	0.002
Male/female	0.93:1	1:1	1.10:1	1.13:1					
Rhinoconjunctivitis									
Current*	43 (1.8%)	83 (2.7%)	98 (3.6%)	105 (3.9%)	50.0#	33.3#	8.3	1.27 (1.02–1.58)	0.037
Male/female	1.15:1	1.03:1	1.13:1	1.10:1					
Lifetime*	51 (2.1%)	104 (3.4%)	125 (4.6%)	136 (5.1%)	61.9\$	35.5#	10.9	1.22 (1.00–1.49)	0.045
Male/female	0.90:1	1.16:1	1.04:1	1.06:1					
Eczema									
Current*	60 (2.5%)	104 (3.4%)	135 (5.0%)	150 (5.6%)	36.0	47.1\$	12.0	1.22 (1.00–1.47)	0.043
Male/female	1.14:1	1.07:1	1.04:1	1.14:1					
Lifetime*	109 (4.5%)	194 (6.3%)	258 (9.5%)	290 (10.8%)	40.0\$	50.8¶	13.7	1.24 (1.08–1.43)	0.003
Male/female	0.91:1	1.13:1	1.04:1	1.13:1					
Any allergy									
Current*	86 (3.6%)	173 (5.6%)	203 (7.4%)	235 (8.7%)	55.6¶	32.1\$	17.6\$	1.22 (1.05–1.42)	0.012
Male/female	1.05:1	0.95:1	1.03:1	1.16:1					
Lifetime*	142 (5.9%)	270 (8.8%)	328 (12.0%)	389 (14.5%)	49.2¶	39.8¶	17.1#	1.24 (1.10–1.40)	0.001
Male/female	0.82:1	1.14:1	1.03:1	1.12:1					

*p < 0.001 for increase in prevalence in overall population, and separately for boys and girls, using the Mantel-Haenszel extension of the chi-square test for trend.

#p < 0.05 for between-surveys comparison.

\$p < 0.01 for between-surveys comparison.

¶p < 0.001 for between-surveys comparison.

Table 2 Prevalence of lifetime allergic disorders (rhinoconjunctivitis, eczema, and any) in children with current (total, persistent, and new onset) wheeze/asthma

	Prevalence (%)				Prevalence Change (%)			<i>p</i> for Trend
	1991	1998	2003	2008	1998 vs 1991	2003 vs 1998	2008 vs 2003	
Current wheeze/asthma								
Rhinoconjunctivitis	8.0	13.0	19.6	29.2	62.5	50.8	49.0*	<0.001
Male/female	0.8:1	0.7:1	0.9:1	0.9:1				0.908
Eczema	13.4	22.3	35.4	38.4	66.4	58.7#	8.5	<0.001
Male/female	1.1:1	1.4:1	1.2:1	1.4:1				0.646
Any	17.9	28.8	43.4	55.7	60.9*	50.7#	28.6*	<0.001
Male/female	1.0:1	1.0:1	1.1:1	1.1:1				0.819
Persistent wheeze/asthma								
Rhinoconjunctivitis	1.6	10.7	16.4	27.7	568.0*	53.2	68.9*	<0.001
Male/female	NA	0.8:1	1.1:1	1.1:1				0.684
Eczema	6.6	22.9	33.3	39.7	244.0*	45.4*	19.2	<0.001
Male/female	1.0:1	1.5:1	1.5:1	1.4:1				0.754
Any	8.2	28.2	37.7	55.3	243.9§	33.7*	47.2§	<0.001
Male/female	0.7:1	1.1:1	1.4:1	1.2:1				0.451
New-onset wheeze/asthma								
Rhinoconjunctivitis	15.7	18.9	36.7	34.1	20.4	94.2	−7.1	0.013
Male/female	1.6:1	0.7:1	0.6:1	0.5:1				0.219
Eczema	21.6	20.8	46.7	34.1	−3.7	124.5*	−27.0	0.046
Male/female	1.2:1	1.2:1	0.6:1	1.5:1				0.965
Any	29.4	30.2	73.3	56.8	2.7	142.0§	−22.5	<0.001
Male/female	1.4:1	1.0:1	0.6:1	0.9:1				0.420

*p < 0.05 for between-surveys comparison.

#p < 0.01 for between-surveys comparison.

§p < 0.001 for between-surveys comparison.

NA = non applicable; only one girl was diagnosed with persistent wheeze/asthma and rhinoconjunctivitis in 1991.

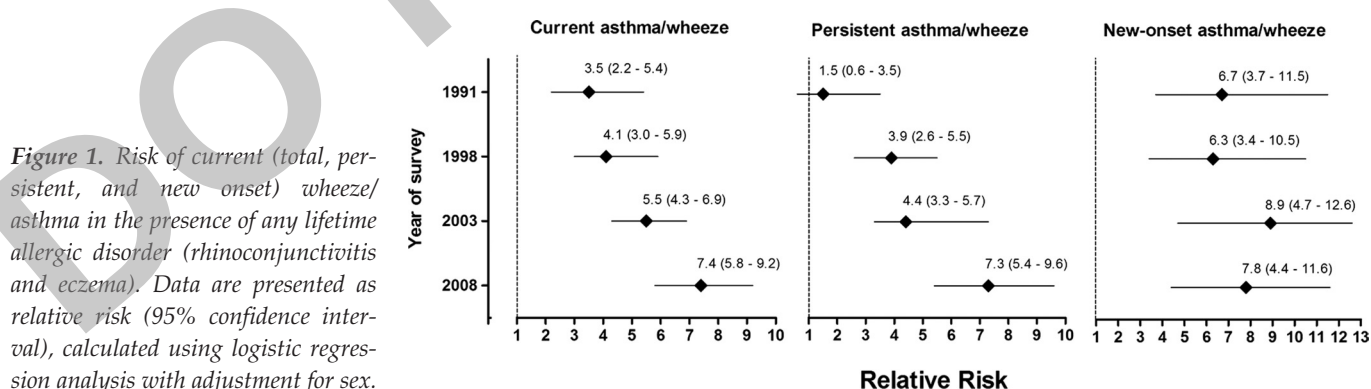


Figure 1. Risk of current (total, persistent, and new onset) wheeze/asthma in the presence of any lifetime allergic disorder (rhinoconjunctivitis and eczema). Data are presented as relative risk (95% confidence interval), calculated using logistic regression analysis with adjustment for sex.

current (total) and persistent wheeze/asthma and the absence of a specific pattern for new-onset wheeze/asthma are evident.

Table 3 shows the percentage of total, persistent, and new-onset current wheeze/asthma that can be attributed to atopy (*i.e.*, presence of rhinoconjunctivitis and/or eczema) during the surveillance period. It is evident that the population attributable risk ratio has

progressively increased in all categories of current asthma, reaching ~50% in 2008.

DISCUSSION

A plateau in the prevalence of diagnosed wheeze/asthma was recently found in a series of cross-sectional surveys (1991, 1998, 2003, and 2008) among 8- to 9-year-old schoolchildren in Patras, Greece. In this ar-

Table 3 Percentage of current (total, persistent, and new onset) wheeze/asthma attributable to any lifetime allergic disorder (rhinoconjunctivitis and eczema)

	Population Attributable Risk Ratio (95% CI)*				<i>p</i> for Trend
	1991	1998	2003	2008	
Atopic wheeze/asthma					
Current	13 (7–21)	21 (15–30)	35 (28–41)	48 (41–54)	<0.001
Persistent	3 (0–13)	20 (12–28)	29 (22–35)	48 (39–55)	<0.001
New onset	25 (14–38)	32 (17–46)	49 (31–58)	50 (33–61)	<0.001

*Calculated using sex-adjusted relative risk.

ticle we examined the trends in the prevalence of rhinitis, rhinoconjunctivitis, and eczema during the same surveillance period. Our results were consistent with the study hypothesis because they showed that the rate of increase in the prevalence of all three conditions has dropped drastically during 2003–2008. We also showed that the contribution of atopic disorders in the prevalence of diagnosed wheeze/asthma has continued to increase throughout the 17-year surveillance period.

Unlike the progressive deceleration in the rate of increase of current wheeze/asthma prevalence, the contribution of atopic wheeze/asthma to the total asthma prevalence continued to rise throughout the surveillance period. However, the high annual rate of increase that occurred over the initial 12 years of surveillance (1991–1998, 9.5%; 1998–2003, 10.1%) dropped to almost one-half this value (5.7%) during the 2003–2008 period. These findings are echoed by the progression of the percentage of current wheeze/asthma that is attributable to allergy (atopic wheeze/asthma). It is intriguing that the attributable risk ratio increased from 35% in 2003 to 50% in 2008 despite the plateau in asthma prevalence during the same period.

In line with our observations, a stabilization in the prevalence of asthma and allergic diseases has been shown in a number of serial surveys conducted during the last 10 years.^{8–11,13,14} Indeed, certain studies, both in children^{13–19} and in adults,^{13,21} have actually revealed a decrease in the prevalence of asthma and/or other allergic conditions in the first 10 years of the new century. Moreover, comparable data on asthma, rhinoconjunctivitis, and eczema have been obtained globally in two cross-sectional surveys of the International Study of Asthma and Allergies in Childhood (ISAAC) Phase-I (established in 1991) and ISAAC Phase-III. The prevalence trends of the three conditions, which were performed at least 5 (a mean of 7 years) years apart, revealed no obvious pattern.¹⁵ In general, the increases were twice as common as the decreases, particularly among younger children (6–7 years), but most centers showed mixed results. The only occasion in which decreases were more common than increases was that of asthma symptoms at high prevalence in the older

age group (13–14 years).¹⁵ The few studies that have focused on the separate contributions of atopic versus nonatopic asthma on prevalence time trends have reached conflicting conclusions.^{22–24} In addition, the Phase II ISAAC study showed that the link between atopic sensitization and asthma symptoms differs strongly between populations and increases with economic development.²⁵

Regarding the influence of sex on the prevalence of childhood asthma, early studies reported a male/female ratio of ~2:1.²² However, recent surveys on the trends of sex-specific prevalence of asthma and other allergic diseases present a mixed picture.^{22,26–29} In our study, although the increase in the prevalence of wheeze/asthma, rhinitis, rhinoconjunctivitis, and eczema was similar in both sexes, a consistent male predominance is evident in all conditions throughout the surveillance period.

The present study was not designed to investigate the risk factors and/or triggers of asthma and allergies or the patterns of change in the prevalence of asthma and allergies over time. The reasons for the variability in temporal and geographical trends of asthma prevalence and the inconsistencies in the influence of sex and atopy on these trends are far from clear.^{8,30} A number of factors may have contributed to this variability. These include the complexities in defining asthma and atopy, the limitations of the epidemiological tools used to measure these conditions, and the changes that have occurred in diagnostic fashion and public awareness over the past decades.^{7,8,12} On the other hand, the “hygiene hypothesis” can not explain why the prevalence of asthma and allergies has leveled off or, indeed, decreased in affluent countries in recent times. Most likely, a wide variety of environmental risk and protective factors—some possibly unidentified as yet—are implicated. Perhaps the gene-environment interaction potential that underlies the development of asthma and allergic diseases and its “saturation” due to environmental “opportunities” have determined these trends. This potential is unknown in any given population but the high prevalence rates observed in certain regions suggest that it can be quite high.^{15,25} The increase in atopic asthma is most likely the result of the rise in atopy, as reflected by the increase of

rhinoconjunctivitis and/or eczema in our population. To reconcile this rise with the plateau in total asthma prevalence, we deduce that nonatopic asthma has decreased in our population. The specific cause(s) of this decrease has not been addressed by this study and is likely to vary in different parts of the world and in time. The dissociation in the time course of wheeze/asthma and allergic disease prevalence is consistent with the concept that the determinants (genetic and/or environmental) of asthma differ, at least in part, from those of atopy. It is plausible that the mixture of risk and protective environmental contributors that drove, until recently, the increase in the prevalence of asthma symptoms has changed in recent years.

At an epidemiological level, asthma and atopy are poorly correlated³⁰ and this has been confirmed at a global level by the ISAAC data.²⁵ Others have shown that children with allergic and nonallergic rhinitis have similar risk of asthma.³¹ Thus, despite the high burden of rhinitis^{32–34} and its higher prevalence when compared with rhinoconjunctivitis and eczema in our population, we elected to exclude rhinitis as a manifestation of allergy in our analysis of “atopic” asthma; similar to others, we included only rhinoconjunctivitis and eczema.²² Nevertheless, it should be borne in mind that the role of atopy in the epidemiology of rhinoconjunctivitis and especially of eczema is also not well defined and appears to be variable.^{35–37}

Among a multitude of studies that have investigated the prevalence of asthma and other allergic diseases throughout the world, the Patras study is one of few that have used identical methodology in a series cross-sectional surveys with large population samples over a long period of time (30 years for asthma and 17 years for rhinitis, rhinoconjunctivitis, and eczema).^{1–3,5–18} Another strength of the study is the large population coverage; in all four Patras surveys >80% of the target population was approached and response rates in excess of 80% were achieved, perhaps because of the passive method of consent of the parents.³⁸

The study strengths and limitations are essentially those inherent to cross-sectional questionnaire surveys conducted over long time periods and have been addressed previously.^{6–8,12} Regarding asthma symptoms, the Patras questionnaire obtained information on physician-diagnosed wheezing and asthma (Appendix 1); these questions were validated against diagnosis of wheeze and/or asthma *via* personal interview with a physician in 1978.^{6,7,12} Although the wording used in the description of rhinitis, rhinoconjunctivitis, and eczema is essentially identical to that of the ISAAC questionnaire, the word “current” in our study refers to the 2 years before surveillance (Appendix 1). Therefore, our results are not comparable with those of the ISAAC surveys. We did not use objective measures to assess prevalence (*e.g.*, bronchial responsiveness for asthma

and skin-prick tests or IgE measurement for atopy). However, standardized symptom questionnaires are considered valid and constitute, by far, the most common method of studying the prevalence of these conditions in large population samples.^{15,25,36,39} In fact, it has been argued that they offer improved validity when compared with measurement of airway hyper-responsiveness in the case of asthma.³⁹ We can not exclude the possibility that changes in public awareness and/or diagnostic fashion of asthma symptoms as well as of symptoms of the nose, conjunctiva, and skin may have influenced our results. However, the strict application of identical methodology reasonably ensures that our findings reflect true changes in the prevalence of these conditions. The inclusion of a small percentage of non-Greek ethnic origin children in our analysis has been discussed previously and bares no influence in the changes in the prevalence of wheeze/asthma or allergies in our population.^{7,8} The possibility of systematic underdiagnosis of asthma and allergies in girls (“Yentl phenomenon”) in the early surveys is probably small and, in any event, it would be expected to have decreased over the surveillance period, thus leading to the convergence in the contribution of male and female subjects in the prevalence of these conditions; the persistence of male predominance in our study refutes this possibility.

In conclusion, our data show that there has been a continuous increase in the prevalence of rhinitis, rhinoconjunctivitis, and eczema during 1991–2008. However, its rate of rise has declined in the period 2003–2008, and boys have continued to contribute to the prevalence of these conditions more than girls. These findings, in conjunction with the unchanged prevalence of current wheeze/asthma during the same period, reveal a dissociation between the time trends of the prevalence of asthma and other allergic conditions. In addition, despite the recent plateau in its prevalence, the percentage of wheeze/asthma attributable to atopy has continued to rise. These observations support the concept that the epidemiological determinants of asthma differ, at least in part, from those of atopy and/or that the contribution of the environmental factors that drove, until recently, the increase in the prevalence of asthma in Westernized societies has changed in recent years.

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