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Tucson Children's Respiratory Study: 1980 to present

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The Tucson Children's Respiratory Study (TCRS), begun in 1980, has followed 1246 subjects from birth together with their family members to delineate the complex interrelationships between a large number of potential risk factors, acute lower respiratory tract illnesses, and chronic lung disorders later in childhood and early adult life, especially asthma. Nine hundred seventy-four (78%) of the original subjects are still being followed. Among its numerous findings, the TCRS has (1) described various wheezing disorders (transient, nonatopic, atopic) and their characteristics; (2) developed an Asthma Predictive Index; (3) delineated the respiratory and atopic outcomes for children who had respiratory syncytial virus–related wheezing illnesses in infancy; and (4) evaluated a large number of risk factors for acute respiratory tract illnesses during the first 3 years of life. Future TCRS studies will focus on (1) factors in infancy and early childhood that relate to persistent asthma and atopy; (2) role of genetic factors in persistent asthma; and (3) determinants of lung function decline in early adult life. (J Allergy Clin Immunol 2003;111:661-75.)

Key words: *Asthma, risk factors, wheezing syndromes, atopy, lower respiratory tract illnesses, Tucson Children's Respiratory Study, lung function, immunology*

The Tucson Children's Respiratory Study (TCRS) was begun in 1980 as a long-term, longitudinal study to investigate the interrelationships between a large number of potential risk factors, acute lower respiratory tract illnesses (LRIs) during the first 3 years of life, and the development of chronic lung disorders, especially asthma, in later childhood and young adult life.[1] By enrolling a large number (N = 1246) of infants at or soon after birth, this cohort study was designed to minimize or avoid many of the problems of previous studies. The strengths of the study include the following: (1) extensive pre-LRI data, including lung function and assessment of various immunologic and allergic parameters; (2) enrollment of a large number of subjects and their family members; (3) a predominantly outpatient population, thereby avoiding the biases of a hospitalized population; (4) extensive data relating to a large number of risk factors (infectious, physiologic, genetic, familial, psychosocial, immunologic, allergic, and environmental) (Table I); (5) extensive microbiologic, virologic, and serologic data relating to the acute LRIs; and (6) long follow-up period with excellent retention of enrolled subjects/families.

The design of the TCRS has facilitated the assessment of the natural history and sequelae of acute LRIs and their relationship, either independent of or in concert with certain other risk factors, to the development of chronic lung disorders, especially asthma, later in life.

Enrollment of index subjects and their families occurred during a 4½-year period, 1980 to 1984. Data have been collected from all family members at numerous time points (Tables II through IV) to maximize pre-illness and follow-up information and to minimize issues related to recall bias. Certain key demographic data are summarized in Table V. The study was originally designed to enroll 1000 neonates and their families. This was predicated on a 25% cumulative rate for LRIs during the first 3 years of life and a 20% to 25% cumulative loss rate during the first 5 years of the study. In fact, the LRI rate was nearly 46% and the dropout rate was 13% during the first 5 years. The overall loss rate has averaged 1.3% per year. LRIs were only studied during the first 3 years of life. Enrollment was extended beyond 1000 to apply newly described tests of lung function for infants[2,3] to a relatively large group of very young babies. This last group of enrollees also afforded the opportunity to do certain tests of immune function early in life, before any LRIs. At present, 974 or 78% of the initial group remain in the study, with 60% still in Tucson. This large number of remaining subjects bodes well for future follow-up studies. The extensive amount of pre-LRI, pre–chronic lung disease, acute LRI, and risk factor data have facilitated many analyses summarized in subsequent sections.

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TABLE I. Potential risk factors evaluated for possible relationships with acute LRI or chronic lung disease (asthma)

Sex, ethnicity
Birth weight
Parents' education, income, age
Respiratory symptoms and illnesses in other household members
Genetic determinants
Number and order of siblings
Bottle/breast-feeding
Day care
Type of home heating, cooking, and cooling
Number and type of pets
Indoor air pollution
Passive/active smoking
Atopy
Immune function
Lung function
Airway reactivity

TABLE II. Data collection

Enrollment (birth)
Questionnaire (family) data
Maternal pregnancy history
Cord blood (IgE, immune studies)
CBC/differential
Periodic data
Well-baby visit forms
Periodic questionnaires on all household members
2 to 3 months of age
Pulmonary function tests
9 to 15 months of age
IgE, CBC and differential, immune studies
LRIs in first 3 years of life
Sign/symptom and history forms
Cultures, serologies, CBC and differential, IgE
Convalescence (3-5 wk post LRI) serologies, IgE, CBC and differential

CBC, Complete blood count.

TABLE III. Number of index subjects in the CRS with data at each evaluation

	Early years of life	In-depth I	In-depth II	In-depth III
Age of index subjects	Birth to 3 y	6 y	11 y	16 y
Respiratory questionnaires*	1055 (age 2 y)	1025	955	509†
LRI evaluations through age 3 y	888	—	—	—
Skin prick tests	—	762	689	397†
Serum IgE	1120 (at birth)	550	633	357†
Peripheral blood eosinophils	880 (at 9 mo)	550	633	357†
Pulmonary function studies	176 (at 4 mo)	676	595	376†
Airway challenge studies	—	368	396	303†
Peak flow variability	—	—	600	383†

*Respiratory questionnaires were also obtained on the enrolled child at age 3 (n = 940), 8 (n = 841), and 13 (n = 714) years. Questionnaires are also being obtained at age 18, but this is still in progress.
†Data collection is still in progress.

Abbreviations used

CRT: Childhood respiratory trouble
FRC: Functional residual capacity
LRI: Lower respiratory tract illness
OR: Odds ratio
RSV: Respiratory syncytial virus
TCRS: Tucson Children's Respiratory Study
$V'_{max}FRC$: Maximal forced expiratory flow at functional residual capacity
WLRI: Wheezing lower respiratory illness

The successes of the TCRS during the past 22 years are attributable to many factors; some of the most important are the following:

1. The use of 1 large HMO, which helped the study avoid economic extremes of the population and facilitated follow-up. Minimal fees for well-baby and acute LRI follow-up visits were great advantages.
2. Involvement by 1 large group of pediatricians who were very interested in the study and participated actively, especially with enrollment and evaluation of LRIs. The pediatricians did the initial approach to the new parents (usually while the mothers and neonates were still in the hospital) regarding enrollment in the study. Enrollment of the index subjects predominantly occurred immediately after delivery; some were enrolled at the 2-week well-child visit. The very high enrollment rate of 78% (Table V) was directly attributable to the pediatricians' extensive involvement.
3. Available space in the HMO offices for the study nurses. Most of the evaluations during the first 5 years of the study were done in the offices of the pediatricians.
4. Long-term involvement by the study nurses (1 nurse has been with the TCRS for 20 years). This allowed the nurses to become very well-acquainted with the enrolled families.
5. Extensive participation, retention, and follow-up methodologies.
6. Lower than anticipated loss rate and higher than expected LRI rate.
7. Minimizing blood draws; being able to do 1 blood draw in the neonatal period at the time of the phenylketonuria test for IgE levels, certain immune tests, and cotinine levels while obtaining a screening hematocrit for the pediatricians. Similarly, at 9

to 15 months of age, the pediatricians routinely checked a hematocrit, which allowed the study nurses to obtain blood for IgE, certain immune tests, and cotinine and to store sera. Except during acute LRIs, infants only had blood drawn for study tests when blood was being drawn for routine clinical assessment.

8. Being able to obtain cord bloods (through the cooperation of the obstetricians in the HMO) for certain analyses.
9. Development of tests of lung function applicable to young infants.
10. Having an outstanding virology laboratory that produced a 62% isolation rate.

This review will summarize the major findings from the TCRS since its inception in 1980 and planned future studies.

ACUTE LRIs

Acute LRIs are common early in life, with rates being highest in infancy. Parents of children in the TCRS were requested to take their children to the pediatrician whenever the child developed certain symptoms (deep or "wet" cough, wheeze, stridor, etc). The pediatrician recorded all relevant signs and symptoms, and nasopharyngeal/throat swabs were obtained for viral culture. The prevalence of wheezing with LRIs in the TCRS among children followed for the entire year was 32.0%, 17.3%, and 12.0% in the first, second, and third years of life, respectively. An etiologic agent was identified, by culture or direct immunofluorescence for antigen detection, in 66% of LRIs.[4] Children for whom an etiologic agent was identified did not differ from those who were culture-negative in clinical characteristics or seroconversion to other respiratory viruses.[5] As anticipated from previous studies,[6,7] respiratory syncytial virus (RSV) was the most common agent identified, followed by parainfluenza virus type 3. Multiple etiologic agents were observed for approximately 24% of episodes.[8]

Several behavioral or environmental factors were associated with risk of having LRIs. Breast-feeding of at least 1 month was associated with lower rates of wheezing LRIs during the first 4 months of life.[9] Further, there appeared to be an interaction between infant feeding practices and other risk factors for RSV infection (such as sharing the room, low maternal education, and low maternal RSV titer), such that the protective effect of breast-feeding was particularly evident for those with additional risks.[9,10] Children of younger mothers were significantly more likely to develop wheezing LRIs compared to children whose mothers were 30 years old or older.[11] Wheezing LRIs were also more common among children who had evaporative coolers in their homes.[12] Use of day care in the presence of 3 or more children was associated with roughly double the risk for LRI[13] from the age of 4 months to 3 years. Maternal smoking was associated with a significantly higher incidence of wheezing LRI in infancy[14,15] and with earlier age of first LRI. In the third year of life, the risk of a wheezing LRI in the presence of a smoking caregiver was 3 times higher than for children who did not have a smoking caregiver.[13] There were no significant gender differences in LRIs early in life.

One unanticipated finding was the observation that nonwheezing LRIs appeared to influence IgE production. Children were divided into 3 groups depending on their LRI history during the first 3 years of life: those who had wheezing LRIs, those with nonwheezing LRIs only, and those with no LRIs.[16] Children who had only nonwheezing LRIs in early life did not differ from never wheezers in terms of IgE production at birth. However, they produced significantly less IgE at 9 months and 6 years. Further, children whose nonwheezing LRIs occurred after blood was drawn at 9 months had normal IgE levels at 9 months but had significantly decreased IgE at 6 years (relative to never wheezers). Because the children with nonwheezing LRIs also had higher IFN-γ levels at 9 months, it is possible that their ability to mount a T-cell response had matured earlier than those who had wheezing LRIs. Alternatively, IgE production in middle childhood may be altered by nonwheezing LRIs, at least in certain hosts.

TABLE IV. Evaluation of family members at in-depth I

	Mothers	Fathers	Siblings
Questionnaire	1008	908	1150
Pulmonary function tests	840	671	625
Blood sample	806	635	540
Allergy skin tests	813	664	847
Methacholine studies	319	272	51

TABLE V. Summary of certain demographic data

Category	Number (%)
Families approached for enrollment	1760
Total eligible for enrollment	1596
Enrolled infants and families	1246 (78)
Number of cord blood specimens	1084 (87)
CBC and differential at time of phenylketonuria test	947 (76)
IgE, CBC and differential at 9-15 mo	959 (77)
Number of children with LRIs, first 3 y	572 (46)
Number of acute LRIs, first 3 y	1052
Number with culture specimens during LRIs (percent is of those referred for acute studies)	756 (88)
Number with pulmonary function tests at 2-3 mo of age	192

ENVIRONMENTAL, SOCIOECONOMIC, AND GENDER STUDIES

One of the most important findings from the TCRS is that events occurring early in life appear to be important determinants of subsequent asthma. For example, umbilical cord blood IgE shows no relation to later asthma. However, IgE near the end of the first year of life is associated with later persistent wheezing and asthma,[15] which suggests that some event in the first year of life

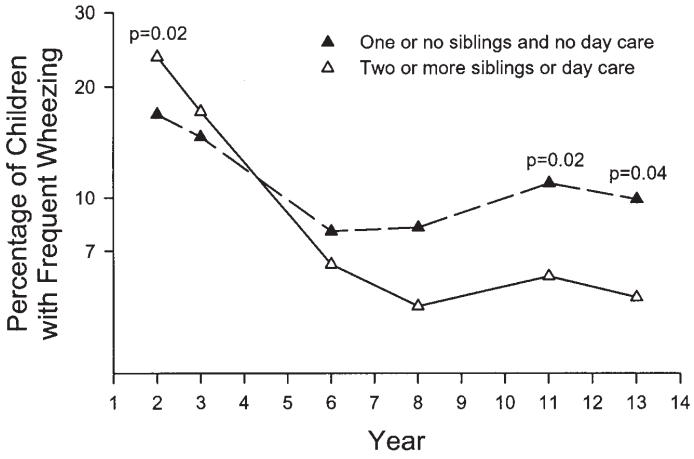

FIG 1. Frequent wheeze by sibling/day care groups in first 6 months of life (from Ball TM, Holberg CJ, Martinez FD, Wright AL. Exposure to siblings and day care during infancy and subsequent development of asthma and frequent wheeze. N Engl J Med 2000;343:538-43).

either alters or unmasks a child's propensity to respond in an allergic fashion.

It has been hypothesized that the reduction in microbial burden that has occurred during the past century in the industrialized world may have altered normal postnatal immune system development,[17] particularly the regulation of the allergen-specific immune responses that underlie allergy. Three findings from the CRS are consistent with this hypothesis. First, we assessed[18] the relation between exposure to other children during the first 6 months of life to wheezing both early in life and later. After adjustment for potential confounders, each additional older sibling in the home (odds ratio [OR], 0.80; 95% CI, 0.66 to 0.96) and attendance in day care during the first 6 months of life (OR, 0.55; 95% CI, 0.32 to 0.94) were found to protect against the development of current physician-diagnosed asthma between ages of 6 to 13 years. In addition, infants exposed to more children at home or day care experienced more frequent wheeze at year 2 (OR, 1.56; 95% CI, 1.14 to 2.12) but less frequent wheeze from year 8 (OR, 0.53; 95% CI, 0.37 to 0.76) through year 13 (OR, 0.25; 95% CI, 0.14 to 0.45). Skin test reactivity at both age 6 and 11 years and elevated serum IgE levels were also inversely related to increased exposure to children at home or in day care during early infancy. Thus, although exposure to children at home or in day care during infancy increased wheeze in early life, it appears to be protective against the development of atopy, asthma, and frequent wheeze in school age children (Fig 1).

A second analysis[19] considered the relation between exposure to pets in early life and the time to first report of frequent (more than 3 episodes in the past year) wheezing. We found that children living in households with 1 or more indoor dogs at birth were less likely to develop frequent wheeze than those not having indoor dogs ($P = .004$). This inverse association was confined to children without parental asthma (hazard ratio, 0.47; $P < .001$, Cox regression) and was not evident for children with parental asthma (hazard ratio, 0.96; $P = .87$). Adjustment by potential confounders did not change the results. Indoor cat exposure was not significantly associated with the risk of frequent wheezing. Neither cat nor dog exposure in early life was associated with skin prick test reactivity or total serum IgE level at any age.

Finally, infant feeding practices may play a role in the development of allergy and asthma. First, the relation of maternal IgE level to IgE level in the child appears to be altered by infant feeding practices. Breast-feeding was associated with lower total serum IgE level at age 6 years for children whose mothers were in the lower 2 terciles of the distribution of IgE. In contrast, breast-feeding was associated with higher IgE level at age 6 years for children whose mothers had high IgE level.[20] We also found that children with maternal asthma were significantly more likely to have asthma if they had been exclusively breast-fed (OR, 8.7; 95% CI, 3.4 to 22.2).[21] This relationship was only evident for atopic children and persisted after adjusting for confounders. Breast-feeding is protective against a wide range of infections, which obviously provided a critical selective advantage under the conditions in which the immune system of *Homo sapiens* evolved. However, these benefits of breast-feeding may reduce the stimulus for maturation of antimicrobial immunity in the context of reduced exposure to microbes, particularly among infants who are doubly susceptible by virtue of both a parental history of asthma and their own atopy.

In the TCRS, although the point prevalence of wheeze declined, the prevalence of active asthma diagnosed by a physician increased at each survey until age 16 years, the last age at which data are currently available. In addition, distinct gender differences were evident (Fig 2). Boys were significantly more likely to wheeze early in life, especially at age 6 and 8 years, and the prevalence of wheeze declined steadily with increasing age. For girls, however, the prevalence of wheeze declined in the first decade of life but then began to increase. Consequently, gender differences in wheeze became borderline at age 13 years ($P < .08$) and disappeared completely by age 16 years ($P < .96$). Similarly, although physician-diagnosed

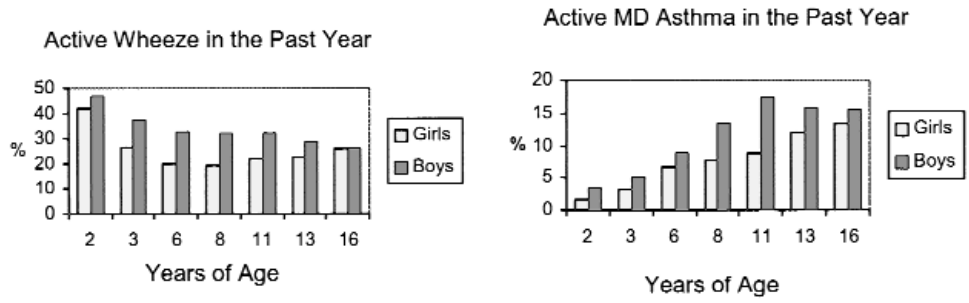

FIG 2. Percent of TCRS children with wheeze *(left)* and active physician-diagnosed asthma *(right)* in the past year, by age and gender.

asthma was more common in boys at all ages, it increased during the first decade of life but then declined for boys starting at age 11 years. For girls, however, active asthma continued to increase through age 16 years (Fig 2). Of particular interest in this context is the finding that girls, but not boys, who were overweight or obese at age 11 years were more likely to have current wheezing at ages 11 and 13 years but not at ages 6 or 8 years.[22] This effect was strongest among girls who started puberty before the age of 11 years. Girls who became overweight or obese between 6 and 11 years were up to 7.1 times more likely to develop new asthma symptoms at age 11 or 13 years than those who did not ($P = .0002$), and they were also significantly more likely to have increased bronchodilator responsiveness and increased variability of peak flow at the age of 11 years. This finding suggests that increase in weight during the preschool years is associated with an increased risk of developing new asthma symptoms and increased bronchial responsiveness in early adolescence for girls.

GENETIC STUDIES

The TCRS was initially conceived as a longitudinal study of the risk factors for and potential sequelae of respiratory diseases. At that time, in 1979, genetic epidemiology per se, and of asthma specifically, was essentially in its infancy. The implementation of the TCRS in 1980 occurred at a most opportune time to take advantage of the growth and development of genetic studies. Thus, although not initially designed as a genetic study per se, the study population (families comprising the index child, all siblings, and both parents, enrolled at random with respect to respiratory diseases) is ideally suited to many forms of genetic analyses. In addition, as genetic studies mature, it is becoming clear that there are important interactions occurring between genes and the environment, which may arise only within a particular time window. Longitudinal studies are essential to defining phenotypes based on, for example, early life events; the longitudinal TCRS data set is particularly relevant and invaluable in this regard. The study of the genetics of asthma in the TCRS has included a broad spectrum of analytic methods, keeping pace with new genetic technologies.

The earliest TCRS genetic studies used classic epidemiologic methods to examine parental histories of childhood respiratory trouble (CRT) as risk factors for LRIs in their infants.[23] After controlling for confounders, a parental history of CRT described as asthma or bronchiolitis with onset before age 3 years was associated with wheezing LRIs in their children (OR, 2.6; $P < .05$), whereas parental CRT described as bronchitis/croup was associated with nonwheezing LRIs in their offspring. Such classic epidemiologic approaches give an indication of familial aggregation within the data but do not indicate whether the trait may be inherited genetically following Mendelian principles. The statistical detection of Mendelian ratios in the transmission of a trait from one generation to another, known as segregation analysis, was the next approach.

Asthma has been characterized as a complex phenotype; the disease is heterogeneous with variability in age of onset and presentation, including the possibility of remission; environmental factors play a crucial role in its expression, and a number of pathogenic processes appear important in its clinical expression. This variation suggests that the disease is not under the control of a monogenic 2-allele locus, but that several major and minor loci plus a strong environmental determinant may be involved in its expression. Given the characterization of asthma as a complex phenotype, there has been considerable emphasis on studying the genetics of phenotypes showing a strong association with asthma, which may also cluster within families. The supposition is that such "intermediate phenotypes," or more specifically the genes regulating their expression, may play a crucial role in the pathogenesis of asthma.[24] Segregation analysis was applied to a number of asthma phenotypes, drawing the study populations from 1151 nuclear families enrolled in the TCRS. The first analysis for total serum IgE levels indicated that the best fit to the data was a model of Mendelian codominant inheritance of a major autosomal gene associated with higher serum IgE level.[25] Tests for genetic heterogeneity showed no significant difference between the 2 ethnic groups (Hispanic and non-Hispanic white). The initial success in statistically identifying a Mendelian major autosomal gene for IgE was not matched in subsequent segregation analyses with other phenotypes, including a self-report of physician-

diagnosed asthma, FEV_1, and the level of circulating eosinophils. For each of these phenotypes, although there were significant parent-offspring and sibling-sibling correlations, results indicated the rejection of the hypothesis of a single 2-allele locus. For the diagnosis of asthma phenotype, either a polygenic/multifactorial mode of inheritance alone or an oligogenic mode, with some evidence of a recessive component, were compatible with the data.[26] Results suggested that lung function is inherited in a polygenic/multifactorial fashion, with evidence of a Mendelian recessive component associated with higher levels of lung function and a genetic or maternal influence in asthmatic families.[27] For eosinophil levels, the results suggested an oligogenic mode of inheritance with an infrequent recessive Mendelian component for low eosinophil levels in non-Hispanic white families.[28] Collectively, these results support the concept of multiple, relatively common genes, interacting to determine genetic susceptibility to asthma.

Concurrent with the statistical modeling approaches, linkage analyses using the sibling pair approach with polymorphic microsatellite markers and association studies assessing known and novel polymorphisms identified by sequencing techniques were begun. The focus of these studies has been mainly on a candidate region in chromosome 5q 31-33, where the interleukin cluster of genes is found.

The earliest TCRS association study reported that subjects with a different genotype for a polymorphism reported by Liggett[29] in the β_2-adrenoreceptor (at amino acid 16 in the coding region [Arg-16]) on chromosome 5q31-33 show differences in the prevalence of positive responses to bronchodilators.[30] Subsequently, linkage of circulating eosinophils, as a percent of total white blood cells, to markers located on chromosome 5q31-33 was demonstrated in this area, and a multipoint analysis showed that the maximal logarithm of the odds favoring genetic linkage (LOD score) was observed for marker D5S658.[31] Further linkage studies showed that a compound atopy-related phenotype obtained by factor analysis demonstrates significant evidence for linkage with markers in 5q31-33, but an "asthma" phenotype, after atopy had been controlled for, showed no evidence for linkage with these same markers.[32] These results suggest that variants in gene(s) in chromosome 5q may determine atopy and, through this mechanism, increase susceptibility to asthma. However, there appear to be no variants that determine asthma independent of the atopic status. A search for variants in this area, which may be associated with these linkage signals, led to the discovery of a number of novel polymorphisms. In the TCRS population, a polymorphism in the 5′ flanking region of the CD14 gene is associated with circulating soluble CD14 levels and with total serum IgE level.[33] The CD14 gene maps to chromosome 5q31.1. Also reported are 7 polymorphisms (6 novel) in IL-13[34]; 4 of these are tightly linked to a variant in the terminal portion of the coding region of the gene that results in a predicted amino acid change in residue130 (Arg130Gln). The Gln form is strongly associated (P = .000002) with increased serum IgE levels in 3 different populations (TCRS and 2 German populations) comprising a total of 1399 children.

IMMUNOLOGIC AND ATOPIC STUDIES

The prospective, longitudinal design of the TCRS, the breadth of phenotypic data, and the more recent addition of genetic information provide opportunity to relate the maturation and regulation of the immune system to acute LRIs in early life and to the development of asthma, allergy, and asthma-related and allergy-related traits and risk factors. The immunology arm of the TCRS was originally designed to test the premise that IgE responses were critical to and likely causative in the development of allergy and asthma. Longitudinal epidemiologic data can provide evidence for genetic regulation in a phenotype if significant tracking occurs within individuals. Data on the index children of the TCRS obtained at birth, at age 9 months, and at 5-year intervals thereafter showed significant tracking of serum IgE levels from birth onward.[35] These data established that regulatory mechanisms for serum IgE levels were already in place at birth despite the very low cord blood values that increase more than 30-fold by 9 months and 300-fold by 11 years of age. IgE levels (once values are above the threshold of detection) provide a log normally distributed variable in the population in keeping with its origin from B cells that class switch as they proliferate in response to antigen stimuli.

Two allergy-related events have shown significant relations to cord blood IgE. The first is the direct predictive relation to the development of eczema in the first year of life.[36] Second is the changing relationship of cord IgE to the prevalence of acute viral LRIs, inverse in the first year of life[36] and direct in the third year.[37] This changing relationship led to further analyses showing that both the children beginning to have LRIs in the third year and those starting with LRIs in the first few years of life and continuing to have them were the children most susceptible to chronic wheezing and asthma.

Cord blood IgE levels did not show an association with the development of asthma; thus the regulatory mechanisms described above appear to be independent of the development of asthma. However, subsequent studies[38] showed that IgE levels were increased acutely during the first LRI in those children who went on to wheeze persistently compared to those who wheezed transiently and only with LRIs in the first year or two of life (Fig 3, *A*).[38] These data support the possibility that children destined to develop persistent wheezing are already "programmed" immunologically before the first LRI to respond differently to a respiratory viral infection. Further support for the hypothesis is provided by this same study that showed that blood eosinopenia, long known to occur with many viral illnesses, did not occur in those children who went on to become persistent wheezers (Fig 3, *B*).[38] IgE levels obtained at ages subsequent to birth do show a relation to asthma; thus IgE levels appear to be regulated both by mechanisms evident at birth that are independent of asthma and by mechanisms regulating responses to environ-

mental insults that enhance or reveal susceptibility to asthma. Whether IgE levels in the latter situation contribute to or simply occur in parallel to asthma development remains an important issue for further study.

The TCRS also provided the opportunity to define the major offending allergens (as detected by skin test responses) in relation to persistent wheezing or asthma at age 6 years.[39] The only allergen skin test responses significantly associated with physician-diagnosed asthma were those to *Alternaria alternata*. Bermuda grass was a much more frequent sensitizer in the general population but did not show a significant association to asthma, and other common local aeroallergens did not also. Interestingly, and despite its frequent association with asthma worldwide, *Dermatophagoides farinae* was an infrequent sensitizer and was not significantly associated with asthma in the TCRS enrollees raised in the Tucson semiarid environment.

As described in the previous genetics section, the TCRS has also provided a rich source of genetic-based immune regulation data that have altered the original premise of a causative role for IgE in asthma development because the data showed that, despite the marked association of total serum IgE with asthma prevalence, the 2 had distinct inheritance patterns. Total serum IgE levels provided evidence for a major gene inherited via a codominant Mendelian mechanism.[25] The familial pattern of asthma inheritance, in contrast, was typical of a complex disease (without evidence for a major gene), and removing total IgE from the analysis did not affect the results.[26] Also, the prevalence of asthma in children, although significantly influenced by parental asthma, was found to be unrelated to parental IgE level (Fig 4; unpublished observations).

As an alternate to the concept that IgE is a major causative factor of asthma, the hypothesis has been put forth that asthmatic airway inflammation may be brought about by T_H2 cells with activities that are independent of their role in initiating IgE synthesis. To test this possibility, we sought evidence for a link between asthma and T_H2 cytokine production from peripheral blood T cells. These studies showed a direct relation between the capacity to produce IL-4 and IgE level[40] and an indirect relation between the capacity to produce IFN-γ early in life and subsequent immediate skin test reactivity.[41] However, they did not show an association between asthma and T_H2 biased cytokine production[40] (manuscript in preparation). Thus, the TCRS studies have altered the concept of IgE acting in a causative role in the development of asthma and alternatively suggest that the close association of IgE levels and asthma might occur by the concept in reverse, ie, as a result of asthma regulating IgE levels by mechanisms different from the IgE regulating mechanisms in the nonasthmatic population.

Further analyses provided evidence for 2 subphenotypes of asthma, one diagnosed most commonly before age 3 years, showing risk related to early life LRIs, high rate of remission between ages 6 and 11 years, no relation to skin tests, but still related to total IgE. A second form of asthma defined by those with positive *Alternaria* skin

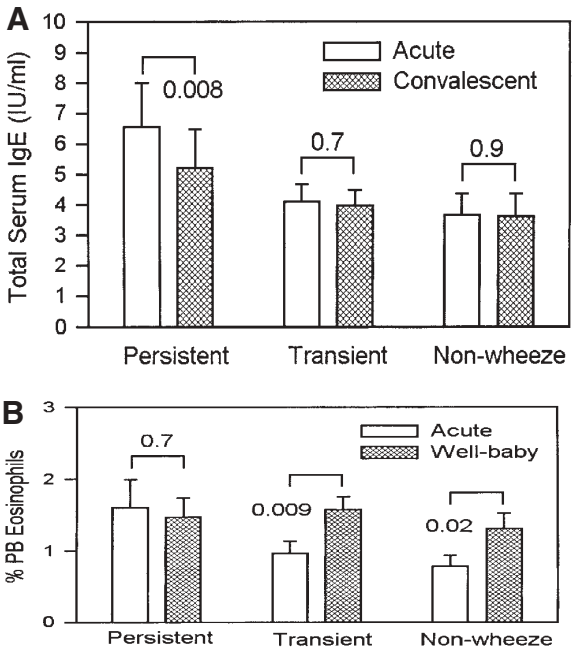

FIG 3. Differences in total serum IgE **(A)** and peripheral blood *(PB)* eosinophil levels **(B)** during and after the first LRI for children grouped as to their subsequent age 6 wheezing patterns. Group sizes for paired bars from *left* to *right* are 49, 88, and 42 for **(A)** and 33, 66, and 43 for **(B)**. Note that children who go on to wheeze chronically do show an acute increase in serum IgE with LRI and do not show the eosinopenia typical of the LRIs in the other children. (From: Martinez FD, Stern DA, Wright AL, Taussig LM, Halonen M. Differential immune responses to acute lower respiratory illness in early life and subsequent development of persistent wheezing and asthma. J Allergy Clin Immunol 1998;102:915-20.)

tests was diagnosed most commonly during or after age 3 years, was unrelated to early life LRIs, did not remit significantly by age 11 years, and was directly associated with total IgE.[42] Whether these forms of asthma occur in distinct subpopulations with different bases of susceptibility seems likely but remains to be determined.

The factors that cause asthma remain unidentified. Evidence is accumulating that both environmental and genetic factors can interact through the innate immune system to provide inhibition of asthma in those individuals who might otherwise be susceptible. Large and variable environmental exposures may influence the immune system (which is in turn genetically variable among individuals) in ways that result in varying degrees of resistance to the development of asthma and allergic manifestations. Recent studies have shown the importance of single nucleotide polymorphisms in the promoter region of the gene for the lipopolysaccharide receptor, CD14, in regulating the level of soluble CD14 and IgE level.[43] Although in our studies a relationship of CD14 genotype to the prevalence of asthma or allergy was not evident, this may have been due to sample size because others have reported a relationship to allergic symptoms.[44] It is unlikely that single nucleotide polymorphisms in a single gene will account for the complex disease phenotype of asthma. Additional studies of this

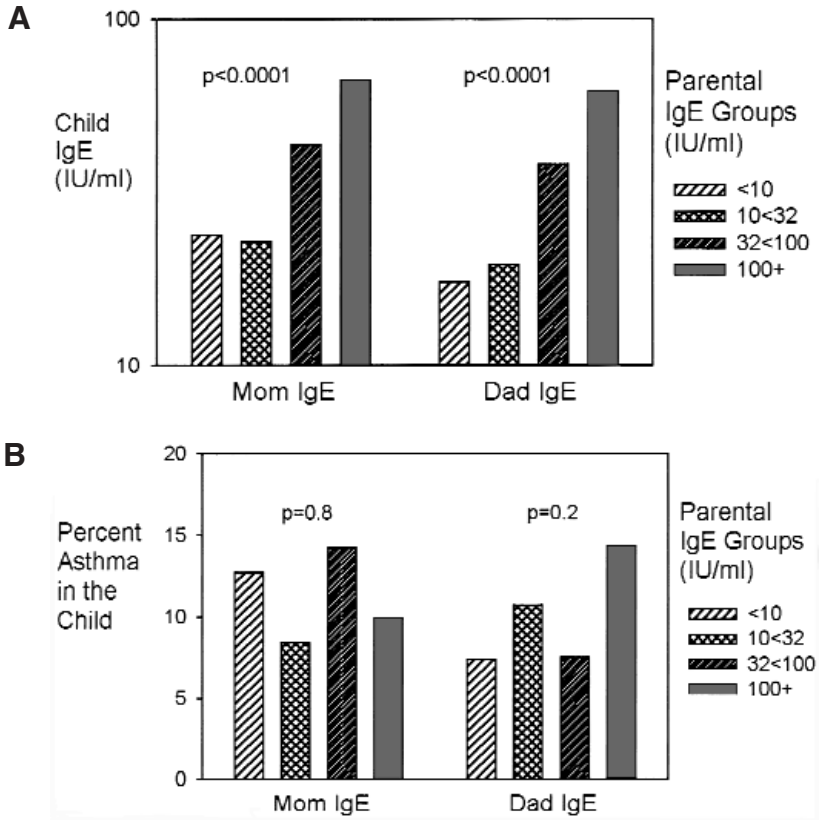

FIG 4. Relationship of child's serum IgE **(A)** and the child's prevalence of asthma **(B)** at age 6 to parental IgE levels. Parental IgE levels are grouped in half log intervals. Ordinate for **(A)** is logarithmic with values given as antilogs. Group sizes in **(A)** from low to high IgE groups for mom are 124, 111, 132, 133, and for dad are 55, 75, 108, 146; group sizes for mom in **(B)** are 181, 178, 190, 172 and for dad are 81, 103, 159, and 196. Note that parental IgE levels significantly influence the IgE level in the children but not the prevalence of asthma.

type are ongoing to identify the role of genetic diversity in the gene for CD14 and in genes for other factors that influence immune responses in ways that may significantly impact the balance between susceptibility and resistance to allergic disease.

PHYSIOLOGIC STUDIES

The prospective measurement of lung function has enabled the TCRS to characterize the impact of wheezing illness on lung development from infancy through adolescence. These measurements have also been central to the evolution of the hypothesis that asthma is a developmental disease determined by the interaction of the immune and respiratory systems in early life. Before the design of the TCRS, several epidemiologic studies had demonstrated a strong association between childhood respiratory troubles and diminished lung function in adulthood.[45] Because these studies were retrospective in nature, however, they suffered from several limitations including substantive recall bias.[46] Also, they could not determine whether early childhood respiratory illness led to decreases in lung function or the converse, ie, that diminished airway conductance led to an increased risk for wheezing in response to viral infections. The TCRS was designed to answer this question by recruiting subjects at birth; thus the relationship between respiratory illness and lung function development has been explored in a truly prospective manner.

Infant lung function was measured by using safe, noninvasive methods including rapid thoracic compression for the measurement of forced expiratory flow, helium dilution measurement of functional residual capacity (FRC), forced oscillation measurement of respiratory conductance, and tidal breathing analysis.[3,47] The rapid thoracic compression method allows the measurement of maximal forced expiratory flow at functional residual capacity ($V'_{max}FRC$) from partial expiratory flow-volume curves. Early in the development of this methodology, additional non-TCRS subjects were recruited to characterize the growth and development of the lung in healthy infants from 8.5 to 25 months after conception.[47,48] This study demonstrated that the highest size-corrected flows ($V'_{max}FRC/FRC$) were seen in newborns and healthy premature infants with values of 2.5 to 2.7 FRC/s. However, with the rapid postnatal growth of lung volume, size-corrected flows decreased by 50% to 1.2 FRC/s, a value that is comparable to older children and adults and that remained relatively constant from 13 to 25 months after conception. Finally, female infants had higher absolute and size-corrected flows than did male infants.

These findings suggested a physiologic basis to the clinical observation that most infantile wheezing lower respiratory illnesses (WLRIs) occur after the neonatal period and that male infants appear to have more severe, if not more prevalent, WLRI. They also suggest that the increased prevalence of WLRI early in life cannot be explained simply by a global reduction of airway conductance in all infants relative to older children and adults.

These infant lung function methodologies were developed relatively late in the TCRS recruitment period; thus only a subset of the 1246 TCRS infants were eligible for lung function testing. Analysis of 124 TCRS infants who had lung function measured before any LRI has led to a greater understanding of risk factors for WLRI in the first 3 years of life.[3] Infants who went on to have at least one WLRI in the first year of life demonstrated diminished respiratory system conductance and alterations in tidal expiration compatible with smaller airways before any LRI. Analysis of WLRI outcomes during the first 3 years of life further supported the relationship between premorbid decreases in lung function and increased risk for WLRI. Those infants who wheezed at least once during the first year of life and had at least 1 additional lower respiratory tract illness by 3 years of age demonstrated 22% lower initial levels of respiratory system conductance and 25% lower initial levels of $V'_{max}FRC$. On the basis of these studies, we concluded that diminished airway function both precedes and predicts recurrent wheezing in the first 3 years of life. This suggests that at least some of the reduction in maximal forced expiratory flow seen in adults who had childhood respiratory troubles may be due to premorbid differences in lung function as opposed to WLRI-associated damage to the developing airway.

Another potential explanation for the high prevalence of WLRI in infancy may be a relative increase in airway reactivity as compared to older children and adults. Airway response to cold, dry air challenge was assessed in 30 healthy infants compared to 12 control subjects who had $V'_{max}FRC$ measured in a similar manner but without any challenge.[49] Although the control group showed no significant change in $V'_{max}FRC$, the cold, dry air group had a mean reduction in $V'_{max}FRC$ of 18%, ie, about 1 intrasubject standard deviation. Combined with data from Tepper,[50] this suggests that even healthy infants have relatively reactive airways. Further, Young et al[51] have shown that in some infants this reactivity may be related to a family history of asthma and parental smoking. Thus, the long-held view that infants do not demonstrate airway reactivity and only wheeze as a result of mechanical obstruction by mucosal edema or luminal secretions has been effectively disproven by these studies of infantile airway response. Indeed, work by Shen et al[52] in rabbits has suggested that airway responsiveness to a nonspecific challenge decreases with age. Such a decrease in airway reactivity with age may explain the decrease in the frequency of wheezing illnesses with age in children who had RSV infections in infancy.[53]

Follow-up of 826 TCRS subjects with data from the first 3 years of life and at age 6 years has demonstrated, however, that diminished growth in airway function can occur in association with recurrent wheezing respiratory tract illness.[15] At the age of 6 years, 51.5% of all children had never wheezed (never wheeze), 19.9% had had at least 1 WLRI during the first 3 years of life but had no wheezing at 6 years (transient wheeze), 15% of all children had no wheezing in the first 3 years but had wheezing at 6 years of age (late wheeze), and 13.7% had wheezing both before 3 years of age and at 6 years (persistent wheeze). Thus, of those subjects who had wheezing before age 3 years, 59% had stopped wheezing by age 6 years. Not surprisingly, this early transient wheeze group had diminished lung function both in infancy and at 6 years of age when compared to children who never wheezed. The persistent wheeze group had $V'_{max}FRC$ values in infancy that were no different from those of the children who never wheezed. By age 6 years, however, the persistent wheeze group had the lowest lung function of the 4 groups with a significant reduction in $V'_{max}FRC$. Lung function in the late wheeze group was no different from that of the never wheeze group at both ages. Fig 5 shows $V'_{max}FRC$ at infancy and 6 years of age expressed as the mean Z-score for each of the 4 groups. The persistent wheezing group demonstrated a decline in lung function from infancy to 6 years, perhaps as a result of recurrent or ongoing airway damage during this period of rapid lung growth. Compared to children who never wheezed, the persistent wheeze group also had higher IgE levels at 1 and 6 years of age and were more likely to have mothers with a history of asthma and to have a physician's diagnosis of asthma. This suggests that the growth of airway function in the persistent group may have been modified by chronic airway inflammation. Although the observed deficits in $V'_{max}FRC$ could have been due to recurrent viral illness in the first 3 years, this seems unlikely because it was not seen in the transient wheeze group, who actually tended to improve their lung function (Fig 5). An important question at this time is whether this deficit in lung function and risk for asthma in high risk children could be prevented by regular anti-inflammatory therapy during the preschool years.

Airway reactivity at age 6 years was assessed using a cold, dry air challenge.[54] Hyperresponsiveness to cold air at age 6 years was associated with the subsequent development of asthma from age 6 to 11 years; however, this was not significant after adjusting for atopy and mild wheezing at age 6. This suggests that the hyperresponsiveness was a biomarker for the development of asthmatic airways due to ongoing allergic inflammation but not an independent risk factor for asthma. Subjects returned for spirometry and methacholine challenge testing at 11 years of age; they also performed 2 weeks of twice daily home peak flow measurement. Neither methacholine hyperresponsiveness nor increased peak flow variability was associated with wheezing that occurred only in the first 3 years of life. However, both measures of airway reactivity were increased in children who wheezed at both 6 and 11 years of age. Peak flow variability was associated with wheezing up to 6 years of age but not at

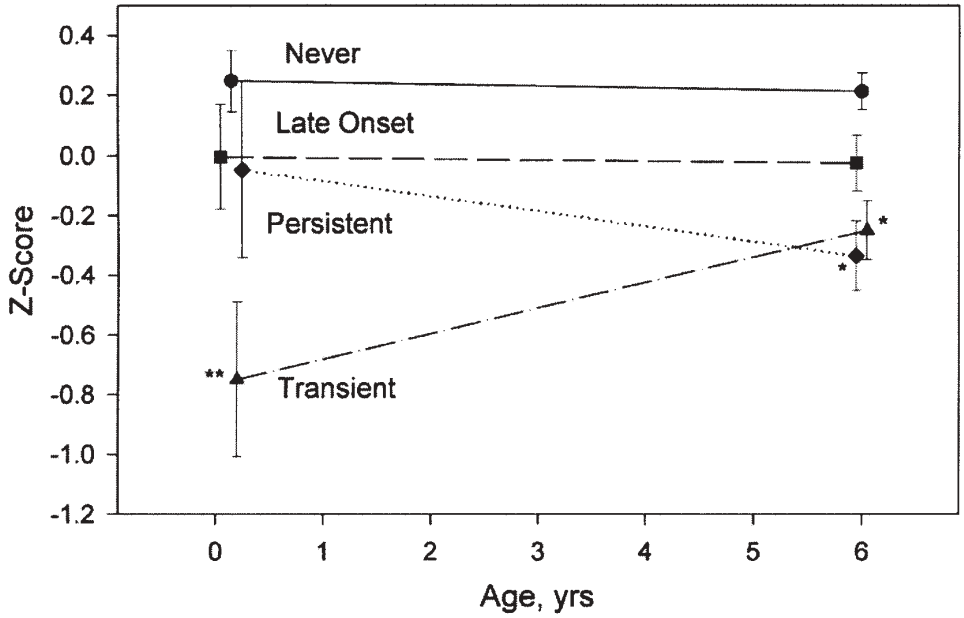

FIG 5. Lung function ($V'_{max}FRC$) at infancy and 6 years of age expressed in Z-scores by wheezing group: ●, never wheeze; ▲, transient early wheeze; ■, late onset wheeze; ◆, persistent wheeze. (*$P < .05$ vs never wheeze group; **$P < .05$ vs never, late, and persistent wheeze groups.)

age 11 in nonatopic children. Methacholine hyperresponsiveness was seen more frequently in boys and was strongly associated with serum IgE levels at age 6 and 11 years. In contrast, peak flow variability was not related to either gender or serum IgE.[55] These findings have helped to confirm and further refine the 3 wheezing phenotypes seen in childhood, which will be discussed later.

Physiologic studies in the TCRS have also clarified the relationship between specific patterns of LRI in early life and later outcomes. The incidence of radiologically confirmed pneumonia in the TCRS population was 7.4% in the first 3 years of life,[56] and the most common etiology defined was RSV (36.4%). Children who had pneumonia were more likely to have a physician diagnosis of asthma by age 11 years and to have lower levels of $V'_{max}FRC$ in infancy and at age 6 years. Children who had RSV-associated LRI in infancy also demonstrated decreased FEV_1 and forced expiratory flow at 25% to 75% of forced vital capacity at age 11 years, which were partly reversible by bronchodilator administration. This suggests that pneumonia in early life is perhaps at one end of the spectrum of viral respiratory illness and that children at risk for later asthma are more likely to develop radiographic changes of air space disease that could represent true pneumonia or simply atelectasis. Although premorbid deficits in lung function could be demonstrated in children who went on to get pneumonia, the number of subjects in this group who had lung function measured in infancy was small, and more work needs to be done to elucidate whether the reductions in lung function seen later in life are predominantly premorbid or due to longer-term chronic airway inflammation in at-risk children.

CHRONIC COUGH, CROUP, OTITIS MEDIA, AND COLIC

Cough variant asthma, first described in 1972,[57] is considered to be a mild form of asthma frequently unrecognized, resulting in inadequate treatment.[58] Risk factors for recurrent cough in childhood and its relation to asthma were assessed in the TCRS. Findings suggested that recurrent cough in the absence of wheeze differs in important respects from asthma.[59] Children having recurrent cough without wheeze were not different from those without symptom for serum IgE levels, skin test response, size corrected forced expiratory flow, or percent decline in flows after cold air challenge. Conversely, those with recurrent cough and wheeze had significantly more respiratory illness, more atopy, lower flow at end-tidal expiration, and greater decline in lung function after cold air challenge than those with neither symptom. In addition, in multivariate analysis, parental smoking was the only significant risk factor for recurrent cough only, with an OR of 1.9 (95% CI, 1.1 to 3.5). In contrast, male gender (OR, 3.5; 95% CI, 1.9 to 6.6), maternal allergy (OR, 2.3; 95% CI, 1.2 to 4.2), wheezing LRIs in early life (OR, 4.0; 95% CI, 2.2 to 7.3), and high IgE level at age 6 years (OR, 2.4; 95% CI, 1.3 to 4.3) were all significant risks for recurrent cough with wheeze, compared to those with neither symptom. These results indicate that not all recurrent coughs are cough variant asthma.

Some retrospective studies have suggested that children with a history of croup may have an increased risk of developing asthma, atopy, or decreased pulmonary function.[60,61] The data gathered in the TCRS were

ideal to prospectively assess the long-term outcome of physician-diagnosed croup in early life. Fifteen percent of children had croup in the first 3 years of life; 10% of these also had wheezing, either with the croup (78%) or as a separate episode (22%); the remaining 5% had croup with no wheezing; 36% had an LRI other than croup, whereas 48% had no LRI.[62] No association was found between markers of atopy during the school years and croup in early life. However, children who had croup with wheeze and those with other LRIs had up to 3 to 4 times the risk of subsequent persistent wheeze and significantly lower levels of lung function in their first, sixth, and eleventh years compared with those with no LRI. Conversely, those with croup without wheeze had significantly higher inspiratory resistance before having an LRI compared with the other groups. These results suggest that croup is a heterogeneous disease, and that children younger than 3 years who present with croup may or may not be at increased risk of subsequent wheezing depending on the initial lower airway involvement, and pre-/post-illness abnormalities in lung function.

At the time of an LRI information was obtained on whether otitis media was also present. A total of 4757 otitis media episodes were recorded in record checks of 1013 infants in the first 3 years of life, 1961 of which were in the first year of life. Breast-feeding was found to be protective,[63] whereas environmental tobacco smoke was a risk factor.[64] Of the 1013 infants followed for their entire first year, 476 (47%) had at least one episode of otitis media and 169 (17%) had recurrent otitis media, defined as at least 3 episodes, 1 month apart, during any 6-month interval in the first year of life. Increasing duration and exclusivity of breast-feeding were associated with a significant decrease in the total otitis media episodes in the first and second 6 months of life and with a decreased risk of recurrent otitis media and nonrecurrent otitis media in the first year of life, independent of other risk factors considered. Infants who were breast-fed but received supplements before 4 months of age had approximately three fourths the risk of recurrent otitis media compared with the reference group who were not breast-fed at all or for less than 4 months. Those infants who were breast-fed exclusively for at least 4 months had one half the risk, and those breast-fed exclusively for 6 or more months had roughly one third the risk of developing recurrent otitis media. Heavy maternal smoking, 20 or more cigarettes per day, was a significant risk factor for recurrent otitis media (OR, 1.8; 95% CI, 1.0 to 3.1) but not for nonrecurrent otitis media, after controlling for other risk factors. In addition, if the infant weighed less than the mean weight (3.5 kg) at birth, heavy maternal smoking was associated with a 3-fold risk for recurrent otitis media (OR, 3.3; 95% CI, 1.7 to 6.4), after controlling for other risk factors.

Infantile colic, a common problem during the first months of life in otherwise healthy, thriving infants, is of unknown origin. Allergy to cow's milk protein has been implicated,[65] suggesting that children with a history of infantile colic may be at increased risk for developing asthma or atopy. In the CRS population there was no increased risk for asthma or wheeze at preschool and school ages for the 9% of infants with a pediatrician diagnosis of colic during the first 2 months of life.[66] There was no association between various markers of allergy (eg, allergic rhinitis, skin tests, total serum IgE) and colic. In addition, we found no relation between colic and breast- or formula-feeding (including cow's milk vs soy-based) in infancy.

WHEEZING SYNDROMES AND ASTHMA

One of the most important findings of the TCRS has been the description of distinct wheezing phenotypes that occur during childhood (Table VI).[15] Although there was the suspicion both from clinical practice and from clinical studies that not all children who wheezed at different times during the growing years had the same pathophysiology, it was only with further analyses of data from the TCRS that these different phenotypes were more extensively characterized. As a result, 3 main syndromes have been described (Fig 6).

Transient infant wheezers

Many children who wheeze during the first 2 to 3 years of life have only a few such episodes and do not wheeze after the age of 3 years. More than 80% of children who wheeze during the first year of life fall under this category; approximately 60% of those wheezing in the second year and 30% to 40% of those wheezing in the third year also belong in this group. These children, when characterized prospectively, are not more likely to have a family history of asthma, and they are not more likely to have atopic dermatitis, eosinophilia, high levels of IgE, or any other marker of an allergic diathesis (Table VI). The main risk factors for this condition, as found in the TCRS, are low levels of lung function before any LRI develops, maternal smoking during pregnancy, and a younger mother.[11] An important finding of the TCRS was that the lower levels of lung function these children had at birth, relative to their peers, improve with time but do not "catch up" with those of children who never wheezed during their growing years (Fig 5). This group of children were also not more likely to wheeze at the ages of 11 and 16 years when compared with children who had no reports of wheezing during the first 6 years of life.

What the fate of these children will be in adult life is difficult to predict, but they may be at increased risk of developing chronic obstructive pulmonary disease, particularly if they start smoking, because of smaller airways.

Nonatopic wheezers

A second group of children continue to wheeze beyond the third year of life after having had an LRI in early life. This group, which we initially called persistent wheezers, is in itself heterogeneous. Approximately 60% of these children are atopic at the age of 6 years, and about 40% are nonatopic.[15] The TCRS allowed us to study these nonatopic wheezers in relation to the etiolo-

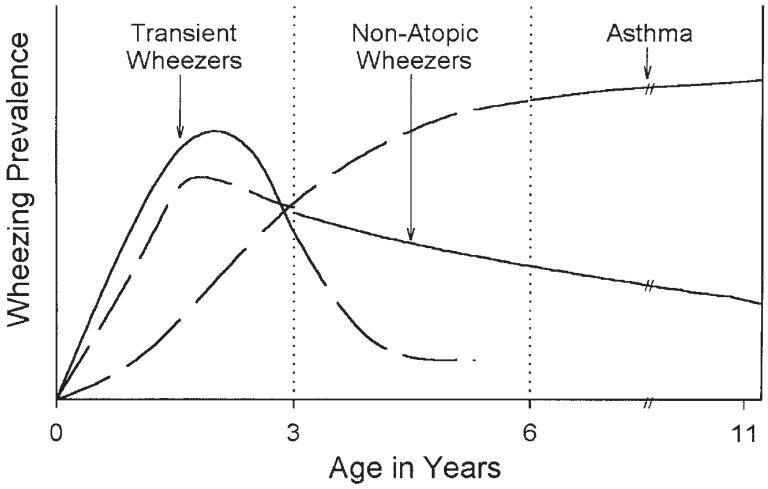

FIG 6. Hypothetical peak prevalence by age for the 3 different wheezing phenotypes. The prevalence for each age interval should be the area under the curve. This does not imply that the groups are exclusive. (Modification [with permission] of Figure 2 in: Stein RT, Holberg CJ, Morgan WJ, Wright AL, Lombardi E, Taussig LM, et al. Peak flow variability, methacholine responsiveness and atopy as markers for detecting different wheezing phenotypes in childhood. Thorax 1997;52:946-52).

TABLE VI. Factors associated with the wheezing phenotypes

	Never wheezed	Transient early wheezing (first 3 y only)	Late onset wheezing (only after 3 y)	Persistent wheezing (< 3 y and at 6)
Percent of total (number)	51.5% (425)	19.9% (164)	15.0% (124)	13.7% (113)
V'_{max} FRC (mL/s) in infancy [n]	123.3 [n = 67]	70.6 [n = 21]*	107.1 [n = 21]	104.6 [n = 16]
(95% CI)	(110.0-138.0)	(52.2-93.8)	(87.5-129.6)	(73.6-144.5)
V'_{max} FRC (mL/s) at age 6 [n]	1262.1 [260]	1097.7 [104]	1174.9 [81]	1069.7 [81]*
(95% CI)	(1217-1308)	(1035-1164)	(1111-1241)	(907-1146)
Total serum IgE (IU/mL) at 9 mo	3.4	3.7	3.8	5.2*
(95% CI)	(3.0-3.9)	(3.1-4.4)	(2.9-5.0)	(3.8-7.2)
Total serum IgE (IU/mL) at 6 y	28.1	31.0	42.1	65.6*
(95% CI)	(22.4-35.3)	(22.3-43.1)	(26.6-66.0)	(45.3-94.4)

*$P < .01$ for comparison with children who never wheezed.
Adapted from Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life: relation with lung function, total serum IgE levels and skin test reactivity to allergens. N Engl J Med 1995;332:133-8.

gy of their LRI in early life.[52] We found that children who had an RSV-LRI were 3 to 5 times more likely to wheeze at the age of 6 years, but this increased risk decreased significantly with age and was almost nonsignificant by the age of 13 years. Other viruses showed similar trends, albeit less consistent than those of RSV-LRI because of small numbers. Of interest was the fact that children who had an RSV-LRI in early life and continued to wheeze beyond the age of 3 years were not more likely to be atopic than other children.[52] The most important difference between this group and children who did not have an RSV-LRI was their lower levels of lung function measured at the ages of 6 and 11 years. Moreover, at the age of 11, a bronchodilator was given to these children, and the results were compared with those children who did not have an RSV-LRI. It was found that children with a history of RSV-LRI were much more likely to show a response to a bronchodilator, and, in fact, their lower levels of lung function completely reversed after bronchodilator, after which time FEV_1 was not significantly different in this group as compared to children who did not have RSV-LRIs.

These results suggested that nonatopic wheezers are probably more likely to develop acute airway obstruction in relation to viral infection because they have an alteration in the control of airway tone that determines this increased risk, and this abnormality in tone may decrease with age. Whether this alteration is present before birth or is the consequence of the RSV-LRI cannot, unfortunately, be determined from the TCRS data.

Atopic wheezers

As several other studies have shown during the last 20 years, the TCRS confirmed that most children who will go on to develop atopic asthma have their first symptoms during the first 6 years of life. Of interest was the fact that in Tucson, contrary to other environments, it was sensitization against *Alternaria* that showed the strongest association with this form of wheezing.[42] It was also of interest that this group of children could be divided into 2

subgroups: early atopic wheezers (who are the majority of what we have called in the past persistent wheezers), ie, those whose symptoms started during the first 3 years of life, and late atopic wheezers (whom in the past we have called late wheezers), ie, whose symptoms started after that age. Both groups were equally likely to be sensitized at the age of 6 years against common aeroallergens, but it was the group whose symptoms started before 3 years of age who showed the lowest levels of lung function at the ages of 6 and 11 years, and it was also this group who showed the highest levels of IgE at the ages of 6 and 11. It thus appears from these studies that, during the first 3 years of life, early initiation of symptoms and perhaps early allergic sensitization may be very important risk factors for more severe disease and for significantly higher deficits in lung function in individuals who develop recurrent episodes of airway obstruction.

ASTHMA PREDICTIVE INDEX

The above discussion has stressed the importance of developing methods to distinguish atopic wheezers from other infants and young children who wheeze in early life but are not destined to have the chronic, more persistent form of asthma-like symptoms. It is possible that, in the future, genetic markers will be used to perform this task. No such markers are yet available, however, and there was the need to test for the predictive capacity of a variety of phenotypic markers that could be used in everyday practice by asthma caregivers. We tested several such markers, all ascertained during the first years of life, and developed an Asthma Predictive Index.[67] To be positive for this index, children needed to have reports of recurrent episodes of wheezing during the previous year and either 1 of 2 major criteria (atopic dermatitis as diagnosed by a physician or physician-diagnosed parental asthma) or 2 minor criteria (peripheral blood eosinophilia, wheezing apart from colds, or physician-diagnosed allergic rhinitis). More than three fourths of all children with a positive index had symptoms consistent with active asthma at least once between the ages of 6 and 13 years, whereas 68% of those with a negative index never had symptoms consistent with active asthma during the school years. We concluded that the subsequent development of asthma can be predicted with reasonable accuracy by using simple, clinically based parameters.

FUTURE STUDIES

During the last 22 years, the TCRS has shown new information for our understanding of the natural history of wheezing phenotypes and asthma during the first years of life. The availability of such a wealth of information regarding events occurring during this crucial period for the development of asthma and allergies will continue to provide the basis of future studies in the TCRS. Areas of focus for the next 5 to 10 years include the following:

1. What factors occurring during childhood determine persistence of asthma beyond the growing years and into early adult life? Several studies have addressed this issue, but all started follow-up during the early school years. Our interest is to determine whether and how various factors, especially atopy, present in infancy and the preschool years can influence the way in which asthma remits, relapses, or persists during early adult years.
2. What is the role of genetic factors in the persistence of asthma into early adult life? The availability of a vast database on environmental factors that can potentially influence the persistence of asthma beyond the childhood years will allow us to determine potential interactions between these factors and genetic markers in many potential asthma-related genes that are being extensively studied in this population.
3. What are the determinants of rapid decline of lung function during the early adult years? Availability of longitudinal data starting at birth will allow us to address this very important issue. It is well-known that losses in lung function that occur during the plateau phase or early during the physiologic decline in lung function with age are very important determinants of subsequent risk for chronic obstructive pulmonary disease. The way in which exposures in early life interact with genetic factors and with the course of asthma and allergies during childhood to determine lung function in early adult life has not been thoroughly studied, and the TCRS is ideal to address these issues.
4. What are the risk factors for incident asthma during the early adult years? Longitudinal studies have suggested that a small number of subjects develop asthma symptoms for the first time during early adulthood, but in most of these studies follow-up started during the school years. The TCRS is the first such study in which follow-up was started at birth, and we will thus have data available that will allow us to determine the role of various types of wheezing in early life and other events occurring during childhood in determining asthma of apparent adult onset.

As can be seen from these few examples, the TCRS intends to continue to provide the caregivers of individuals with asthma and the scientific community with important information regarding the natural history of and the risk factors for recurrent airway obstruction and chronic obstructive pulmonary disease. We are convinced that these studies will allow us in the upcoming years to better design strategies for the primary and secondary prevention of asthma and perhaps will also allow us to address the beginnings of chronic obstructive pulmonary disease, which is today one of the 5 main causes of death in the United States.

A large number of people have been involved with this study during the past 22 years. We thank these technicians, fellows, graduate students, post-docs, statisticians, typists, et cetera, for all of their assistance. Special mention needs to be made of the study nurses, Bonnie Presbrey, Marilyn Smith Lindell, and Lydia de la Ossa, who have been involved in the study for many years. We also wish to thank Group Health Medical Associates pediatricians, who were most instrumental and helpful in enrolling the neonates and their families and obtaining the well-child and acute lower respiratory tract illness data.

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