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The atopic march: what's the evidence?

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Abstract

Objective—To review and compile data from published studies that provide support for the existence of the atopic march.

Data Sources—Relevant articles and references found via a PubMed search using the following keywords: *atopic march*, *allergic march*, *atopic dermatitis*, *eczema*, *atopic eczema*, *atopy*, *rhinitis*, *wheeze*, *bronchiolitis*, and *asthma*.

Study Selection—All articles were reviewed and the most relevant were selected for inclusion in this review and for the compilation and graphical presentation of disease trends.

Results—Data on the prevalence of each phenotype of the atopic march confirm the temporal pattern of progression from eczema to allergic rhinitis and asthma. However, the atopic march as it is currently defined, is lacking precision, which affects its usefulness. Early events in the atopic march, such as eczema, may be more useful with more careful refinement of the phenotype into atopic and nonatopic eczema.

Conclusion—Evidence supports that the atopic march is a useful paradigm to describe the clinically observed progression of atopy in certain children. There may be more precise phenotypes of the early stages of the atopic march that may improve its utility in predicting the development of later atopic, comorbid chronic disease.

INTRODUCTION

The *atopic march* is a term that describes the progression of atopic disorders, from eczema in young infants and toddlers to allergic rhinitis and finally to asthma in older toddlers and children.¹ *Atopy* is derived from a Greek word meaning “strange or out of place” and was first introduced by Coca and Cooke in 1923.² Atopy is defined as a personal and/or familial tendency to produce IgE antibodies and sensitization in response to ordinary exposures.³ Atopy is associated with the development of eczema, rhinoconjunctivitis, and asthma, all components of the atopic march.⁴ In clinical practice, these conditions appear to be

interrelated; however, their exact relationship to each other is debated and is likely not as simple as one disease “progressing” to another. In addition, the risk of developing all 3 diseases is likely multifactorial, involving genetic and environmental influences. The temporal pattern described in the atopic march is confirmed when examining data on the prevalence of each atopic disease across the lifespan. Typically, the clinical signs of eczema precede the development of allergic rhinitis and asthma, suggesting that eczema marks the commencement of the atopic march.¹ The progressive nature of the atopic march is important, providing identifiable phenotypes that could allow for risk stratification and early intervention or prevention, if available. Because most infants with eczema do not develop asthma and increasing evidence suggests that eczema may not be a specific marker of atopy, eczema as is currently defined may be too general of a definition, including many children who are not at risk of subsequent atopic diseases.^{5,6} The goals of this review are to examine the existing studies and present composite data from published studies that support there being an order and temporal relationship among the atopic diseases and to summarize the literature on whether there are more specific predictors that define each stage.

THE BEGINNING OF THE ATOPIC MARCH: ECZEMA

Eczema is a chronic relapsing inflammatory skin condition characterized by dry skin lesions with lichenification, pruritic excoriations, and a predilection for skin flexures.^{7,8} It is the most common inflammatory skin disease in childhood, with most cases manifesting within the first year of life.^{9,10} In a population-based US study, the prevalence of eczema among children ages 5 to 9 years was estimated at 17.2%.¹¹ In the International Study of Asthma and Allergies in Childhood, the prevalence of eczema in children 13 or 14 years of age varied more than 60-fold among the 56 countries involved (0.3%–20.5%) but showed consistent trends in increasing disease prevalence over time.^{12,13}

Whether eczema, as is currently defined, is an atopic disease is much debated. There is a growing body of literature to suggest there are 2 variants of eczema, an atopic form and a nonatopic form.^{6,14–17} A systematic review of the literature examining the relationship between atopy and eczema found that up to two-thirds of persons with eczema are not atopic,¹⁴ indicating IgE sensitization may not be integral in the development of all cases of eczema. An Australian birth cohort study of children born to atopic parents, 1 of a few longitudinal population-based studies that examine the relationship between atopy and eczema, found that risk factors for atopic eczema (the phenotype of eczema plus specific IgE sensitivity) were different from those with nonatopic eczema. The atopic form of eczema was associated with a number of risk factors for childhood atopic diseases, including male sex and the development of food allergy, allergic rhinitis, or asthma by 5 years of age.⁶

LINKING STAGES OF THE ATOPIC MARCH: ECZEMA, RHINITIS, AND ASTHMA

The prevalence of eczema is increasing, similar to that of other atopic disorders, including allergic rhinitis and asthma, which could support shared environmental and genetic triggers.^{13,18} Few longitudinal studies have examined the relationship between eczema and subsequent allergic rhinitis. In a German birth cohort, eczema present before the age of 2

years was a significant risk factor for the development of seasonal allergic rhinitis by 7 years of age (adjusted odds ratio [OR], 2.5).¹⁹ In another cohort of children with established eczema, 45% developed allergic rhinitis by the age of 7 years,²⁰ a proportion much higher than the general population.¹⁹

The proportion of children with eczema who later develop asthma has been more extensively studied and has great variability, ranging from 25% to 80%. A systematic review of the literature by van der Hulst and colleagues⁵ included 13 prospective cohort studies, 4 birth cohort studies and 9 cohort studies of children with established eczema, from 1950 to 2006. The pooled OR for the risk of asthma after eczema, compared with children without eczema, in birth cohort studies was 2.14. In eczema cohort studies, the prevalence of asthma by the age of 6 years was 29.5%. These authors concluded that there is an increased risk of developing asthma by 6 years among children with precedent eczema; however, asthma develops in only approximately 1 in every 3 children with eczema. Admittedly these results should be interpreted with caution because of the heterogeneity of the cohorts and the criteria used to determine eczema; however, the proportion of children with eczema developing asthma is clearly higher than among those without eczema, and the “attack rates” for asthma are 3- to 4-fold higher than in the general population.

Longitudinal studies also support an association between eczema and asthma (Table 1).^{20–24} In the Tucson Children’s Respiratory Study, a longitudinal investigation of 1,246 children enrolled at birth,²¹ 18% of children with persistent wheezing at the age of 6 years had eczema before 2 years of age, compared with only 7.7% of children who never wheezed. This birth cohort has now been followed up to 22 years of age, and eczema before the age of 2 years was associated with asthma onset in childhood but not with adult-onset asthma.²² In addition, in a cohort of 94 Swedish children with eczema followed up from a median age of 17 months to 7 years,²⁰ 43% developed asthma by 7 years of age. Because the atopic march is described as a progression, this temporal association between eczema and childhood asthma could indicate that eczema may influence or act as a risk marker for asthma in childhood, although this does not appear to be the case for adult-onset asthma.²²

Lastly, differentiating atopic and nonatopic eczema phenotypes may more accurately predict progression to allergic rhinitis and asthma. There are 2, albeit small, longitudinal studies that have examined the relationship between atopic and nonatopic eczema and the subsequent development of asthma.^{23,24} Both studies defined atopic eczema as eczema associated with specific IgE antibodies to common environmental allergens and independently demonstrated that atopic eczema, present by the ages of 2 to 4 years, is more strongly associated with the subsequent development of asthma compared with nonatopic eczema. Thus, atopic eczema appears to more precisely define the initial step and risk factor for the subsequent development of other atopic diseases.

THE INFLUENCE OF EARLY SYMPTOMS OF ASTHMA IN TODDLERS: ECZEMA, EARLY WHEEZE, AND ASTHMA

The German Multicenter Atopy Study is a population-based, prospective birth cohort that evaluated the phenotype of eczema with and without the cofactor of early wheeze. Those

with eczema and without early wheeze were not at increased risk for the development of asthma, suggesting that eczema alone may not be the first most predictive phenotype in the atopic march.²⁵ Early eczema, defined as eczema before 2 years of age, was significantly associated with early wheeze, defined as wheezing before the age of 3 years. Early eczema without the cofactor of early wheeze and without a specific pattern of atopic sensitization was not associated with an increased risk of wheezing at 7 years of age (adjusted OR, 1.11). The authors suggest that the combination of eczema with early wheeze is a distinct phenotype rather than a representation of a progressive pattern of atopic diseases. However, the risk for development of asthma at 7 years of age among children with early eczema and atopic sensitization to less common antigens but without concomitant wheeze was stronger (adjusted OR, 6.68) than the association between early eczema with early wheezing (adjusted OR, 2.84), perhaps consistent with the pattern of the atopic march in that eczema with atopic sensitization places an individual at a higher risk for the development of atopic respiratory disease.

When examining the development of asthma it is important to delineate children with early transient wheezing from those with persistent asthma. The Tucson Children's Respiratory Study led to the defining of patterns of childhood wheezing into 4 groups: (1) children who never wheezed, (2) children with wheezing associated with 1 or more lower respiratory tract illnesses during the first 3 years of life but without wheezing at 6 years of age (transient early wheezers), (3) children with no wheezing before the age of 3 years but with wheezing at the age of 6 years (late-onset wheezers), and (4) wheezing both before the age of 3 years and present at the age of 6 years (persistent wheezers).²¹ The authors found that one-third of children had at least 1 respiratory tract illness with wheezing before the age of 3 years, but importantly 60% of these children were no longer wheezing at the age of 6 years. These transient early wheezers were later shown to remain as unlikely to wheeze up to the age of 16 years as children who never wheezed in the first 6 years of life,²⁶ highlighting the importance of delineating wheezing in early childhood from persistent asthma. The Tucson cohort did not differentiate between atopic or nonatopic eczema; however, the investigators found that eczema during the first year of life was significantly associated with persistent wheezing (OR, 2.4) and not with transient early wheeze (OR, 1.3).²¹ From this cohort, a clinical index of asthma risk, the Asthma Predictive Index (API), was developed to define the risk of developing asthma among children 2 years or older with wheezing.^{27,28} The API uses both major and minor criteria, and physician-diagnosed eczema is 1 of the 2 major criteria. Although the positive predictive value of the API is modest (47.5% for the development of asthma at the age of 6 years), the negative predictive value is high, with 91.6% and 84.2% of children with a negative API remaining free of asthma by the ages of 6 and 13 years, respectively. The updated criteria have added allergic sensitization to at least 1 aeroallergen to its major criteria. The ability to use the presence of early eczema and atopic sensitization to predict the later development of asthma also supports the temporal sequence described in the atopic march.

The presence of atopy, regardless of overt wheezing during the first 3 years of life, has been associated with impaired lung function at 3 years of age.²⁹ The reduction in lung function before the clinical presence of wheeze correlates with the concept of a predisposition for respiratory disease in an atopic child. It has also been shown that the presence of IgE-

mediated sensitization in a child with wheezing at 3 years of age predicts the persistence of wheezing at 5 years,³⁰ indicating that the presence of atopy among children with early wheeze predisposes them to the later development of asthma.

EARLY RESPIRATORY VIRAL-ASSOCIATED WHEEZING ILLNESS, ATOPY, AND ASTHMA

Several birth cohorts have established a strong association between early childhood viral respiratory tract infections and the subsequent development of childhood asthma.^{21,31–40} Thus, specific respiratory viral infections early in the life of a child, particularly a child with an atopic predisposition, could influence the development of asthma in later childhood, indicating that environmental factors, in this case respiratory viruses, influence progression along the atopic march and/or that an atopic predisposition is associated with more severe respiratory viral infections. This concept could also explain the findings seen in the German Multicenter Atopy Study in that eczema was more strongly associated with asthma if it was also associated with early wheeze and/or atopy.²⁵

There are many factors that contribute to early wheeze in young children and early wheezing, although distinguishing a group of children who are at higher risk of developing asthma than the general population, is not as a single risk factor highly predictive of asthma. The potential influence of viral triggers in the development of atopy and asthma is important because these are environmental factors that may be modifiable and interventions could be developed that could halt the progression along the atopic march in a young child with atopy, eczema, or early wheeze.

THE RELATIONSHIP BETWEEN RHINITIS AND ASTHMA

Allergic rhinitis is clinically defined as a symptomatic disorder of the nose characterized by IgE-mediated inflammation induced by allergen exposure to the mucosal membranes.⁴¹ Epidemiologic studies have consistently reported strong associations between rhinitis and asthma (Tables 2 and 3).^{42–48} The prevalence of asthma in patients with rhinitis varies from 10% to 40%, depending on the study, and is much higher than in the general population without rhinitis.^{42,49–51} Conversely, among asthmatic patients, the co-occurrence of rhinitis varies as well but has been reported to be as high as 80%.⁴¹ Furthermore, rhinitis, even in the absence of atopy, has been shown to be a powerful predictor of adult-onset asthma.^{42,45,48,52,53} Rhinitis in combination with atopy, however, is an even stronger predictor of adult-onset asthma.^{45,53}

Using methacholine inhalation challenge to define bronchial hyperreactivity in 2,347 male naval recruits, Cipriandi and colleagues⁵⁴ determined that bronchial hyperreactivity was present in 82.2% of individuals with perennial allergic rhinitis. In addition, significant seasonal variability was found in the degree of bronchial hyperreactivity with lower forced expiratory volume in 1 second in patients with seasonal allergic rhinitis during their season of allergy ($P < .05$). This finding supports the notion of an already existing predisposition among individuals with allergic rhinitis to develop asthma. The strong link between allergic rhinitis and asthma is also highlighted in expert opinion documents such as the Allergic

Rhinitis and its Impact on Asthma document, which recommends empiric evaluation for asthma in patients with allergic rhinitis, particularly in those with severe and/or persistent allergic rhinitis.⁴¹

When examining the temporal relationship between rhinitis and asthma, several studies demonstrate that rhinitis in infancy or childhood is associated with the development of asthma later in life.^{43,55,56} In the Tasmanian Asthma Study, childhood allergic rhinitis (present by 7 years of age) increased the likelihood of both new-onset asthma and having asthma persist from childhood into middle age.⁴³ The Tucson Children's Respiratory Study found that rhinitis in the first year of life was associated with more respiratory symptoms and the diagnosis of asthma at 6 years of age.⁵⁵

This relationship is further strengthened when we examine the impact of treating allergic rhinitis and the subsequent development of asthma. Allergen immunotherapy has been well established as an effective treatment of allergic rhinitis,^{57,58} and data indicate that treatment of allergic rhinitis in childhood with immunotherapy can actually decrease the risk of developing asthma.^{59–62} The ability to decrease the risk of asthma development, the final step of the atopic march, by treating an earlier disease further supports both the conceptual validity and usefulness, as well as the sequential nature of the atopic march.

Lastly, data compiled from numerous studies investigating the relationship among eczema, allergic rhinitis, and asthma are plotted together to show the temporal relationship of each disease over the age continuum in Figure 1 and confirm the pattern described in the atopic march.

DISCUSSION

The atopic march is a useful paradigm to describe the clinically observed progression of atopic diseases in certain children. Whether each step in the march is necessary for progression to the next or further defining of these phenotypes would be more useful in identifying children at risk for developing lifelong chronic diseases is still a matter of debate. Better understanding of what places a subset of children with eczema or allergic rhinitis into the risk group for developing asthma is critically important for risk stratification, identifying modifiable risk factors, and developing preventive strategies and targeted interventions. Given that most infants with eczema or early wheezing do not develop rhinitis and asthma, further refinement of these early phenotypes or additional risk factors is important for them to be useful. We know that the presence of eczema in early childhood increases a child's risk of developing asthma later in childhood compared with a child without eczema and that this risk is increased further with comorbid atopy or wheezing. We also know that early wheeze, particularly severe wheezing, and rhinitis both independently place a child at risk for the development of asthma, and again these factors are more strongly associated with the subsequent development of asthma by the presence of atopy. Thus, more specific definitions of entry points into the atopic march may be necessary for improved predictability, as has been used in the development of tools such as the API.^{27,28} It has also been established that rhinitis is associated with subclinical signs of

asthma, such as bronchial hyperresponsiveness, revealing the presence of the last stage of the march in its most mild form, although not clinically evident in some.

CONCLUSIONS

Numerous investigations support the existence of a temporal trend of atopic diseases that comprise the atopic march. The identification of early-life diseases or phenotypes in the atopic march as predictors for the development of lifelong chronic diseases offers entry points for primary or secondary disease prevention. Current evidence suggests that further refining early childhood eczema phenotypes may represent a more robust measure of the first phenotype of the atopic march, with a greater predictive value of identifying those at risk of developing allergic rhinitis and asthma. It is encouraging that treatment of allergic rhinitis with allergen immunotherapy modifies the risk of developing asthma.^{59–62} If other preventive strategies are identified for asthma and allergic rhinitis, early-risk group identification will be critical in identifying those who should receive these interventions to prevent lifelong chronic diseases associated with significant morbidity and mortality.

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References

1. Spergel JM, Paller AS. Atopic dermatitis and the atopic march. *J Allergy Clin Immunol*. 2003; 112(6 suppl):S118–S127. [PubMed: 14657842]
2. Coca AF, Cooke RA. On the classification of the phenomena of hypersensitiveness. *J Immunol*. 1923; 8:163–182.
3. Johansson SG, Bieber T, Dahl R, et al. Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol*. 2004; 113:832–836. [PubMed: 15131563]
4. Wright AL. The epidemiology of the atopic child: who is at risk for what? *J Allergy Clin Immunol*. 2004; 113(1 suppl):S2–S7. [PubMed: 14694343]
5. van der Hulst AE, Klip H, Brand PL. Risk of developing asthma in young children with atopic eczema: a systematic review. *J Allergy Clin Immunol*. 2007; 120:565–569. [PubMed: 17655920]
6. Kusel MM, Holt PG, de Klerk N, Sly PD. Support for 2 variants of eczema. *J Allergy Clin Immunol*. 2005; 116:1067–1072. [PubMed: 16275378]
7. Williams HC. Clinical practice: atopic dermatitis. *N Engl J Med*. 2005; 352:2314–2324. [PubMed: 15930422]
8. Williams HC, Burney PG, Pembroke AC, Hay RJ. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis, III: independent hospital validation. *Br J Dermatol*. 1994; 131:406–416. [PubMed: 7918017]
9. Galli E, Gianni S, Auricchio G, Brunetti E, Mancino G, Rossi P. Atopic dermatitis and asthma. *Allergy Asthma Proc*. 2007; 28:540–543. [PubMed: 18034972]
10. Wadonda-Kabondo N, Sterne JA, Golding J, Kennedy CT, Archer CB, Dunnill MG. A prospective study of the prevalence and incidence of atopic dermatitis in children aged 0–42 months. *Br J Dermatol*. 2003; 149:1023–1028. [PubMed: 14632809]
11. Laughter D, Istvan JA, Tofte SJ, Hanifin JM. The prevalence of atopic dermatitis in Oregon schoolchildren. *J Am Acad Dermatol*. 2000; 43:649–655. [PubMed: 11004621]

12. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet*. 1998; 351:1225–1232. [PubMed: 9643741]
13. Asher MI, Montefort S, Björkstén B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC phases one and three repeat multicountry cross-sectional surveys. *Lancet*. 2006; 368:733–743. [PubMed: 16935684]
14. Flohr C, Johansson SG, Wahlgren CF, Williams H. How atopic is atopic dermatitis? *J Allergy Clin Immunol*. 2004; 114:150–158. [PubMed: 15241359]
15. Williams HC, Johansson SG. Two types of eczema—or are there? *J Allergy Clin Immunol*. 2005; 116:1064–1066. [PubMed: 16275377]
16. Tepper RS, Llapur CJ, Jones MH, et al. Expired nitric oxide and airway reactivity in infants at risk for asthma. *J Allergy Clin Immunol*. 2008; 122:760–765. [PubMed: 18760452]
17. Sehra S, Tuana FM, Holbreich M, et al. Scratching the surface: towards understanding the pathogenesis of atopic dermatitis. *Crit Rev Immunol*. 2008; 28:15–43. [PubMed: 18298382]
18. Eichenfield LF, Hanifin JM, Beck LA, et al. Atopic dermatitis and asthma: parallels in the evolution of treatment. *Pediatrics*. 2003; 111:608–616. [PubMed: 12612244]
19. Kulig M, Klettke U, Wahn V, Forster J, Bauer CP, Wahn U. Development of seasonal allergic rhinitis during the first 7 years of life. *J Allergy Clin Immunol*. 2000; 106:832–839. [PubMed: 11080703]
20. Gustafsson D, Sjöberg O, Foucard T. Development of allergies and asthma in infants and young children with atopic dermatitis: a prospective follow-up to 7 years of age. *Allergy*. 2000; 55:240–245. [PubMed: 10753014]
21. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life: The Group Health Medical Associates. *N Engl J Med*. 1995; 332:133–138. [PubMed: 7800004]
22. Stern DA, Morgan WJ, Halonen M, Wright AL, Martinez FD. Wheezing and bronchial hyper-responsiveness in early childhood as predictors of newly diagnosed asthma in early adulthood: a longitudinal birth-cohort study. *Lancet*. 2008; 372:1058–1064. [PubMed: 18805334]
23. Wuthrich B, Schmid-Grendelmeier P. Natural course of AEDS. *Allergy*. 2002; 57:267–268. [PubMed: 11906351]
24. Novembre E, Cianferoni A, Lombardi E, Bernardini R, Pucci N, Vierucci A. Natural history of “intrinsic” atopic dermatitis. *Allergy*. 2001; 56:452–453. [PubMed: 11350313]
25. Illi S, von Mutius E, Lau S, et al. The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. *J Allergy Clin Immunol*. 2004; 113:925–931. [PubMed: 15131576]
26. Morgan WJ, Stern DA, Sherrill DL, et al. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. *Am J Respir Crit Care Med*. 2005; 172:1253–1258. [PubMed: 16109980]
27. Guilbert TW, Morgan WJ, Zeiger RS, et al. Atopic characteristics of children with recurrent wheezing at high risk for the development of childhood asthma. *J Allergy Clin Immunol*. 2004; 114:1282–1287. [PubMed: 15577824]
28. Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med*. 2000; 162(4 pt 1): 1403–1406. [PubMed: 11029352]
29. Lowe L, Murray CS, Custovic A, Simpson BM, Kissen PM, Woodcock A. Specific airway resistance in 3-year-old children: a prospective cohort study. *Lancet*. 2002; 359:1904–1908. [PubMed: 12057553]
30. Lowe LA, Simpson A, Woodcock A, Morris J, Murray CS, Custovic A. Wheeze phenotypes and lung function in preschool children. *Am J Respir Crit Care Med*. 2005; 171:231–237. [PubMed: 15502115]
31. Noble V, Murray M, Webb MS, Alexander J, Swarbrick AS, Milner AD. Respiratory status and allergy nine to 10 years after acute bronchiolitis. *Arch Dis Child*. 1997; 76:315–319. [PubMed: 9166022]

32. Kotaniemi-Syrjnen A, Vainionp R, Reijonen TM, Waris M, Korhonen K, Korppi M. Rhinovirus-induced wheezing in infancythe first sign of childhood asthma? *J Allergy Clin Immunol*. 2003; 111:6671. [PubMed: 12532098]
33. Sigurs N, Bjrnason R, Sigurbergsson F, Kjellman B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. *Am J Respir Crit Care Med*. 2000; 161:15011507. [PubMed: 10806145]
34. Sigurs N, Gustafsson PM, Bjrnason R, et al. Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. *Am J Respir Crit Care Med*. 2005; 171:137141. [PubMed: 15516534]
35. Henderson J, Hilliard TN, Sherriff A, Stalker D, Al Shammari N, Thomas HM. Hospitalization for RSV bronchiolitis before 12 months of age and subsequent asthma, atopy and wheeze: a longitudinal birth cohort study. *Pediatr Allergy Immunol*. 2005; 16:386392. [PubMed: 16101930]
36. Lemanske RF Jr, Jackson DJ, Gangnon RE, et al. Rhinovirus illnesses during infancy predict subsequent childhood wheezing. *J Allergy Clin Immunol*. 2005; 116:571577. [PubMed: 16159626]
37. Jackson DJ, Gangnon RE, Evans MD, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med*. 2008; 178:667672. [PubMed: 18565953]
38. Kusel MM, de Klerk NH, Keadze T, et al. Early-life respiratory viral infections, atopic sensitization, and risk of subsequent development of persistent asthma. *J Allergy Clin Immunol*. 2007; 119:11051110. [PubMed: 17353039]
39. Wu P, Dupont WD, Griffin MR, et al. Evidence of a causal role of winter virus infection during infancy on early childhood asthma. *Am J Respir Crit Care Med*. 2008; 178(11):11239. [PubMed: 18776151]
40. Carroll KN, Wu P, Gebretsadik T, et al. Season of infant bronchiolitis and estimates of subsequent risk and burden of early childhood asthma. *J Allergy Clin Immunol*. 2009; 123:964966. [PubMed: 19181372]
41. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy*. 2008; 63(suppl 86):8160. [PubMed: 18331513]
42. Leynaert B, Neukirch C, Kony S, et al. Association between asthma and rhinitis according to atopic sensitization in a population-based study. *J Allergy Clin Immunol*. 2004; 113:8693. [PubMed: 14713912]
43. Burgess JA, Walters EH, Byrnes GB, et al. Childhood allergic rhinitis predicts asthma incidence and persistence to middle age: a longitudinal study. *J Allergy Clin Immunol*. 2007; 120:863869. [PubMed: 17825896]
44. Peroni DG, Piacentini GL, Alfonsi L, et al. Rhinitis in pre-school children: prevalence, association with allergic diseases and risk factors. *Clin Exp Allergy*. 2003; 33:13491354. [PubMed: 14519139]
45. Shaaban R, Zureik M, Soussan D, et al. Rhinitis and onset of asthma: a longitudinal population-based study. *Lancet*. 2008; 372:10491057. [PubMed: 18805333]
46. Bugiani M, Carosso A, Migliore E, et al. Allergic rhinitis and asthma comorbidity in a survey of young adults in Italy. *Allergy*. 2005; 60:165170. [PubMed: 15647036]
47. Magnan A, Meunier JP, Saugnac C, Gasteau J, Neukirch F. Frequency and impact of allergic rhinitis in asthma patients in everyday general medical practice: a French observational cross-sectional study. *Allergy*. 2008; 63:292298. [PubMed: 18028246]
48. Guerra S, Sherrill DL, Martinez FD, Barbee RA. Rhinitis as an independent risk factor for adult-onset asthma. *J Allergy Clin Immunol*. 2002; 109:419425. [PubMed: 11897985]
49. Downie SR, Andersson M, Rimmer J, et al. Association between nasal and bronchial symptoms in subjects with persistent allergic rhinitis. *Allergy*. 2004; 59:320326. [PubMed: 14982515]
50. Linneberg A, Henrik NN, Frolund L, Madsen F, Dirksen A, Jorgensen T. The link between allergic rhinitis and allergic asthma: a prospective population-based study: The Copenhagen Allergy Study. *Allergy*. 2002; 57:10481052. [PubMed: 12359002]

51. Bauchau V, Durham SR. Epidemiological characterization of the intermittent and persistent types of allergic rhinitis. *Allergy*. 2005; 60:350–353. [PubMed: 15679721]
52. Leynaert B, Bousquet J, Neukirch C, Liard R, Neukirch F. Perennial rhinitis: an independent risk factor for asthma in nonatopic subjects: results from the European Community Respiratory Health Survey. *J Allergy Clin Immunol*. 1999; 104(2 pt 1):301–304. [PubMed: 10452748]
53. Plaschke PP, Janson C, Norrman E, Bjornsson E, Ellbjär S, Jarvholm B. Onset and remission of allergic rhinitis and asthma and the relationship with atopic sensitization and smoking. *Am J Respir Crit Care Med*. 2000; 162(3 pt 1):920–924. [PubMed: 10988106]
54. Ciprandi G, Cirillo I, Vizzaccaro A, et al. Seasonal and perennial allergic rhinitis: is this classification adherent to real life? *Allergy*. 2005; 60:882–887. [PubMed: 15932377]
55. Wright AL, Holberg CJ, Martinez FD, Halonen M, Morgan W, Taussig LM. Epidemiology of physician-diagnosed allergic rhinitis in childhood. *Pediatrics*. 1994; 94(6 pt 1):895–901. [PubMed: 7971008]
56. Porsbjerg C, von Linstow ML, Ulrik CS, Nepper-Christensen S, Backer V. Risk factors for onset of asthma: a 12-year prospective follow-up study. *Chest*. 2006; 129:309–316. [PubMed: 16478846]
57. Compalati E, Penagos M, Tarantini F, Passalacqua G, Canonica GW. Specific immunotherapy for respiratory allergy: state of the art according to current meta-analyses. *Ann Allergy Asthma Immunol*. 2009; 102:22–28. [PubMed: 19205281]
58. Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. Allergen injection immunotherapy for seasonal allergic rhinitis. *Cochrane Database Syst Rev*. 2007; 1:CD001936. [PubMed: 17253469]
59. Moller C, Dreborg S, Ferdousi HA, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol*. 2002; 109:251–256. [PubMed: 11842293]
60. Johnstone DE, Dutton A. The value of hyposensitization therapy for bronchial asthma in children: a 14-year study. *Pediatrics*. 1968; 42:793–802. [PubMed: 5685362]
61. Niggemann B, Jacobsen L, Dreborg S, et al. Five-year follow-up on the PAT study: specific immunotherapy and long-term prevention of asthma in children. *Allergy*. 2006; 61:855–859. [PubMed: 16792584]
62. Jacobsen L, Niggemann B, Dreborg S, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy*. 2007; 62:943–948. [PubMed: 17620073]

Figure 1.

The prevalence of current eczema, allergic rhinitis, and asthma estimated from compiled data over the age span of birth to 70 years, incorporating studies from 1980 to 2008. Prevalence data used to generate these figures were from studies that used questionnaire data from developed countries, including the United States, Western Europe, and the United Kingdom.

Table 1

Select Studies Examining the Relationship Between Childhood Eczema and the Subsequent Development of Asthma

Study	Study population	Relationship between eczema and asthma
Tucson Children's Respiratory Study; Martinez and colleagues ²¹	Birth cohort; N = 826; cohort unselected for risk of atopy; birth to 6 years	Eczema during the first year of life was an independent risk factor for persistent wheezing (adjusted OR, 2.4; 95% CI, 1.3–4.6). Eczema in the first year of life was not a significant risk factor for lack of wheezing, transient early wheeze, or late-onset wheeze. Prevalence of eczema among persistent wheezers was 18% compared with 10.2% in transient early wheezers, 6.3% in late-onset wheezers, and 7.7% in nonwheezers.
Tucson Children's Respiratory Study; Stern and colleagues ²²	Birth cohort; N = 849; cohort unselected for risk of atopy; birth to 22 years	The presence of eczema by the age of 2 years in childhood was associated with inactive and chronic asthma (OR, 3.8; 95% CI, 1.9–7.8; and OR, 2.0; 95% CI, 1.0–4.1, respectively). Childhood eczema was not associated with newly diagnosed asthma in adulthood (OR, 1.1; 95% CI, 0.4–3.3).
German Multicenter Atopy Study; Illi and colleagues ²⁵	Birth cohort; N = 1,314; cohort unselected for risk of atopy; birth to 7 years	Early wheeze and a specific sensitization pattern were significant predictors for wheezing at 7 years, irrespective of eczema. Early eczema without these cofactors showed no increased risk of wheeze at 7 years (adjusted OR, 1.11; 95% CI, 0.56–2.20).
Porsbjerg and colleagues ⁵⁶	Population-based cohort unselected for risk of atopy; N = 291; 7–17 years to 19–29 years	Asthma developed in 45 patients (16.1%) during the follow-up period. Eczema predicted the development of asthma (OR, 3.2; 95% CI, 1.0–10.4).
Gustafsson and colleagues ²⁰	Eczema cohort; N = 94; 4–35 months to 7 years	Eczema improved in 82 of 94 children, but 45% of children developed allergic rhinitis and 43% developed asthma by 7 years of age.
Tepper and colleagues ¹⁶	Eczema cohort; N = 114; median age of 10.7 months	Infants with atopic eczema compared with infants with nonatopic eczema had lower flows (FEF ₇₅ , 336 vs 285 mL/s; $P < .003$) and lower provocative concentrations to decrease FEF ₇₅ by 30% ($P < .02$). Infants with total serum IgE levels of >20 IU/mL had higher eNO levels compared with infants with IgE levels ≤ 20 IU/mL.
Wuthrich and colleagues ²³	Eczema cohort; N = 22; 2–4 years to 10–12 years	Forty-five percent (10/22) of the cohort developed asthma; however, 60% (9/15) of the children with atopic eczema developed asthma compared with 14% (1/7) with nonatopic eczema.
Novembre and colleagues ²⁴	Eczema cohort; N = 77; 2–11 years	None (0/12) of the children with nonatopic eczema developed asthma by 11 years, compared with 25% (4/16) of those with late-onset atopy and eczema and 59% (29/49) with early atopy and eczema (χ^2 for trend, $P < .0002$).

Abbreviations: CI, confidence interval; eNO, exhale nitric oxide; FEF₇₅, forced expiratory flow of 75%; OR, odds ratio.

Table 2**Select Cross-sectional Studies Examining the Relationship Between Rhinitis and Asthma**

Study	Study population	Relationship between rhinitis and asthma
Leynaert and colleagues ⁴²	N = 10,210; ages 20–44 years	Asthma and bronchial hyperreactivity were more frequent in patients with rhinitis (OR, 6.63; 95% CI, 5.44–8.08; and OR, 3.02; 95% CI, 2.66–3.43, respectively) than in those without. Seventy-one percent of patients with asthma reported rhinitis. The association between rhinitis and asthma remained significant after adjustment for total IgE, parental history of asthma, and allergen sensitization (OR, 3.41; 95% CI, 2.75–4.21). The association between asthma and nonallergic rhinitis (OR, 6.2; 95% CI, 4.3–8.8) was stronger than between asthma and allergic rhinitis (OR, 3.1; 95% CI, 2.4–4.0).
Peroni and colleagues ⁴⁴	N = 1,402; ages 3–5 years	Rhinitic children showed a significant increase in asthma diagnosis (20.8% vs 6.2%, $P < .0001$) and wheezing in the last 12 months (25.0% vs 9.4%, $P < .001$) compared with nonrhinitic children. Rhinitis was associated with atopy (adjusted OR, 2.46; 95% CI, 1.71–3.54).
Bugiani and colleagues ⁴⁶	N = 17,666; ages 20–44 years	Allergic rhinitis was positively associated with asthma ever (OR, 7.89; 95% CI, 7.07–8.08). Sixty percent of asthmatic patients also reported allergic rhinitis. Patients with allergic rhinitis had an 8-fold risk of comorbid asthma compared with patients without allergic rhinitis.
Magnan and colleagues ⁴⁷	N = 4,251; ages 18–60 years	The frequency of rhinitis among asthmatic patients was 55.2%. The frequency and severity of rhinitis increased with the severity of asthma ($P < .001$). Allergic rhinitis was associated with worse asthma control, regardless of asthma severity ($P < .001$).

Abbreviations: CI, confidence interval; OR, odds ratio.

Select Longitudinal Studies Examining the Relationship Between Rhinitis and the Subsequent Development of Asthma

Study	Study population	Results
Tucson Children's Respiratory Study; Wright and colleagues ⁵⁵	Birth cohort; N = 747; cohort unselected for risk of atopy; birth to 6 years	Seventy-seven percent of all children with rhinitis in the first year of life (n = 204) had physician-diagnosed allergic rhinitis by the age of 6 years compared with 57% of those who did not have rhinitis in the first year of life (n = 214) ($P < .0005$). Children who developed rhinitis in the first year of life were significantly more likely to have physician-diagnosed asthma by 6 years of age (23% vs 13%, $P < .005$). Risk factors for physician-diagnosed allergic rhinitis in a multivariate model included the diagnosis of asthma (OR, 4.06, 95% CI, 2.06–7.99) and total serum IgE > 100 IU/mL at the age of 6 years (OR, 1.93, 95% CI, 1.18–3.17).
Tucson Children's Respiratory Study; Martinez and colleagues ²¹	Birth cohort; N = 826; cohort unselected for risk of atopy; birth to 6 years	Children with persistent wheezing were more likely to have elevated serum IgE levels at 9 months of age ($P < .01$) than children who never wheezed. Serum total IgE was significantly higher among persistent wheezers (65.6 IU/mL) compared with those who never wheezed (28.1 IU/mL) ($P < .001$). A total of 42% of children with persistent wheezing at 6 years of age experienced rhinitis. Rhinitis in the first year of life was independently associated with persistent wheeze at 6 years of age (OR, 2.0; 95% CI, 1.2–3.2).
Tasmanian Asthma Study; Burgess and colleagues ⁴³	Birth cohort (composed of 98.9% of children born in Tasmania in 1961); N = 8,583; surveys obtained at 7, 13, and 43 years	Childhood allergic rhinitis was associated with a 7-fold increased risk of incident asthma in preadolescence, a 4-fold increased risk in adolescence, and a 2-fold increased risk in adult life. Childhood allergic rhinitis was associated with an increased risk of having childhood asthma persist to the age of 44 years (OR, 3.00; 95% CI, 1.98–4.56). Asthma incidence after the age of 7 years was more than 3 times higher among those with childhood allergic rhinitis compared with those never having allergic rhinitis.
Shaaban and colleagues ⁴⁵	Population-based cohort from the European Community Respiratory Health Survey followed up for a mean of 8.8 years; N = 6,461; ages 20–44 years at enrollment	Cumulative incidence of asthma was 2.2% during 8.8 years. Probability of developing asthma during 8.8 years: 4.0% among patients with allergic rhinitis, 3.1% among patients with nonallergic rhinitis, 1.9% among those with atopy but without rhinitis, and 1.1% among those without rhinitis and without atopy. Compared with controls, patients with nonallergic rhinitis had a 2.75-fold (95% CI, 1.76–4.29) greater risk of asthma onset and those with allergic rhinitis had a 3.65-fold (95% CI, 2.37–5.61) greater risk of asthma onset. Atopic patients without rhinitis had no significantly higher risk than the controls of developing asthma.
Downie and colleagues ⁴⁹	Prospective cohort of dust mite sensitive patients with rhinitis and nonallergic controls followed up for 1 year; N = 37 rhinitis patients and 19 controls; ages 18–64 years at enrollment	Bronchial hyperresponsiveness was present in 32.4% (95% CI, 17.3–47.5%) of rhinitic patients on at least 1 occasion during the year compared with 5.3% (95% CI, 0.3–28.1%) in controls ($P = .04$). Bronchial responsiveness to histamine was greater in rhinitic patients (OR, 2.2; 95% CI, 1.5–3.0) compared with controls (OR, 0.7; 95% CI, 0.4–1.1) ($P = .004$). Airway inflammation as measured by eNO was greater in rhinitic patients (OR, 17.2; 95% CI, 15.1–19.7) compared with controls (OR, 9.7; 95% CI, 8–11.9) ($P < .0001$).
Linneberg and colleagues ⁵⁰	Population-based cohort followed up for 8 years; N = 734; ages 15–69 years at enrollment	One hundred percent of patients (52/52) with allergic asthma to pollen had allergic rhinitis to pollen. There were 28 incident cases of asthma to pollen; all patients had allergic rhinitis to pollen at baseline or developed allergic rhinitis to pollen. Eighty-nine percent (31/35) of patients with allergic asthma to animals had allergic rhinitis to animals. There were 10 incident cases of allergic asthma to animals; 90% (9/10) of patients had allergic rhinitis to animals at baseline or developed allergic rhinitis to animals. Ninety-five percent (19/20) of patients with allergic asthma to mite had allergic rhinitis to mite. There were 10 incident cases of allergic asthma to mite; all patients had allergic rhinitis to mite at baseline or developed allergic rhinitis to mite.
Porsbjerg and colleagues ⁵⁶	Population-based cohort followed up for 12 years; N = 291; ages 7–17 years at enrollment	The point prevalence of asthma increased from 4.1% at enrollment to 11.7% at the follow-up, at which point 19.6% of the sample had ever experienced asthma symptoms. Asthma developed in 45 patients (16.1%) during the follow-up period. Allergic sensitization to dust mite predicted the development of asthma (OR, 2.9; 95% CI, 1.2–7.1). Rhinitis did not predict the development of asthma (OR, 1.7; 95% CI, 0.7–3.9).
Guerra and colleagues ⁴⁸	Nested case-control study from the longitudinal cohort of the Tucson Epidemiologic Study of Obstructive Lung Diseases; N = 173 incident patients with physician-confirmed asthma compared with 2,177 controls without asthma	Rhinitis was a significant risk factor for asthma (crude OR, 4.13; 95% CI, 2.88–5.92). After adjustment for year of follow-up, age, sex, atopic status, smoking status, and presence of chronic obstructive pulmonary disease, the risk was still significant (adjusted OR, 3.21; 95% CI, 2.19–4.71). Rhinitis increased the risk of development of asthma by approximately 3 times in atopic and nonatopic patients and by more than 5 times among patients in the highest IgE tertile.

Abbreviations: CI, confidence interval; eNO, exhale nitric oxide; OR, odds ratio.

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