



Factors predicting the persistence of asthma insights from the Tucson children's respiratory study

Facteurs prédictifs de persistance de l'asthme. Données de la cohorte de Tucson

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Abstract

The Tucson Children's Respiratory Study (TCRS) is a longitudinal, epidemiology study of respiratory health, which enrolled a birth cohort of over 1200 children from 1980 to 1984. Over 800 of these children were still being followed at adolescence allowing the characterization of several distinct wheezing phenotypes throughout childhood, as well as, those risk factors associated with the development of asthma and its persistence. Evaluating the persistence of asthma is a complex issue. There are several distinct wheezing phenotypes in childhood, which vary in prevalence and course with age. The challenge here is that the phenotypes of wheezing illness change with age; i.e. in infancy most children with wheezing illnesses are transient wheezers who will cease wheezing by age six. In contrast, by age six most children with wheeze have either persisted since infancy without apparent remission or have late onset wheeze. Both of these groups have increased rates of atopy representing dysregulated immune systems. Although its prevalence decreases substantively by early adolescence, non-atopic wheeze continues in a relevant proportion of school age children. Further, although the majority of adolescents with asthma have developed wheeze by age six, there are some who first present with asthma after this age. Thus, as children age, the meaning of wheezing transitions from most likely not being asthma in the first 3 years to most likely being asthma by late adolescence. This article will review the progression of wheezing from infancy through early adolescence and will address both changes in phenotypes as well as risk factors for both persistent and incident asthma in childhood.

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Résumé

L'étude respiratoire pédiatrique de Tucson est une étude épidémiologique longitudinale de santé respiratoire ; une cohorte de 1200 enfants a été enrôlée depuis naissance, entre les années 1980 à 1984. Huit cents de ces enfants sont toujours suivis à l'adolescence, ce qui permet de caractériser plusieurs phénotypes distincts de sifflements et aussi de mettre en évidence les facteurs de risques associés au développement et à la persistance de l'asthme. Evaluer la persistance de l'asthme est d'une réelle complexité. Il existe chez l'enfant plusieurs phénotypes de sifflements dont la prévalence et l'évolution varient avec l'âge. Le « challenge » est que les phénotypes de sifflements changent avec l'âge. La plupart des nourrissons siffleurs sont des siffleurs transitoires qui s'arrêtent de siffler à six ans. En revanche, à l'âge de six ans, la plupart des enfants siffleurs soit n'ont jamais arrêté vraiment de siffler soit ont commencé à siffler tardivement. Dans ces deux groupes, la fréquence de l'atopie est élevée, témoin d'une dysrégulation immunitaire. Les sifflements non atopiques, même si leur fréquence diminue notablement en préadolescence, persistent chez une proportion significative d'enfants d'âge scolaire. De plus, même si la majorité des adolescents asthmatique avait débuté leur asthme avant l'âge de six ans, chez certains, l'asthme n'apparaît qu'après cet âge. Ainsi, au fur et à mesure que les enfants vieillissent, la signification des sifflements (wheezing) se transforme : asthme fort peu probable jusqu'à trois ans mais asthme fort probable en fin d'adolescence. Cet article décrit la progression des sifflements depuis le nourrisson jusqu'au début de l'adolescence, les changements des phénotypes ainsi que les facteurs de risque de l'asthme persistant et de l'asthme épisodique.

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1. Introduction

The Tucson Children's Respiratory Study is a birth cohort study of over 1200 children begun in 1980 which has characterized in detail the phenotypes of and risk factors for respiratory illness in childhood [1,2]. Wheezing illness in childhood takes several forms, which vary with age, early life events, and immune phenotype. Most wheezing illness in the first 3 years of life is transient and resolves by age 6 years [3]. Lung function in early life appears to be a major risk factor for this form of wheezing [3,4] in addition to environmental exposures such as daycare and environmental tobacco smoke [2]. The reduced lung function seen in these children partially improves over the first 6 years of life, but they persist with lower lung function than non-wheezing children several years after they no longer wheeze [3]. Although most remit, approximately 40% of children who wheeze in the first 3 years continue to do so later in life [3]. This has lifelong implications for respiratory health. Indeed, the majority of wheezing illness in adolescents and adults appears to have begun in the first 3 years of life [3,5]. It is characterized immunologically by increased rates of atopy and physiologically by reductions in lung function that develop in the preschool years, are evident in childhood [3], and appear to persist until middle age [6]. It has therefore been suggested by Martinez [5] that any approach to preventing asthma must therefore begin early in life and a study of secondary prevention with inhaled corticosteroid therapy in high-risk preschool children is currently underway [7]. However, given the clear immunologic alterations seen in infancy in children with wheeze persisting into school age [3,8], any approach to primary prevention will likely need to be immunomodulatory in nature and occur either pre-natally and/or in early infancy. This article will review those factors associated with the persistence of early wheezing illness into early adolescence and, by extension, into later life.

2. Wheezing in the first 6 years of life

Martinez et al. [3], classified TCRS participants by wheezing history in the first 6 years into those who never wheezed (51.5%) and those who wheezed only in the first 3 years of life (19.9%; transient wheeze), only at age six (15.0%; late onset wheeze), or both early in life and at age six (13.7%; persistent wheeze). As compared to the never wheeze group, the persistent wheeze group demonstrated increased eczema, rhinitis apart from colds, maternal asthma, Hispanic ethnicity, male gender, and maternal smoking. Late onset wheezers were more likely than those who had never wheezed to have mothers with asthma, to be male, and to have had rhinitis in

the first year of life. In contrast the transient wheeze group demonstrated only greater rates of maternal smoking. Although cord blood IgE levels obtained at birth were not different between groups, by age 9 months persistent wheezers had already developed increased serum IgE and by age six both persistent and late onset wheezers had higher rates of positive skin tests to local allergens. Persistent wheezers also demonstrated differential responses to acute lower respiratory illness with higher IgE levels during the acute phase as compared to convalescence and a failure to suppress eosinophil levels during the illness [9]. Early immune phenotype also appears to play a role in risk for recurrent wheeze in the first year of life [10] with recurrent wheezers demonstrating lower interferon gamma and soluble CD14 levels. Guerra et al. [10], suggested that CD14's role as a sentinel molecule in the innate immune system was diminished in these infants perhaps leading to less efficient stimulation by environmental factors such as endotoxin and hence lower interferon gamma levels. This finding suggests one potential mechanism for the development immune dysregulation in favor of a T-helper type 2 (Th2) phenotype with increased atopy.

The early wheeze phenotypes are associated with different alterations in lung function across the preschool years. Compared to never wheezers, only the transient wheeze group had diminished lung function in early infancy; however, at age six both the transient and persistent wheezers had decreased forced expiratory flows (Fig. 1). Coupled with increased clinical and biomarker evidence of an atopic state early in life, this reduction in lung function in the persistent wheeze group suggests that airway development was negatively impacted by chronic or recurrent allergic airway inflammation. Thus, the development of atopic immune dysregula-

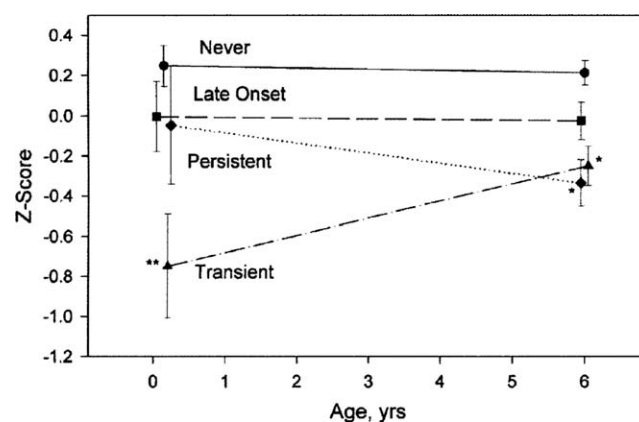


Fig. 1. Lung function (V' maxFRC) at infancy and 6 years of age expressed in Z-scores by wheezing group: Circles—never wheeze, triangles—transient early wheeze, squares—late onset wheeze, diamonds—persistent wheeze. (* $P < 0.05$ vs. never wheeze group; ** $P < 0.05$ vs. never, late, and persistent wheeze groups; from reference [2] with permission).

tion early in life may be a critical event that leads to worsened clinical and physiologic outcomes.

3. Wheezing phenotypes in school age children

As children enter school age, those who continue to wheeze can be further classified to better clarify the pathways to recurrent wheezing illness. Stein et al. [11] used methacholine reactivity and peak flow variability at age 11 years together with markers of atopy (skin test reactivity and serum IgE) to identify three wheezing phenotypes in the TCRS population. Transient early wheezers continued to have wheezing limited to the first 3 years of life and unrelated to airway lability or atopy. Children with IgE-associated wheeze likely represented those who would go on to long-term asthma and were characterized by wheezing throughout childhood, methacholine reactivity, and markers of atopy. As suggested by Wilson [12], a third phenotype, however, became clear; there was a group of non-atopic children with wheeze who demonstrated increased peak flow variability, but not methacholine hyperresponsiveness. It is likely that this group represents many of the children who wheeze through the early school years and then 'grow out' of their asthma (Fig. 2). It appears that developing a respiratory tract illness in early life due to respiratory syncytial virus (RSV) in early life is also associated with this non-atopic form of wheezing [13]. TCRS participants with wheezing lower respiratory tract illness caused by RSV were more likely to have both infrequent and frequent wheeze at ages 6 and 11 years, but not by age 13 years. They also demonstrated lower measurements of forced expiratory flow at baseline, but not after inhalation of salbutamol suggesting that airway smooth muscle tone may have accounted for the reduction. Importantly, children with RSV-associated wheeze in early life were not more likely to have allergic sensitization, suggesting that some forms of wheezing, particularly in response to viral infection, may be mediated by mechanisms other than atopic airway inflammation. These non-atopic

wheezers may have structural or functional alterations in the lung that facilitate wheezing illness in childhood, but lacking a dysregulated, atopic immune system they are able to grow out of their illness by early adolescence. Thus, as children proceed into adolescence, both the transient wheezers and non-atopic wheezers no longer contribute substantively to the prevalence of wheezing illness. The remaining group of children with wheeze now clearly fit the picture of extrinsic asthma combining atopy, airway reactivity [14], and in the case of the persistent wheeze group, diminished lung function in their clinical presentation [3].

4. Factors modifying the development of atopic asthma

Although many children who never wheeze develop atopy by school age, those who have atopy and recurrent wheeze are likely to persist with wheezing illness through childhood [3,15]. Understanding factors modifying the development of atopy in association with wheeze thus becomes important to assessing risk for progression to the atopic wheeze or asthmatic phenotype. Halonen et al. [16], analyzed the relationship between physician diagnosed asthma at age 6 and 11 and allergen sensitization patterns in TCRS participants. Although sensitivity to bermuda grass was common in children with allergic rhinitis, responses to the mold *Alternaria alternata* were most common in the children with asthma. *Alternaria* was the only allergen independently associated with increased risk for asthma at both ages 6 and 11 particularly in those with the onset of wheezing in early life. However, in other non-arid environments the candidate allergens associated with asthma are different (cat, dust mite, cockroach), thus suggesting that the key issue may be the ability of the dysregulated immune system to respond to a relevant allergen exposure rather than the allergen per se. There is a growing body of evidence that links the development of an allergic or Th2 weighted immune phenotype to improvements in hygiene during modern times [17,18]. Briefly, the concept is that our immune systems have evolved to develop during early life through an interaction with the environment around us. Lacking an atavistic exposure to infectious agents and chemicals such as endotoxin, the immune system begins to respond inappropriately to agents that represent no survival risk; e.g. cats, dust mite, cockroach, or *alternaria*. The TCRS has provided supportive evidence for this hypothesis. Remes et al. [19], demonstrated that children born into households with at least one dog had lower rates of wheezing in childhood. This effect was, however, only demonstrable in those children without a history of parental asthma. This exposure to common pets was also associated with reduced bronchial responsiveness to methacholine in boys, but not in girls. It is also compatible with the findings of Ownby et al. [20] that exposure to two or more dogs or cats in the first year of life reduced the risk of sensitization to multiple allergens. Siblings and other children likely represent another important source of exposure to infection, as well as endotoxin, during early life. Ball et al.

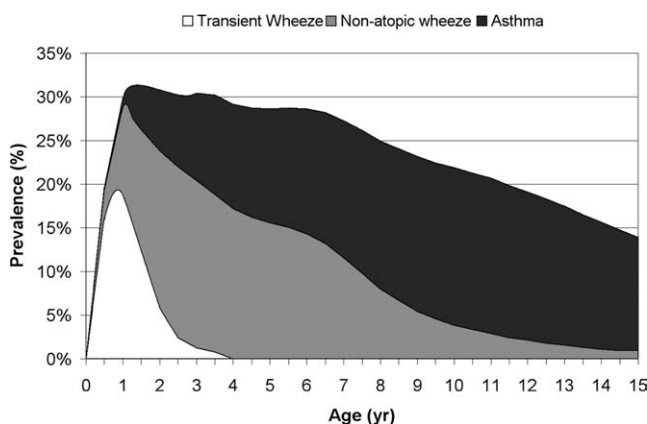


Fig. 2. Schematic chart of childhood wheezing phenotypes against age presented as a stacked area chart. The prevalence of each phenotype at any age is the height of that band and the total prevalence of wheeze at any age is the sum of the three wheeze phenotypes. (From concepts presented in Stein et al. *Thorax*. 1997;52(11):946–52).

[21], demonstrated that TCRS children who were exposed to older siblings or daycare before 6 months of age were more likely to wheeze early in life, but much less likely to asthma by age 13. They were also less likely to be sensitized to *Alternaria* or other allergens and less likely to have high serum IgE; again suggesting that proper stimulation of the immune system in early life may be protective against the development of asthma.

5. Predicting asthma persistence

The prevalence of wheeze at age three is made up of primarily of children with phenotypes not destined to continue with asthma; i.e. transient early wheeze and non-atopic wheeze. This can make both diagnosis and management challenging for the practitioner. Castro et al. [22] used the TCRS population to develop an index to predict asthma in later childhood in children with early onset wheezing, the asthma predictive index (API). A stringent API included frequent wheezing during the first 3 year of life and either one major risk factor (parental history of asthma or eczema) or two of three minor risk factors (eosinophilia, wheezing without colds, and allergic rhinitis). Children with a positive stringent API had an odds ratio of having subsequent asthma at age 13 of 3.0 (95% C.I. 1.9–4.6) compared to those with a negative API. Moreover, 76% of children with a positive had active asthma in at least one survey during the school years, while over 95% of children with a negative stringent index never had active asthma between ages 6 and 13. A modified version of the API is currently being used in the multi-center Prevention of Early Asthma in Kids (PEAK) study [7]. Participants ages 24–48 months with a history of recurrent wheeze and a positive modified API were evaluated for allergen sensitization by skin prick test and/or specific IgE testing. Over 60% were sensitized to at least one food or aeroallergen with 54% sensitized to at least one aeroallergen [23], thus demonstrating that children with a positive API who are likely to have persistent asthma are commonly sensitized to inhaled allergens in their environment at an early age.

In addition to an altered immunomodulatory environment which coupled with inherited risk may lead to atopic wheeze [17–19,21], the last few decades have seen the development of a marked increase in the prevalence obesity. Obesity is a pro-inflammatory condition [24], which has been associated with asthma onset in adolescence or adulthood particularly in females [25,26]. Guerra et al. [15], assessed factors predicting remission of asthma following puberty in the TCRS population. In addition to frequent wheezing before puberty, obesity, early onset of puberty, active sinusitis, and skin test sensitization were significant and independent predictors of unremitting asthma after the onset of puberty. Perhaps the most striking finding was the low rate of remission (42%) and the lack of a gender effect once age at puberty was included in the analysis. The role of obesity in early life, however, is less clear and further study is needed [26] and it

remains to be definitively demonstrated if the development of asthma can be limited by reducing the prevalence of obesity.

6. Conclusion

The Tucson Children's Respiratory Study has contributed to our understanding of the ontogeny of wheezing phenotypes in childhood and has offered insights into the potential mechanisms leading to chronic or recurrent asthma in childhood. Predicting persistence of wheezing illness through childhood can be facilitated by an understanding of the phenotypes of early wheeze [3,11] and the use of the asthma predictive index [22]. As children move from the preschool years through puberty much of the apparent remission of wheezing illness or asthma is simply the reduction in non-asthmatic wheeze leading to a predominance of atopic wheeze (asthma) in later childhood. Conversely, once asthma is established by the pre-teen years, there are clear predictors of persistence through puberty including the frequency of early wheeze, obesity, and atopy amongst others. The development of unremitting asthma is thus clearly associated with altered immune system development. The theme, which emerges is that early immune maldevelopment is critical to set the stage for later asthma. Thus, as suggested by Martinez [5], strategies to prevent the development and progression of this disease likely need to focus early in life, well before we 'have learned to read'.

References

- [1] Taussig LM, Wright AL, Morgan WJ, Harrison HR, Ray CG, Associates GHMA. The Tucson Children's Respiratory Study: I Design and implementation of a prospective study of acute and chronic respiratory illness in children. *Am J Epidemiol* 1989;129:1219–31.
- [2] Taussig LM, Wright AL, Holberg CJ, Halonen M, Morgan WJ, Martinez FD. Tucson Children's Respiratory Study: 1980 to present. *J Allergy Clin Immunol* 2003;111:661–75.
- [3] Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first 6 years of life. *N Engl J Med* 1995;332:133–8.
- [4] Martinez FD, Morgan WJ, Wright AL, Holberg CJ, Taussig LM. Diminished lung function as a predisposing factor for wheezing respiratory illness in infants. *N Engl J Med* 1988;319:1112–7.
- [5] Martinez FD. Toward asthma prevention--does all that really matters happen before we learn to read? *N Engl J Med* 2003;349:1473–5.
- [6] Sears MR, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM, et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med* 2003;349:1414–22.
- [7] Guilbert TW, Morgan WJ, Krawiec M, Lemanske RF, Sorkness C, Szeffer SJ, et al. The Prevention of Early Asthma in Kids study: design, rationale and methods. *Control Clin Trials* 2004;25:286–310.
- [8] Stein RT, Martinez FD. Asthma phenotypes in childhood: lessons from an epidemiological approach. *Paediatr Respir Rev* 2004;5:155–61.

- [9] Martinez FD, Stern DA, Wright AL, Taussig LM, Halonen M. Differential immune responses to acute lower respiratory illness in early life by subsequent development of persistent wheezing and asthma. *J Allergy Clin Immunol* 1998;102:915–20.
- [10] Guerra S, Lohman IC, Halonen M, Martinez FD, Wright AL. Reduced interferon gamma production and soluble CD14 levels in early life predict recurrent wheezing by 1 year of age. *Am J Respir Crit Care Med* 2004;169:70–6.
- [11] Stein RT, Holberg CJ, Morgan WJ, Wright AL, Lombardi E, Taussig L, et al. Peak flow variability, methacholine responsiveness and atopy as markers for detecting different wheezing phenotypes in childhood. *Thorax* 1997;52:946–52.
- [12] Wilson NM. The significance of early wheezing. *Clin Exp Allergy* 1994;24:522–9.
- [13] Stein RT, Sherrill D, Morgan WJ, Holberg CJ, Halonen M, Taussig LM, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet* 1999;354:541–5.
- [14] Lombardi E, Morgan WJ, Wright AL, Stein RT, Holberg CJ, Martinez FD. Cold air challenge at age 6 and subsequent incidence of asthma. A longitudinal study. *Am J Respir Crit Care Med* 1997;156:1863–9.
- [15] Guerra S, Wright AL, Morgan WJ, Sherrill DL, Holberg CJ, Martinez FD. Persistence of asthma symptoms during adolescence: role of obesity and age at the onset of puberty. *Am J Respir Crit Care Med* 2004;170:78–85.
- [16] Halonen M, Stern DA, Wright AL, Taussig LM, Martinez FD. Alternaria as a major allergen for asthma in children raised in a desert environment. *Am J Respir Crit Care Med* 1997;155:1356–61.
- [17] Weiss ST. Eat Dirt—The Hygiene Hypothesis and Allergic Diseases. *N Engl J Med* 2002;347:930–1.
- [18] Braun-Fahrlander C, Riedler J, Herz U, Eder W, Waser M, Grize L, et al. Environmental Exposure to Endotoxin and Its Relation to Asthma in School-Age Children. *N Engl J Med* 2002;347:869–77.
- [19] Remes ST, Castro-Rodriguez JA, Holberg CJ, Martinez FD, Wright AL. Dog exposure in infancy decreases the subsequent risk of frequent wheeze but not of atopy. *J Allergy Clin Immunol* 2001;108:509–15.
- [20] Ownby DR, Cole Johnson C, Peterson EL. Exposure to Dogs and Cats in the First Year of Life and Risk of Allergic Sensitization at 6 to 7 Years of Age. *JAMA* 2002;288:963–72.
- [21] Ball TM, Castro-Rodriguez JA, Griffith KA, Holberg CJ, Martinez FD, Wright AL. Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. *N Engl J Med* 2000;343:538–43.
- [22] 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;162:1403–6.
- [23] Guilbert TW, Morgan WJ, Zeiger RS, Bacharier LB, Boehmer SJ, Krawiec M, et al. Atopic characteristics of children with recurrent wheezing at high risk for the development of childhood asthma. *J Allergy Clin Immunol* 2004;114:1282–7.
- [24] Fantuzzi G. Adipose tissue, adipokines, and inflammation. *J Allergy Clin Immunol* 2005;115:911–9.
- [25] Castro-Rodriguez JA, Holberg CJ, Morgan WJ, Wright AL, Martinez FD. Increased incidence of asthmalike symptoms in girls who become overweight or obese during the school years. *Am J Respir Crit Care Med* 2001;163:1344–9.
- [26] Ford ES. The epidemiology of obesity and asthma. *J Allergy Clin Immunol* 2005;115:897–909.