# Relationship between atopic asthma and the population prevalence rates for asthma or atopy in children: Atopic and nonatopic asthma in epidemiology

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## ABSTRACT

*Innumerable articles have tried to solve the "continuing enigma of atopic and nonatopic asthma" but notwithstanding the strenuous efforts to substantiate the few well-known clinico-epidemiologic differences between these two forms of asthma most studies have hitherto generated inconclusive statements. In a recent study based on the review of epidemiologic studies conducted worldwide in unselected populations of children, we documented that the prevalence of atopic asthma (AA) was high in the populations with a high prevalence of atopy. We systematically reviewed 36 articles that studied 48 populations of unselected children and reported prevalence rates for asthma and atopy in the total sample and in the subpopulations. No significant difference was found in the prevalence of asthma cases in the quartiles of childhood populations subdivided for the prevalence of atopy. In addition, atopy did not increase significantly in the subgroups of populations subdivided by asthma quartiles. In both subgroups, however, AA increased with increasing atopy or with increasing asthma ($p < 0.001$). Using a positive skin-prick test reaction to define cases of asthma as cases of AA is misleading because the prevalence of subjects so defined is heavily influenced by the environmentally generated changes in the prevalence of atopy or asthma. Asthma in a child should be labeled as a case of AA only if skin-prick tests yield a positive reaction and the clinical history documents asthma symptoms triggered by allergen exposure.*

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**Key words:** Allergy, asthma, atopic asthma, atopy, children, nonatopic asthma, population, prevalence

Over the past 60 years innumerable studies have tried to solve the "continuing enigma of extrinsic, atopic asthma (AA) and intrinsic, non-AA (NAA)."[1] However, notwithstanding the strenuous efforts to substantiate the few well-known clinico-epidemiologic differences between these two forms of asthma (including later onset, female prevalence, more severe clinical course, and less evident family history of asthma in NAA)[2] with immunopathological features, most studies have hitherto generated substantially inconclusive statements.[3,4]

The lack of evidence that atopy suffices to identify an asthma phenotype casted doubts on the rationale for classifying asthma cases as intrinsic or extrinsic and reinforced the hypothesis that the propensity to develop asthma and to develop inappropriate IgE responses could be independent traits that are commonly juxtaposed in individuals.[5] Our understanding of these relationships is made even more complex by the two parallel epidemics of asthma and atopy, both taking place all over the world, albeit at different speeds and starting from different levels in the various geographical settings.[6–8]

In a recent review of several epidemiologic studies conducted worldwide in unselected populations of children, even though the prevalence of both atopy and asthma varied more than 10-fold, we found a strict correlation between the prevalence of atopy in the asthmatic subjects and the prevalence of atopy in the nonasthmatic part of the population.[9] We therefore concluded that when atopy increases in certain populations it increases in parallel in asthmatic and nonasthmatic subjects. No study has shown whether asthma increases in a similar way in atopic and nonatopic subjects. To understand how the epidemiologic differences in the prevalence of asthma and of atopy influence the prevalence of AA, in this article, we reexamined the findings for 48 populations of unselected children (37 analyzed in our previous article and 11 reported in recently published articles).[11–46]

## METHODS

In selecting articles for our review we used the same criteria followed by Pearce *et al.*[10] (Medline, English

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language, key words "IgE or skin tests or hypersensitivity, immediate," combined with "epidemiologic studies, cross sectional, case-control, prevalence, longitudinal, epidemiology of asthma"). We searched the literature for studies conducted from 1980 onward in unselected groups of children and reporting data on the prevalence of "asthma ever" or "current asthma" and the prevalence of atopy (positive allergen skin-prick tests, ASPT) in the asthmatic and nonasthmatic part of the population.

Our final list included 48 children populations described in 36 articles. Of these 48 children populations, 12 were studied by our group between 1983 and 2003, addressing cohorts of ~150–200 unselected schoolchildren (cumulative number, 2005 subjects) aged 9–10 years who completed a standardized questionnaire concerning respiratory and allergic illnesses and who underwent ASPT for common environmental allergens. Six of these 12 studies were conducted in central Italy, north of Rome (Ronciglione, 1983, 1992, 1998, 2001, and 2003, and Guardea, 2001); three others were conducted in Poland (Starachowice, 1998 and 2001, and Legnica, 2001), two were conducted in Libya (Samno and Al-Azyzia, 2001); and one was conducted in Slovakia (Poprad, 2003).[11–17] The list of articles fulfilling our search criteria also included 29 articles by other investigators: the 8 articles Pearce *et al.* reviewed in 1999[18–25] and an additional 11 articles published before 2005 (25 children populations, numbers 13–37, shown in the Table 1),[26–36] which we used in our previous publication,[9] and 10 articles recently published (11 children populations, numbers 38–48, shown in Table 1).[37–46] Unlike our 12 studies, which always rigorously followed the same protocol, the 29 articles by other investigators describe studies that differed widely: the number of studied subjects (range, 172–27,000), race (including Europeans, Americans, Australians, and Asians), study design (national or local surveys, cross-sectional studies, and cohorts), age (range, 5–18 years), definition of asthma (including current, "ever", doctor diagnosed, and history of wheezing), technique of ASPT (immunoreactivity set at 2 or 3 mm or according to a score or based only on erythema), and number of tested allergens (range, 4–16).

### Statistical Methods

The prevalence rates of atopy in asthmatic and nonasthmatic persons and of asthma in atopic and nonatopic persons were normally distributed (Kolmogorov-Smirnoff goodness of fit test). Pearson's correlation coefficient ($r$) was used to determine the relationship between variables. Linear regression analysis was used to assess the slope of the relationship between variables. Data were analyzed with the statistical software package SPSS 9.0 for Windows. Two-tailed values of $p < 0.05$ were considered statistically significant.

## RESULTS

The prevalence rates for asthma and atopy in the 48 childhood populations selected for review ranged more than 10-fold (asthma from 1.8 to 44.1% and atopy from 5.8 to 63.9%; Table 1). When we subdivided these populations in quartiles for the prevalence of atopy we found similar mean asthma prevalence rates in the four groups (from 14.9 to 18.6%). In these quartiles the proportion (%) of asthmatic and nonasthmatic persons with atopy nevertheless increased, passing from the low to the high quartiles ($p < 0.001$ for both categories, Fig. 1 *A*).

When we similarly subdivided the populations under study in quartiles for the prevalence of asthma we found no significant difference in the prevalence of atopy in the population among the quartiles (from 28.3 to 33.9). In these quartiles, however, the proportion (%) of atopic and nonatopic persons with asthma increased significantly, passing from the low to the high quartiles ($p < 0.001$ for both categories; Fig. 1 *B*).

The increased percentage of asthma persons with atopy in populations with high atopy levels was graphically documented by the highly significant correlation between the percentage AA/total asthma and the prevalence of atopy in the general population ($r = 0.895$; $p < 0.001$; Fig. 2 *A*). The slope of the regression line (1.295) showed that the prevalence of atopy among asthmatic persons was from 10 to 30% larger than the prevalence of atopy in the general population.

Similarly, the increased percentage of atopic persons with asthma in populations with high asthma levels was documented by the highly significant correlation between the percentage AA/total cases of atopy and the prevalence of asthma in the general population ($r = 0.909$; $p < 0.001$; Fig. 2 *B*). The slope of the regression line (1.397) showed that the prevalence of asthma among atopic persons is always from 5 to 20% larger than the prevalence of asthma in the general population.

All of the foregoing correlations remained highly significant and unchanged when we separately analyzed the data for our 12 well-standardized unselected children populations ($r = 0.892$, $p < 0.001$, for the correlation described in Fig. 2 *A* and $r = 0.867$, $p < 0.001$, for the correlation described in Fig. 2 *B*) and the 36 children populations drawn from the literature ($r = 0.887$, $p < 0.001$, for the correlation described in Fig. 2 *A* and $r = 0.926$, $p < 0.001$, for the correlation described in Fig. 2 *B*).

## DISCUSSION

Reexamining the data drawn from our own studies and those reported in the literature we found that in populations of unselected children, epidemiologic differences in the prevalence of asthma and atopy

Table 1 **Forty-eight children population-based studies reporting the prevalence rates for atopy, asthma, and atopic and nonatopic asthmatic patients**

| | Setting | Year of Study | Reference | Atopy | | Asthma | | | Setting | Year of Study | Reference | Atopy | | Asthma | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Prevalence (%) | Percentage of Atopic Persons with Asthma (AA) | Prevalence (%) | Percentage of Asthmatic Persons with Atopy (AA) | | | | | Prevalence (%) | Percentage of Atopic Persons with Asthma (AA) | Prevalence (%) | Percentage of Asthmatic Persons with Atopy (AA) |
| 1. | Italy, Ronciglione | 1983 | 11 | 15.9 | 32.2 | 13.5 | 39.1 | 25. | Finland, Kuopio | 1995 | 27 | 51.4 | 26.1 | 17.4 | 77 |
| 2. | Italy, Ronciglione | 1987 | 12 | 26.3 | 21.9 | 14.7 | 39.1 | 26. | Sweden, Norrbotten | 1996 | 28 | 20.6 | 18.1 | 8.0 | 46.6 |
| 3. | Italy, Ronciglione | 1998 | 13,14 | 25.3 | 23.9 | 14.6 | 41.4 | 27. | Estonia, Tallin, Tartu | 1996 | 29 | 13.3 | 46.6 | 24.0 | 25.8 |
| 4. | Poland, Starachowice | 1998 | 15 | 16.7 | 39 | 21.0 | 31 | 28. | Sweden, Linköping | 1996 | 29 | 24.6 | 49.2 | 24.2 | 50.0 |
| 5. | Italy, Ronciglione | 2001 | 16,17 | 27.7 | 34.8 | 19.9 | 48.5 | 29. | Sweden, Ostersund | 1996 | 29 | 33.7 | 57.3 | 33.3 | 58.0 |
| 6. | Italy, Guardea | 2001 | 16,17 | 31.7 | 43.7 | 26.7 | 51.9 | 30. | Albania, Tirana | 2001 | 30 | 14.9 | 9.5 | 4.8 | 29.6 |
| 7. | Poland, Starachowice | 2001 | 16,17 | 17.9 | 35 | 28.6 | 21.9 | 31. | United Kingdom, West Sussex | 2001 | 30 | 17.8 | 37.3 | 16.6 | 39.8 |
| 8. | Poland, Legnica | 2001 | 16,17 | 18.0 | 44.4 | 27.3 | 29.3 | 32. | Peru, Lima | 1997 | 31 | 23.9 | 24.4 | 20.5 | 28.4 |
| 9. | Libya, Al Azizia | 2001 | 16,17 | 5.8 | 1.7 | 9.1 | 1.1 | 33. | Australia, Perth | 1989 | 32 | 41.5 | 24.8 | 18.5 | 55.5 |
| 10. | Libya, Samno | 2001 | 16,17 | 6.7 | 1.5 | 4.4 | 2.3 | 34. | Australia, Canberra | 1999 | 33 | 45.6 | 43.6 | 34.3 | 58.0 |
| 11. | Italy, Ronciglione | 2003 | 16,17 | 31.7 | 23.1 | 18.9 | 38.7 | 35. | United Kingdom, Ashford | 1990 | 34 | 16.7 | 42.3 | 17.4 | 40.6 |
| 12. | Slovakia, Poprad | 2003 | 16,17 | 21.9 | 45.4 | 36.8 | 27.0 | 36. | United States, Detroit | 1987 | 35 | 33.6 | 13.8 | 7.0 | 66.0 |
| 13. | United States, Nation.study | 1976 | 18 | 22.6 | 13.4 | 6.7 | 45.1 | 37. | Australia, Perth | 1995 | 36 | 55.2 | 23.1 | 15.1 | 84.6 |
| 14. | United States, Tucson | 1971 | 19 | 46.8 | 13.9 | 8.2 | 79.0 | 38. | United Kingdom, Isle of Wight | 1999 | 37 | 27.7 | 43.3 | 21.4 | 56.1 |
| 15. | New Zealand, Dunedin | 1985 | 20 | 44.6 | 56.4 | 44.1 | 57.0 | 39. | Norway, Oslo | 2002 | 38 | 29.3 | 21.5 | 11.1 | 56.8 |

Table 1 **(Continued)**

| | Setting | Year of Study | Reference | Atopy | | Asthma | |
|---|---|---|---|---|---|---|---|
| | | | | Prevalence (%) | Percentage of Atopic Persons with Asthma (AA) | Prevalence (%) | Percentage of Asthmatic Persons with Atopy (AA) |
| 16. | Sweden, Umeå | 1987 | 21 | 42.7 | 17 | 11.0 | 66.0 |
| 17. | Hong Kong | 1992 | 22 | 57.7 | 16.9 | 12.1 | 80.7 |
| 18. | Malaysia, Kota Kinabalu | 1992 | 22 | 63.9 | 9.2 | 6.5 | 90.5 |
| 19. | China, San Bu | 1992 | 22 | 49.0 | 3.1 | 1.8 | 83.3 |
| 20. | Germany, Munich | 1989 | 23 | 38.7 | 9.6 | 5.4 | 69.1 |
| 21. | Germany, Leipzig | 1991 | 23 | 18.8 | 8.1 | 3.8 | 40.0 |
| 22. | United States, Tucson | 1980 | 24 | 41.3 | 40.3 | 29.7 | 56.0 |
| 23. | United Kingdom, Leicester | 1995 | 25 | 31.4 | 33.9 | 19.7 | 54.0 |
| 24. | Estonia, Tallin, Tartu | 1992 | 26 | 11.1 | 19.9 | 7.7 | 28.7 |
| 40. | Spain, Cartagena, Madrid, Almeria | 2005 | 39 | 36.8 | 22.3 | 13.1 | 62.6 |
| 41. | Denmark, Copenhagen | 1986 | 40 | 24.1 | 15.8 | 5.3 | 71.7 |
| 42. | Denmark, Copenhagen | 2001 | 40 | 19.4 | 28.4 | 11.9 | 46.2 |
| 43. | United Kingdom, Bristol | 1999 | 41 | 20.6 | 37.9 | 20.0 | 39.0 |
| 44. | Greece, Crete | 2001 | 42 | 22.8 | 5.3 | 4.4 | 27.3 |
| 45. | United States, Boston | 2002 | 43 | 55.0 | 14.7 | 11.1 | 73 |
| 46. | Finland, Kuopio | 2001 | 44 | 33.9 | 10.9 | 6.1 | 60.7 |
| 47. | New Zealand, Dannevirke | 2002 | 45 | 32.4 | 56.2 | 33.8 | 53.9 |
| 48. | Australia, Perth | 2004 | 46 | 51.4 | 22.4 | 14.7 | 78.2 |

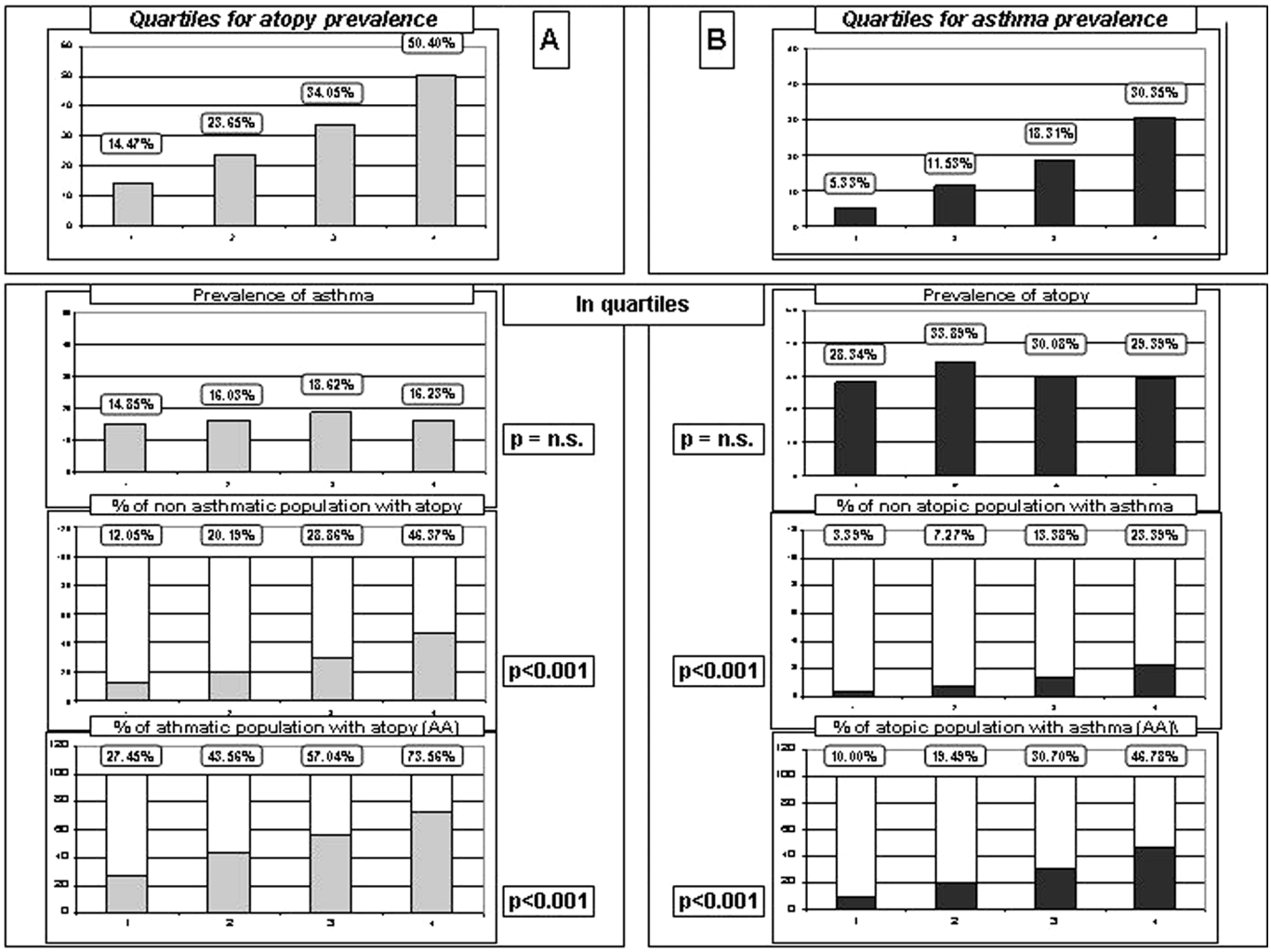


***Figure 1.*** *The 48 populations reported in Table 1 were subdivided into quartiles for the prevalence of (A) atopy (first row) and (B) of asthma (first row). The following rows report the figures of the indicated parameters in the quartiles.*

strongly influence the prevalence of AA. Indeed, the prevalence of atopy in the general childhood population accurately predicts the percentage of persons with asthma who have AA ($p < 0.001$). Similarly, the prevalence of asthma in the general childhood population accurately predicts the percentage of atopic subjects who have AA ($p < 0.001$).

We consider it unlikely that our findings are flawed by artifacts because we avoided a bias in literature selection by using standard research criteria and reporting all of the articles thus found. Because a lack of homogeneity in the experimental data can only reduce, not increase, the strength of a statistical correlation, we believe that the various environments, geographical settings, and socioeconomic conditions represented among the populations included in this systematic review and the large number of populations studied practically ensure that confounders (including socioeconomic conditions, peculiar quality of geographical settings, and climate) have no significant influence on the strength of the correlations obtained. Accordingly, when we analyzed separately the data for our 12 well-standardized children populations and the 36 children populations drawn from the literature, all of the correlations remained highly significant and unchanged.

Our findings in this systematic review unequivocally document the previously underlined concept that at the epidemiologic level, asthma and atopy substantially behave as two independent variables.[1,9,47–49] Atopy and asthma, under the influence of powerful although largely unknown environmental factors, variably increase in populations. In this process, atopy affects children with or without asthma and asthma affects children with or without atopy in a strictly proportional manner. The positive slopes of the regression lines show that environmental factors tend to induce atopy measurably more frequently in asthmatic patients than in non asthmatic patients (Fig. 2 *A*) and asthma measurably more frequently in atopic than in nonatopic persons (Fig. 2 *B*). Quantitatively, atopic per-

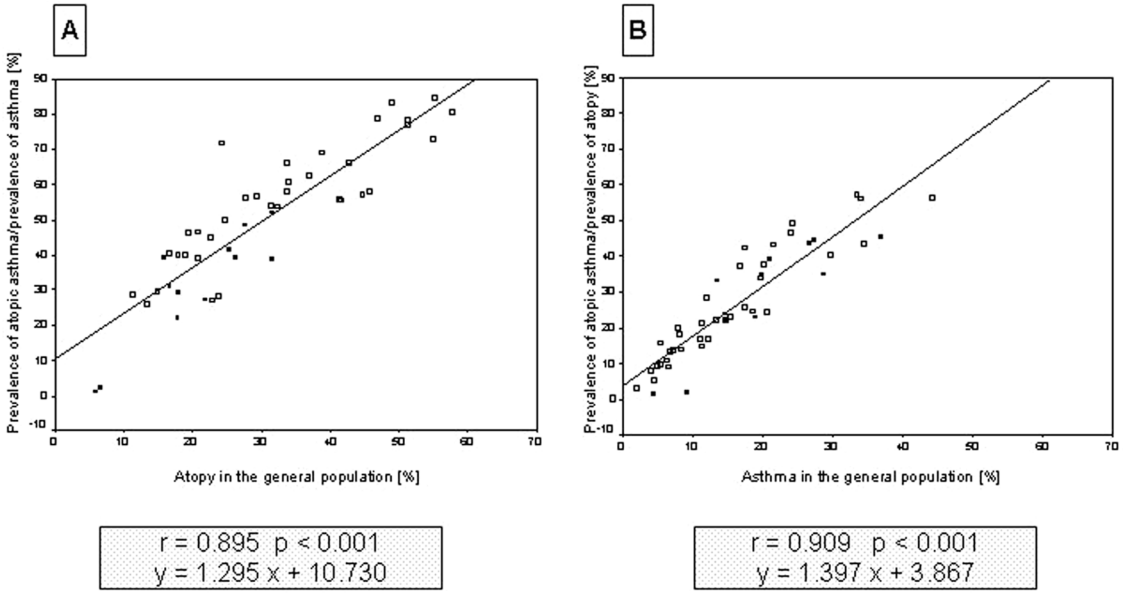


***Figure 2.*** *(A) Linear correlation between the prevalence of atopy (at least one positive skin-prick test) and the proportion of asthmatic persons who are atopic in the 48 studied populations ($y = 1.295x + 10.730$; $p < 0.001$, $r = 0.895$). (B) Linear correlation between the prevalence of asthma and the proportion of atopic persons who are asthmatic in the 48 studied populations ($y = 1.397x + 3.867$; $p < 0.001$, $r = 0.909$). ■, Populations studied by the author's group; □, populations derived from the published studies of the other groups (the square symbols, black and white, have been inverted).*

sons are more likely than nonatopic persons to be asthmatic (about +10–30%), and asthmatic persons are more likely than nonasthmatic persons to be atopic (about +5–20%). Owing to the complex interaction of environmental and personal factors, the percentage of asthma cases that can be labeled as AA (extrinsic asthmas) varies widely in the various geographical settings; *i.e.*, in our 48 childhood populations AA ranges from <2 to >90% of the total cases of asthma (Table 1).

A likely interpretation of these epidemiologic trends is that, at least in children, the same predisposition to asthma or to atopy, in different subjects could be accompanied or not by atopy or asthma. Whether these conditions coincide depends on differences in the genetic background and on the influence of the appropriate environmental factors.

Does this interpretation receive support from studies concerning the cellular and molecular immunopathology of asthma? The heterogeneous features of the various published studies make this question difficult to answer. Some concepts, however, emerge well documented. First, inflammatory cytokines or cellular infiltrates are reportedly elevated in the bronchial tissue or somewhere else in the body of both AA and NAA patients.[50–55] These findings, the cornerstone of the difference between asthmatic and nonasthmatic subjects, provide evidence that asthma is an inflammatory disease. Unexpectedly, most studies investigating the pathogenetically important cytokines and cell populations found that AA and NAA are almost identical diseases.[1,3,5,56] More important, the biological variables in the bronchial mucosa that document "an inappropriate control or production of IgE (local hyper production of $T_H2$ cell cytokines, and chemokines[1,5,56,57]) and of eosinophils[1,5,58–61]" have been regularly found elevated in AA and NAA patients, suggesting that IgE plays an important role in asthma, regardless of conventionally defined atopic status (positive ASPT or serum IgE or both). This concept is reinforced by the high total serum IgE levels even in the sera of asthmatic patients who tested negative for specific IgE.[19,62,63] The existing immunologic data therefore appear not to substantiate a difference in the pathophysiology of intrinsic or extrinsic asthma and provide no support for those who maintain that intrinsic and extrinsic asthma represent different phenotypes of the illness.[1,3,4]

We believe that current knowledge and the data from our systematic review suggest that the definition of AA as a pathological entity opposed to NAA now needs reappraisal. If an allergen exposure can exacerbate (trigger) and cause clinical symptoms of asthma in atopic individuals, this process should be included in the definition.[64] Hence, the definition of AA should be extended to include, along with evidence of IgE hyperproduction, a history of allergic symptoms in response to specific exposures. In theory, a case of asthma should probably be classified as AA only if the patient's predominant symptoms are those triggered by allergens.

*Vice versa*, in most epidemiologic studies (*i.e.*, in most of the articles included in Table 1) the cases of AA were defined simply based on positive serum or ASPT for specific IgE. Our findings in this review suggest that if this definition is used, environmental factors can produce rapid changes (increases) in the prevalence of AA.

AA simply defined as a subject with asthma and positive ASPT does not necessarily correspond to the phenotype hypothesized by Rackemann *et al.*[65] >60 years ago, as the one mainly triggered by exogenous causes. These authors, analyzing all of the asthma cases in the whole population, in both sexes and in a wide age range, indicated some clinical characteristics as relevant in differentiating extrinsic (AA, mainly triggered by exogenous causes) and intrinsic (NAA) asthma.[2,66,67] They could describe two separate ideal phenotypes of asthma. AA tended to be present in younger children, male sex, and atopic persons, and NAA tended to be present in older subjects, female sex, aspirin sensitive, prone to nasal polyposis, and nonatopic persons. Because of the difference in age, these two could even represent different time points of the same underlying airway inflammation. Two simple considerations: first, the conclusion we previously reported, that at the epidemiologic level, asthma and atopy substantially behave as two independent variables,[1,9,47–49] derives from the analysis of studies of asthma cases in the pediatric age, the one in which AA, the "atopic" phenotype (the one caused by atopy) is commonly considered by practitioners to be highly prevalent. Second, we feel not right to persist in labeling people who differ widely in their predisposition to disease and susceptibility to various triggers with the same abused term (asthma): in agreement with recent qualified suggestions[68] we think it better to limit semantic confusion, avoiding qualifying the term asthma with terms (*e.g.* atopic) of equivocal clinical meaning.

In summary, our new study in numerous childhood worldwide populations provides convincing evidence that intrinsic and extrinsic asthma can no longer be diagnosed simply based on a positive or negative ASPT. Whether asthmatic children have positive or negative ASPT reactions and whether atopic or nonatopic subjects have asthma appears to depend on a complex interplay between personal traits and the environment where they live.

This dynamic disease process makes it impossible to classify asthma into two rigid phenotypes. Although asthma in children who have positive ASPT reactions can obviously be triggered by allergens, whether these children have "AA" should be ascertained from their clinical history; a case of asthma should probably be classified as AA only if the patient's predominant symptoms are those triggered by allergens.

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