

Letter to the Editor

Do all asthmatics with atopy have atopic asthma?

To the Editor:

Distinguishing between atopic (extrinsic or allergic) asthma and nonatopic (intrinsic or nonallergic) asthma is important for clinicians in making appropriate treatment decisions, such as whether to recommend anti-IgE therapy. It is also important in epidemiological and clinical research for defining an accurate asthma phenotype. In their asthmatic patients, clinicians often confirm atopy by allergy skin testing or allergen-specific IgE testing. An important question with both clinical and research relevance is “Do all asthmatics with atopy have atopic asthma?” I believe that most clinicians and researchers would agree that the presence of atopy among asthmatic patients is not always indicative of atopic asthma. However, I suspect that most would be surprised at the high probability of atopy and asthma being present in an individual without being related.

For almost any disease, people who have a risk factor for a disease can develop the disease through a mechanism that does not include that risk factor. Greenland and Rothman,¹ in the book *Modern Epidemiology*, illustrated this point with the following example:

[A] smoker may develop lung cancer through some mechanism that does not involve smoking (e.g., one involving asbestos or radiation exposure). For such lung cancer cases, their smoking was incidental; it did not contribute to the cancer causation. ... Therefore, exposed cases include some cases of disease caused by the exposure, if the exposure is indeed a cause, and some cases of disease that occur through mechanisms that do not involve the exposure.

The attributable risk proportion, a fundamental measure in epidemiology that estimates the proportion of disease among the exposed that is due to that exposure, can reveal how much asthma among atopic patients is due to atopy. In the following analysis of data from the 2005-2006 National Health and Nutrition Examination Survey (NHANES), the results provide evidence that a large proportion of asthma cases among atopics are not atopic asthma cases.

A detailed description of the NHANES 2005-2006 survey design and methods can be found online at <http://www.cdc.gov/nchs/nhanes.htm>. For this analysis, *current asthma* was defined as a positive response to both of the following questions: “Has a doctor or other health professional ever told you that you have asthma?” and “Do you still have asthma?” The NHANES tested participants 6 years of age or older for allergen-specific IgE antibodies to 15 aeroallergens and 4 foods. *Atopy* was defined as at least 1 positive test result (specific IgE ≥ 0.35 kU/L). A sensitivity analysis was conducted with 3 other definitions of atopy (Table I). This analysis was limited to the 7245 persons aged 6 years and older who had complete information on the 19 allergens and asthma. The prevalence of current asthma, adjusted for sex, age, and race-ethnicity, was estimated with the PREDMARG statement in the SUDAAN logistic regression procedure (release 10.0.1, SAS-Callable; RTI International, Research Triangle Park, NC). The attributable risk and attributable risk proportion were calculated.² The sample weight variable WTMEC2YR

was used in all analyses to obtain nationally representative statistics. The survey design variables SDMVSTRA and SDMVPSU were used to adjust the variances.

The adjusted prevalence of current asthma among persons aged 6 years and older in the US population was 5.6% among nonatopics and 13.0% among atopics (Fig 1). The elevated prevalence of asthma among the nonatopics is the prevalence of asthma due to background risk factors, such as viral infections, tobacco smoke exposure, obesity, and psychological stress, to name a few. The risk of asthma that these background factors confer among atopics cannot be known with certainty because not all the background factors are known, but for the calculation of attributable risk proportion, it is assumed that everyone in the population shares the background risk,² even the atopics. Thus, the total prevalence of asthma among the atopics is the sum of the background prevalence, shared by everyone, and the prevalence attributable to atopy alone (Fig 1). The prevalence of asthma attributable to atopy alone is the total prevalence of asthma among atopics (13.0%) minus the background prevalence (5.6%)—a difference of 7.4% (Fig 1). The proportion of the total prevalence of asthma among atopics that was attributable to atopy was 0.57 (7.4% divided by 13.0%). In other words, only 57% of the asthma cases among atopics could be considered atopic asthma cases. For the remaining 43% of the asthma cases among atopics, their atopy was incidental. The attributable risk proportions by age group were 0.59 for 6 to 17 years, 0.63 for 18 to 40 years, 0.57 for 41 to 54 years, and 0.47 for 55 years or older.

Table I shows the attributable risk proportions for atopy defined as a positive test to at least 1, 2, or 3 of the 19 allergens and as a positive test to at least 1 of the 15 aeroallergens. Even with the more stringent definitions, the results suggest that at least 30% of asthmatic patients with atopy do not have atopic asthma.

The clinical implication of these findings is that a proportion of asthma patients with atopy may not have an allergic etiology to their asthma and may not, therefore, respond to allergy-related treatment strategies, such as anti-IgE therapy, subcutaneous immunotherapy, or allergen avoidance. To improve the probability of a correct diagnosis of atopic asthma, and thus effective treatment, clinicians should always consider allergy skin or IgE test results in the context of a thorough patient history that provides evidence of an association between allergen exposures and asthma symptoms.

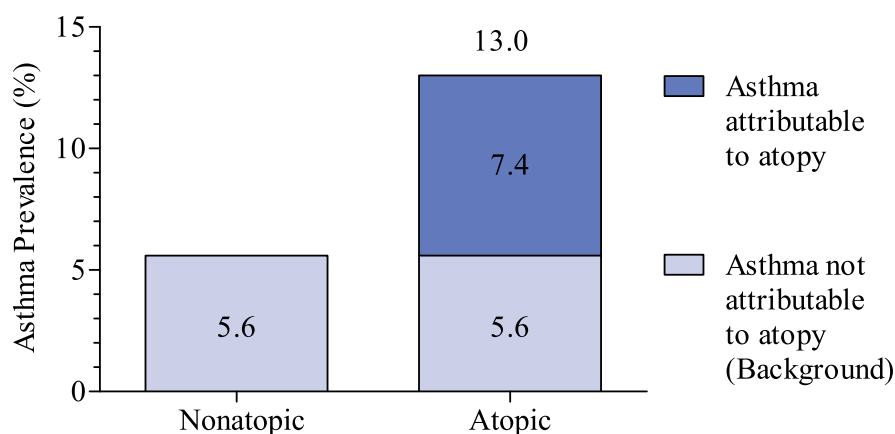
Limitations of this study include the cross-sectional nature of the survey and the potential misclassification of participants by atopy and asthma. Although the information on current asthma and atopy used in this analysis was collected cross-sectionally, the results should be relevant to clinical practice because, in most circumstances, a clinician assesses atopy and asthma at or near the same point in time, that is, cross-sectionally. Because not all known allergens were included in the panel of 19 allergens, and because the test results could have been negative at the time of testing due to the absence of allergen exposure, some nonatopics may be misclassified. Such misclassification could affect the background rate of asthma and ultimately the attributable risk proportion. However, because most atopics were sensitive to multiple allergens (mean = 4.3), the probability of an atopic participant being positive to any untested allergen and not to at least 1 of the tested allergens is likely low, as is the probability of a

TABLE I. Proportion of asthma cases among atopics attributable to atopy in the US population aged 6 years and older

Varying definitions of atopy*	Prevalence of current asthma (% SE)†			Proportion of asthma cases among atopics attributable to atopy (A – B)/A
	Atopics A	Nonatopics B	Attributable to atopy A – B	
≥1 Positive test of 19 allergens	13.0 (0.98)	5.6 (0.41)	7.4 (0.99)	0.57
≥1 Positive test of 15 aeroallergens	13.4 (0.97)	5.6 (0.41)	7.8 (0.96)	0.58
≥2 Positive tests of 19 allergens	15.5 (1.28)	5.6 (0.39)	9.9 (1.33)	0.64
≥3 Positive tests of 19 allergens	18.7 (1.59)	5.7 (0.39)	12.9 (1.59)	0.69

*Allergen-specific IgE tests of serum were conducted for 15 aeroallergens and 4 foods. A positive test result was defined as 0.35 kU/L or more.

†Adjusted for sex, age in years (6-17, 18-40, 41-54, and ≥55), and race-ethnicity (Mexican American, non-Hispanic white, non-Hispanic black, and all others).

**FIG 1.** Prevalence of current asthma in the US population aged 6 years and older, adjusted for sex, age in years (6-17, 18-40, 41-54, and ≥55), and race-ethnicity (Mexican American, non-Hispanic white, non-Hispanic black, and all others).

transiently negative IgE panel. Finally, it would seem unlikely that the use of subject-reported, doctor-diagnosed asthma as opposed to a clinical assessment or medical chart review would change the main finding of this study, which is that a large proportion of asthma patients with atopy do not have atopic asthma.

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