

Epidemiology of Allergic Rhinitis

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“Eat dirt!” The recommendation of the television program was only partly facetious. Specialists featured in the British program described evidence for the “hygiene hypothesis” to explain increases in prevalence of allergy and asthma (1). What is the evidence of changes in prevalence of allergic rhinitis, and how can we best explain differences in prevalence?

Rhinitis

Allergic rhinitis is an inflammation of the nasal mucosa characterized by nasal congestion and discharge, sneezing, nasal itching, often with ocular itching and conjunctival injection. Seasonal allergic rhinitis or hay fever typically occurs in association with seasonal allergens. Perennial allergic rhinitis may be owing to perennial exposure to allergens such as animals or dust mites, or seasonal exposure to multiple pollens prevalent at different times of the year.

Nonallergic rhinitis can be due to infection but also may include vasomotor rhinitis and eosinophilic nonallergic rhinitis, which is more frequent in adults than children. Nasal obstruction also can be owing to choanal atresia in infants, adenoidal hypertrophy, nasal septal deviation, nasal polyposis, encephalocele, tumors, chronic cocaine abuse, or rhinitis medicamentosa (2,3).

Most epidemiologic surveys have depended on self-reported allergic rhinitis not further defined.

Table 1
Current Prevalence (%) of Allergic Rhinitis in the United States at the Times of Various Surveys

Reference	Year	Location	Number	Age	Seasonal	Perennial	Combined
Freeman	1964	Denver, CO	2235	8th grade 12th grade	15.9 21.5	7.3 5.6	
Broder	1962-1965	Tecumseh, MI	9226	Males: 0-4 5-9 10-15 16-24 25-34 35-44 45-54 55-64 65-74 75+ Overall			Probable 1.4 4.4 7.6 12.0 9.6 8.4 10.6 11.2 7.6 8.9 7.8
				Females: 0-4 5-9 10-15 16-24 25-34 35-44 45-54 55-64 65-74 75+ Overall			Suspect 1.1 2.4 1.2 3.2 6.4 5.2 3.3 3.5 0.0 0.0 3.1
							1.0 3.5 7.8 12.5 12.0 11.2 11.2 7.8 7.6 4.3 8.2

Table 1
Continued

Reference	Year	Location	Number	Age	Seasonal	Perennial	Combined
Hagy	1962–1963	Providence, RI	1836	College freshmen	21.1		
Settipane	1985		1021	40–42	30.9	5.2	
Turkeltaub	1976–1980	National	12,742	12–74	W:9.8 B:8.1	9.5	
(NHANES II)					W:20.4 B:19.2		
Wright	1986–1990	Tucson, AZ	747	6	42		
Nathan	1993	National	22,285	All	8.2	9.9	18.3
					8.8	5.4	14.2

Prevalence in the United States

In 1963, a mail questionnaire survey of eighth and twelfth-grade students attending Denver public schools disclosed current prevalence of allergic rhinitis in 15.9% of 960 eighth-grade students (14.7% of girls and 17.1% of boys) and perennial allergic rhinitis in an additional 7.3% (7.6% of girls, 7.0% of boys) (*see* Table 1) (4). Current prevalence of seasonal allergic rhinitis among 1275 twelfth-grade students was somewhat higher at 21.5% (18.0% of girls, 24.7% of boys), whereas 5.6% had nonseasonal allergic rhinitis (4.4% of girls, 6.8% of boys.) Onset of seasonal allergic rhinitis had occurred before 5 yr of age in 29% (before 2 yr of age in 6%) and at 5–10 yr of age in 42%. Perennial allergic rhinitis had started before 5 yr of age in 38% (before 2 yr of age in 12%) and at 5–10 yr of age in 34% (4). Earlier seasonal allergic rhinitis had resolved in only 6.8% of these adolescents; perennial allergic rhinitis, in 4.4% (5).

Prevalence of allergic rhinitis may have been somewhat greater in Denver than some other communities, including Tecumseh, MI, where Broder et al. surveyed the population from 1959–1960 and again from 1962–1965 (6). Trained interviewers collected data from 82% of the population in the second survey, and physicians then reviewed the questionnaires, completed physical examinations, and established diagnoses. Diagnostic criteria for allergic rhinitis were a report of hay fever, sinus trouble, or persistent nasal symptoms with at least two of three other features: 1) associated ocular, nasal, or throat itching or burning, watering, or redness of eyes; 2) attribution to exposure to allergen; 3) diagnosis of allergic rhinitis or hay fever by the examining physician. A diagnosis of “suspect allergic rhinitis” was established by a report of hay fever, sinus trouble, or persistent nasal symptoms together with either attribution to allergenic exposure or diagnosis by the examining physician or alternatively when hay fever was reported together with the symptoms of feature 1. Persistent nasal symptoms or sinus trouble was accepted as indicative of allergic rhinitis only when one of the other confirmatory features was diagnosis by the physician.

The survey disclosed a current prevalence across all ages of 7.8% of males with suspected allergic rhinitis in an additional 3.1% and 8.2% of females with suspected allergic rhinitis in an additional 2.7%. Current prevalence peaked at 16–24 yr of age at 12% of men with suspected allergic rhinitis in an additional 3.2% and 12.5% of women with an additional 3.1% with suspected allergic rhinitis (*see* Table 1).

Cumulative prevalence also peaked for men at 16–24 yr of age at 16.3% with suspected allergic rhinitis in an additional 3.8% and for women at 25–34 yr of age at 15.3% with suspected allergic rhinitis in an additional 3.9% (6).

In 1962–1963, a questionnaire survey of 1836 Brown University freshmen disclosed seasonal allergic rhinitis in 21.1% (7). Allergic rhini-

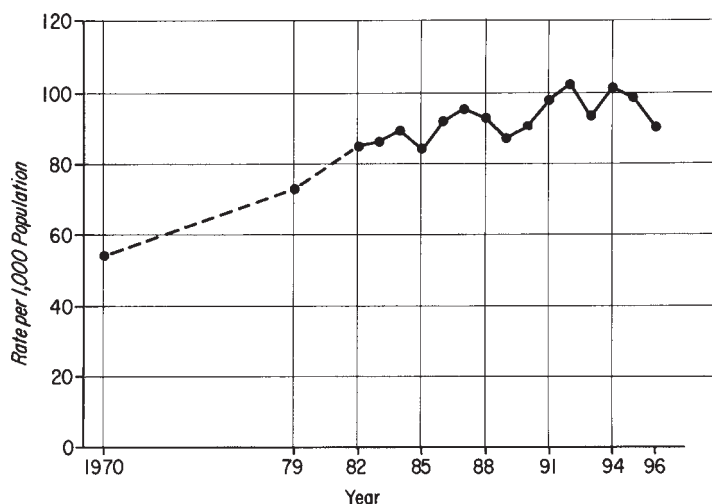


Fig. 1. Prevalence of hay fever without asthma in the United States in 1970, 1979, and 1982–1996 from National Health Interview Surveys, based on responses to the question, “During the past 12 months did anyone in the family have hay fever?”

tis or hay fever was defined by histories of watery, itchy eyes, rhinorrhea, and sneezing that had occurred during the same seasonal period for at least two consecutive years. There was nonseasonal allergic rhinitis in 5.2%.

The second National Health and Nutrition Examination Survey (NHANES II) of 1976 through 1980 was a representative national sample of the noninstitutionalized civilian population of the United States. It included 12,742 adolescents and adults 12–74 yr old for whom complete data were available for prevalence of allergic (seasonal) rhinitis and chronic rhinitis (8). Allergic rhinitis was defined as physician-diagnosed hay fever that was active or frequent nasal or ocular symptoms that had varied by season and pollen exposure during the previous 12 mo apart from colds or the flu (9). Chronic rhinitis was defined as frequent nonseasonal nasal or ocular symptoms during the previous 12 mo apart from colds or the flu.

Prevalence of seasonal allergic rhinitis was 9.8% among whites 12–74 yr of age and 8.1% among blacks (8). Prevalence of chronic rhinitis was 20.4% among whites and 19.2% among blacks. Both allergic rhinitis and asthma occurred in 2% of whites and 3.1% of blacks (8).

The NHANES II included 4295 whites 6–24 yr of age. Among these self-reported allergic rhinitis increased with age from 6% at 6–11 yr of age to 9% at 18–24 yr of age (9). Prevalence of chronic rhinitis increased from 15% at 6–11 yr of age to 17% at 18–24 yr of age (9).

The Tucson Children’s Respiratory Study, however, disclosed 42% of 747 children followed for their first 6 yr of life until 1986–1990 had

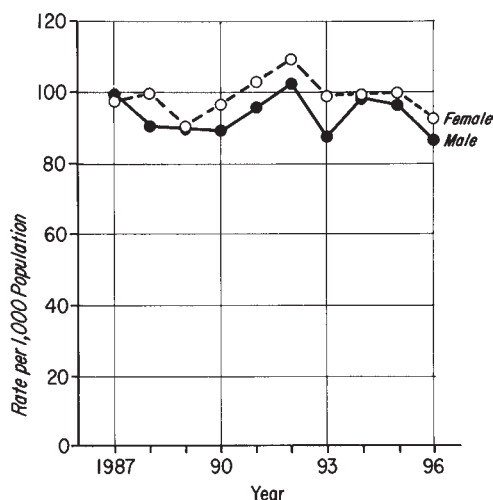


Fig. 2. Prevalence of hay fever without asthma in the United States, 1987–1996, by sex at less than 45 yr of age, from National Health Interview Surveys.

physician-diagnosed allergic rhinitis (10). Physicians had diagnosed allergic rhinitis in 7% of the 747 children by 6 mo of age and in an additional 14% by 12 mo of age. At 6 yr of age an additional 21% of children had rhinitis not considered allergic. Prevalence of rhinitis may be higher in Arizona than other parts of the country because of a different genetic pool. Among families prone to respiratory illnesses, there may be a perception that the climate of Arizona is salubrious.

National Health Interview Surveys have indicated increases in prevalence of hay fever from 5.42% in 1970 to 10.22% in 1992 with some stabilization since then (*see* Fig. 1). Health Interview Surveys estimate current prevalence of certain chronic conditions from data collected from a probability sample of the civilian noninstitutionalized population of the United States. Personnel of the U.S. Bureau of the census conduct the household interviews. They asked about hay fever in 1970 and each year since 1979. The estimates are for hay fever without asthma. Inclusion of those with asthma also would have increased the estimated prevalence of hay fever. The NHANES II (1976–1980) indicated 2.0% of whites and 3.1% of blacks 12–74 yr of age had both allergic rhinitis and asthma (8). Nevertheless, these estimates from the nationwide Health Interview Surveys are lower than prevalence reported by others, possibly owing to the method of collection of data. Health Interview Surveys include many other questions regarding acute and chronic conditions unrelated to allergic rhinitis (11). It is important that this periodic collection of data by consistent methods has indicated increases in prevalence at least until 1992 (Fig. 1).

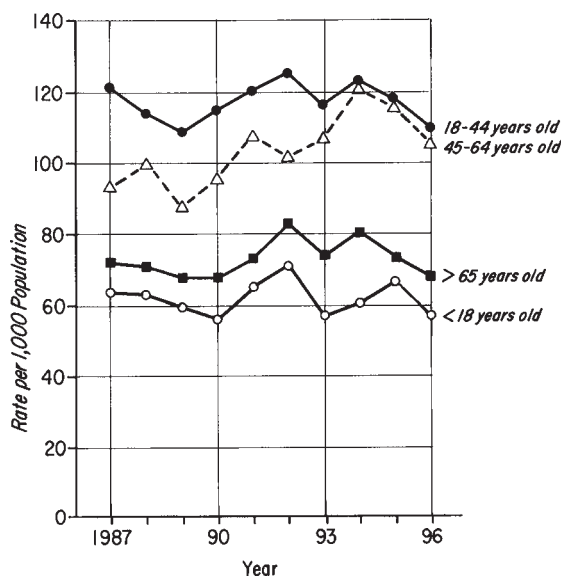


Fig. 3. Prevalence of hay fever without asthma in the United States, 1987–1996, by age, from National Health Interview Surveys

These trends have been similar for both sexes. In 1970 prevalence over all age groups was 5.13% for males and 5.69% for females. By 1992, this had increased for males to 10.24% at less than 45 yr of age, 9.82% at 45–64 yr of age, and 6.23% at 65 yr of age and older. The increases for females in 1992 were to 10.92% at less than 45 yr of age (*see* Fig. 2), 10.48% at 45–64 yr of age, and 9.76% at 65 yr of age and older.

Prevalence of hay fever has been lower in children than adults and lower after 65 yr of age than in younger adults (*see* Fig. 3), confirming the observations of Broder et al. (6) in a single community. Increases in prevalence have occurred in all age groups. Prevalence in 1970 was 3.43% at less than 17 yr of age, 7.80% at 17–44 yr of age, 5.20% at 45–64 yr of age, and 3.72% after 65 yr of age (11). Prevalence of hay fever has been higher among whites than blacks at least since 1987 (*see* Fig. 4). Higher prevalence has been associated consistently with higher family incomes since 1970 (*see* Fig. 5). Prevalence has tended to be slightly higher in the South and West than in the Northeast and Midwest (*see* Fig. 6).

Redesign in the National Health Interview Survey in 1997 included a change in the relevant question from, “During the past 12 months did anyone in the family have hay fever?” to “During the past 12 months have you been told by a doctor or health professional that you had hay fever?” This change might have been expected to decrease reported prevalence of hay fever, but preliminary data for 1997 indicate slight additional increases to 9.55% (owing to increases at less than 18 yr of

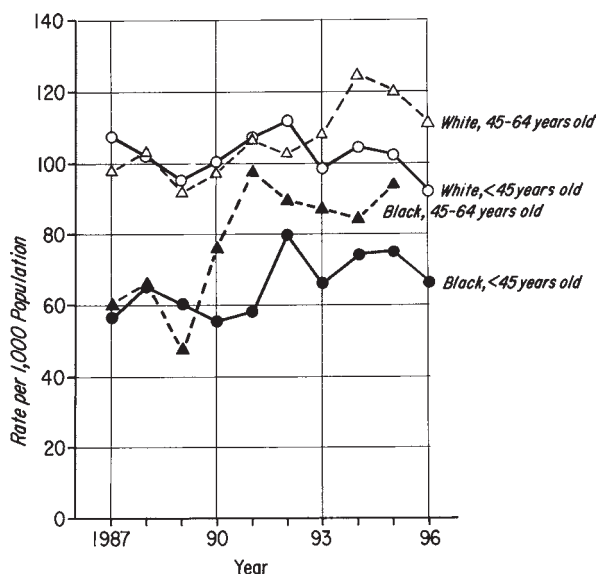


Fig. 4. Prevalence of hay fever without asthma in the United States, 1987–1996, by race and age, from National Health Interview Surveys.

age from 5.67% in 1996 to 10.34% in 1997) and slight increases in the Northeast, Midwest, and West (D. Blackwell, National Center for Health Statistics, personal communication).

Another nationwide survey agreed with the 1993 Health Interview Survey estimate of prevalence of hay fever without asthma of 9.34%. The 1993 self-administered questionnaire survey of 1065 respondents represented a base population of 22,285, 92% white (the resident population of the US was approx 83% white in 1993 [12]). This national survey indicated a prevalence of physician-diagnosed hay fever of 8.2%, rhinitis in 4.2%, and persistent stuffy nose in 5.7%, for a total of 18.3% with possible allergic conditions of the eyes, nose, or throat (13). There were possible sampling errors in this survey. An initial screening questionnaire was sent to 15,000 households randomly selected from a nationwide panel of approx 200,000 households; there was a 66.3% response. The detailed questionnaire then was sent to “a balanced sample” of 1450 people, from whom the response rate was 73.4%. Nevertheless, the report of self-diagnosed seasonal rhinitis by 8.8% differs little from the Health Interview Survey estimate of 9.34% for the same year. An additional 5.4% reported self-diagnosed perennial allergic rhinitis (13).

Our national Health Interview Surveys indicate prevalence of seasonal allergic rhinitis has been near 10% since 1992, having nearly

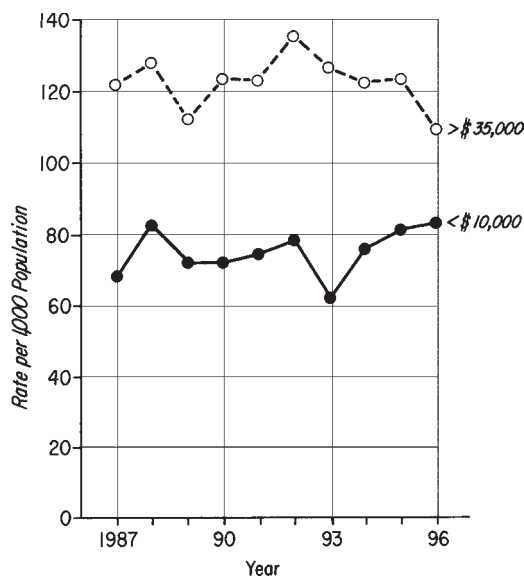


Fig. 5. Prevalence of hay fever without asthma in the United States, 1987–1996, by family income, from National Health Interview Surveys.

doubled since 1970 (Fig. 1). Prevalence of perennial allergic rhinitis probably is double that of seasonal allergic rhinitis among young adults (8). Earlier reports of higher prevalence probably were owing to differences in methods of collection of data, differences in allergenic exposure, and differences in family income that may relate to allergenic exposure or other risk factors.

Prevalence Around the World

Prevalence of allergic rhinitis also has increased in the United Kingdom. Interviews of parents of 11,195 children born in England, Wales, and Scotland during 1 wk of March, 1958, and 9,387 born 1 wk of April, 1970, disclosed 16 yr later in 1974 and 1986, respectively, increases in 12-mo period prevalence of allergic rhinitis or hay fever from 12.0% in the earlier cohort to 23.3% in the later cohort (14). Prevalence had nearly doubled (prevalence ratio 1.93, 95% confidence interval [CI] 1.82–2.06). The current prevalence of eczematous rashes also increased from 3.1% in the earlier cohort to 6.4% in the later cohort (prevalence ratio 2.04, 95% CI 1.79–2.32).

Prevalence of hay fever was significantly greater among young people of higher birth order and those who had been breastfed for more than 1 mo (14). Prevalence decreased sharply between social classes I (professional and managerial) and V (unskilled) in agreement with differences by family income in the United States (see Fig. 5) (11). This

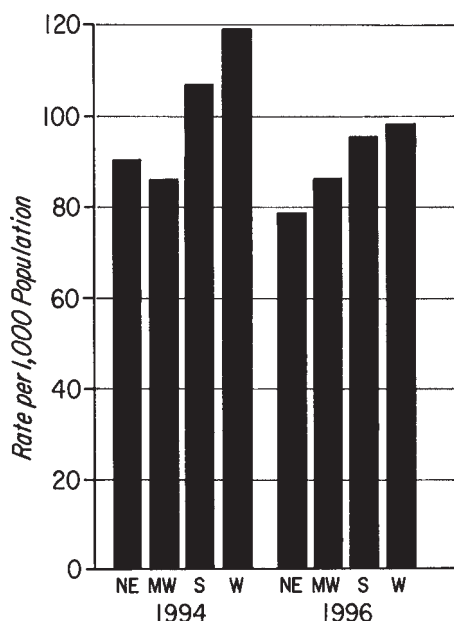


Fig. 6. Prevalence of hay fever without asthma in the United States, 1994 and 1996, by region, from National Health Interview Surveys. NE, Northeast; MW, Midwest; S, South; W, West.

observation disagrees with data from our NHANES II, possibly because of insensitivity of classification only into those above or below the poverty index (6).

Prevalence of hay fever in this British study increased significantly with maternal age up to 30–34 yr and was lower among adolescents whose mothers had smoked during their pregnancy (14). After adjustment for these factors, the relative odds of hay fever comparing 1986 with 1974 increased from 2.23 (95% CI 2.05–2.43) to 2.40 (95% CI 2.19–2.63). Overall these variables did not account for the increase in prevalence of hay fever in 1986 compared with 1974, but the authors speculated correlates of these variables that have changed across time might have contributed to the increase in prevalence of hay fever (14).

Interviews in 1981 of 12,355 members of the British cohort born during the same week of March, 1958, disclosed a current prevalence of hay fever at 23 yr of age of 16.5% (15). Prevalence fell with increasing family size when they were 11 yr old and was lower among offspring of unskilled and semiskilled manual workers than professional, managerial, and intermediate social classes. The number of older children in the household had a greater effect on likelihood of allergic rhinitis at 23 yr if age than the number of younger children at 11 yr of age had on prevalence at 23 yr of age.

Those who were regular smokers at 23 yr of age reported less hay fever than nonsmokers (15). Prevalence of hay fever among ex-smokers and those who had never smoked was similar. Smoking was less common among those with hay fever at 23 yr of age only if they had had hay fever or allergic rhinitis at 11 or 16 yr of age. Adolescents and young adults with hay fever may be less likely to take up regular cigarette smoking (15).

An intergenerational study of two Scottish communities from 1972–1976 and again in 1996 disclosed an increase in prevalence of hay fever at 45–54 yr of age in the later group as compared with their parents 20 yr earlier (16). Participants included 1708 parents who were 45–54 yr of age in 1972–1976 and 1124 offspring of those ages 20 yr later. They responded to the question, “Do you suffer from, or have you ever suffered from, hay fever?” There also were questions about asthma and wheezing, and participants underwent “cardiorespiratory examination.” Cumulative prevalences of hay fever increased from 5.4% and 5.8% in men and women, respectively, in 1972–1976 to 15.4% and 20.0% in their children in 1996 (16).

Surveys of Aberdeen schoolchildren 8–13 yr of age in 1964 and 1989 have disclosed increased prevalence of hay fever from 3.2% to 11.9% (17). An additional survey in 1994 disclosed a prevalence of 12.7%, not significantly different from 1989 (18). These reports provide more details about asthma than hay fever, but the questionnaires apparently sought information about current prevalence.

Prevalence of allergic rhinitis among compulsory military Swedish conscripts 17–20 yr of age (95% 18 yr of age) increased from 4.4% in 1971 to 8.4% in 1981 (19). Prevalence was significantly higher in the most northern region of the country and higher in the urban than rural areas except in the most northern region. Questionnaire surveys completed by parents of 7-yr-old schoolchildren in 1979 and 7–9-yr-old children in 1991 disclosed an increase in prevalence of allergic rhinitis from 5.45% to 8.08% in Sweden (20).

A diagnosis of allergic rhinitis was accepted only when the medical history was confirmed by allergy-prick skin testing in a study of conscripts for the Italian Navy from Liguria, a region in northern Italy (21). The authors suggest this requirement may partly account for the low prevalence of allergic rhinitis of 1.54% found in 1983 in the 18-yr-old men. This increased to 2.2% among the men of the same age conscripted from the same area from 1993–1995.

Increases in prevalence of allergic rhinitis in industrialized nations have been evident not only from prospective, longitudinal studies, but also from a large, cross sectional study. The International Study of Asthma and Allergies in Childhood (ISAAC) included prevalence surveys among representative samples of schoolchildren in various loca-

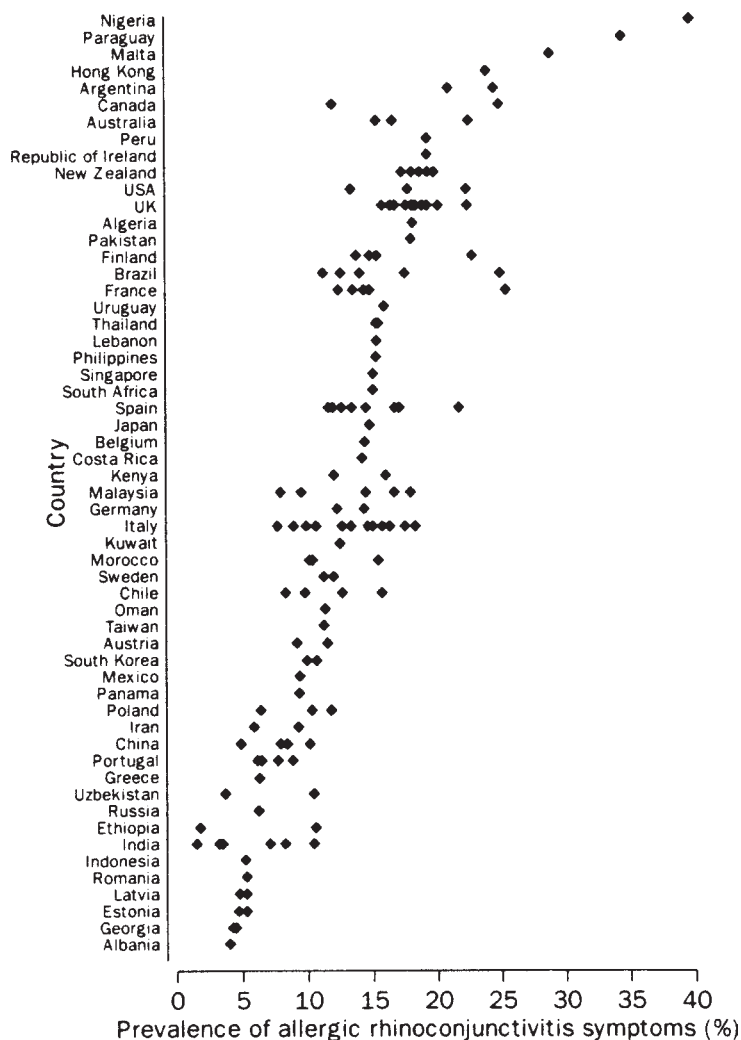


Fig. 7. Prevalence of symptoms of allergic rhinoconjunctivitis within the previous 12 mo at 13–14 yr of age as determined in 1997 in the International Study of Asthma and Allergies in Childhood (ISAAC). Adapted with permission from ref. (23).

tions throughout the world (22). Parents of 257,800 children 6–7 yr of age at 91 centers in 38 countries and the 463,801 13—and 14-yr-old children themselves at 155 centers in 56 countries completed written symptom questionnaires in the local languages. They answered questions about rhinitis, defined as sneezing or a runny or blocked nose not owing to a cold or the flu, with additional questions about associated itchy, watery eyes, timing of symptoms within the previous 12 mo, extent of interference with daily activities, and whether the child had ever had hay fever.

Prevalence of rhinoconjunctivitis in 1997 at 6–7 yr of age varied from 0.8% to 14.9% (22). Prevalence was low at centers from eastern Europe and central and southern Asia and high in countries on the Pacific rim (Australia, Hong Kong, New Zealand, South Korea, Taiwan, Thailand) and in South America. Prevalence at 13–14 yr of age varied from 1.4% to 39.7% (Fig. 7) (22,23). Prevalence at these ages also was the lowest in parts of eastern Europe and south and central Asia. Prevalence at 13–14 yr of age was highest in countries that again included Australia and New Zealand, but also was high in Chicago and Hamilton, Ontario (Fig. 7) (22,23).

The authors acknowledge that “dialect and familiarity with the written language may lead to spurious differences to responses even when language is held constant,” and cultural factors independent of language may affect perception and reporting of symptoms, but wide variance in reported symptom prevalence within groups of centers sharing common languages argued against language barriers as explanations of variations in prevalence (22). Wide variations in prevalence within some countries suggest the likely importance of environmental factors to development of allergic rhinitis (23). Anticipated further study will be necessary to identify specific factors responsible for these variations. Amartya Sen has observed, however, that “a population that has little experience of medical care and widespread health problems as a standard condition of existence can have a very low perception of being medically ill” (24).

The European Community Respiratory Health Survey of 1994, a questionnaire survey of representative samples of 20–44-yr-old men and women at 48 centers, mostly in Western Europe, also indicated wide variations in prevalence of “nasal allergies and hay fever,” in this case a range from 9.5–40.9% (25). Among cities with the highest prevalence were four in New Zealand (35.1–37.8%), Melbourne, Australia (40.9%), and Portland, OR (39.4%).

Risk Factors

A parental history of allergic rhinitis is the best-established risk factor for allergic rhinitis (10,26,27). Risk for allergic rhinitis is increased if one parent has allergic rhinitis, but is highest if both parents have allergic rhinitis (27,28). Studies of twins have disclosed much higher concordance for allergic rhinitis in monozygotic than dizygotic twins, approx 0.45 and 0.25, respectively, in a Swedish study of 7000 twin pairs and 0.61 and 0.25, respectively, in a study of 3808 pairs of Australian twins (29,30). Furthermore, concordance rates for seasonal rhinitis and asthma in monozygotic twins reared apart are quite similar to those of monozygotic twins reared together and significantly greater than those

of dizygotic twins (31). Total serum IgE concentrations also have been similar for monozygotic twins whether reared together or apart (31).

An association of symptoms of rhinitis with exposure to certain substances was recognized long before identification of IgE, well before introduction of the term "allergy," and even before John Bostock introduced the term "hay fever," in 1828 (32). Allergy skin testing of 10,854 white adolescents and adults during the second National Health and Nutrition Examination Survey (NHANES II) of 1976–1980 confirmed the strong association of allergy as defined by positive allergy skin tests with allergic rhinitis (9,33). Participants were prick-tested with eight unstandardized allergenic extracts (house dust, cat, dog, *Alternaria*, ragweed, oak, perennial ryegrass, and Bermuda grass). The association of allergic rhinitis with one positive skin test in these 12–74-yr-old participants was significant both for indoor allergens (house dust, dog, cat, odds ratio 2.3, 95% CI 1.4, 4.0) and for outdoor allergens (odds ratio 5.0, 95% CI 3.5, 7.2) as compared with the negative reactors (33). The association was significant for outdoor allergens (odds ratio 9.6, 95% CI 6.7, 13.7) and for both indoor and outdoor allergens (odds ratio 11.7, 95% CI 9.3, 14.8) for those with two or more positive skin tests. Allergic rhinitis was defined as either frequent seasonal nasal or ocular symptoms or report of physician-diagnosed hay fever. Associations with positive skin tests were even stronger and significant for both indoor and outdoor allergens for those who reported physician-diagnosed allergic rhinitis (33). There was no association of chronic rhinitis with positive skin tests to these allergens.

Analysis of data from 4295 participants in NHANES II who were 6–24 yr of age disclosed significant associations of self-reported allergic rhinitis with positive skin tests to perennial rye (odds ratio 2.8, 95% CI 1.8, 4.3), house dust (OR 2.5, 95% CI 1.6, 3.9), ragweed (OR 2.3, 95% CI 1.5, 3.3), and *Alternaria* (OR 2.3, 95% CI 1.5, 3.4) (9). Chronic rhinitis, on the other hand, was associated only with positive skin tests to dog (OR 1.8, 95% CI 1.1, 2.9) after controlling for reactivity to other allergens, sex, age, smoking, and region. Although the relevance of specific allergens must vary with exposure, results of this national survey were virtually identical for each of four large regions of the country (9).

Positive skin tests not only are associated with increased prevalence of allergic rhinitis but also increase the risk of subsequent allergic rhinitis in those who have had no previous respiratory symptoms. A 23-yr follow-up of 563 Brown University freshmen who initially had no histories of hay fever disclosed development of hay fever in the intervening years in 42.9% of the 105 who had had positive skin tests to at least 1 of 12 allergenic extracts as freshmen but in only 18.8% of the 458 whose prick tests all had been negative (34).

Factors that increase allergenic exposure can increase risk of allergic rhinitis. Damp housing, for example, has been associated with sensitization to dust mites (35) and prevalence of allergic rhinitis, asthma, and eczema (36). High humidity fosters proliferation of dust mites and growth of fungi (37,38).

The Tucson Children's Respiratory Study disclosed significantly increased prevalence of physician-diagnosed allergic rhinitis during the first 6 mo of life in infants who received foods other than breast milk during their first 2 mo (10) although the British cohort study indicated increasing prevalence with increasing duration of breastfeeding (14). In the British study, odds of hay fever were 20% higher for infants breast-fed for more than one month compared with bottle-fed infants (14). In the Tucson study risk factors for allergic rhinitis at 6 yr of age included parental allergy, maternal asthma, a dog in the household, and serum IgE greater than 100 IU/mL (10).

The Tucson study did not indicate an association of early introduction of foods with onset of allergic rhinitis after the first 6 mo of life (10). Although some other studies have indicated reduced prevalence of allergic rhinitis, asthma, and atopic dermatitis after avoidance of cow milk and other allergenic foods during the first 6 mo of life (39–42), others have not (43).

There was no difference in prevalence of allergic rhinitis, asthma, atopic dermatitis, or food allergy at 7 yr of age in a prospective, randomized, controlled study of 103 children who avoided allergenic foods in infancy and 185 control children with follow-up of 57% of both groups at 7 yr of age (43). Mothers of the infants in the experimental group also avoided cow milk, egg, and peanut during the last trimester of pregnancy and while breast-feeding the infants, and the infants avoided cow milk during the first year, egg during the first 2 yr, and peanut and fish during the first 3 yr. Some did receive casein hydrolysate during the first year. Breastfeeding "for at least 4–6 mo" was recommended to both groups, which might have affected results. There was a significant reduction in prevalence of food allergy and allergy to cow milk during the first 2 yr in the prophylactic group. Children with food allergy by 4 yr of age had higher prevalence of allergic rhinitis and asthma at 7 yr of age, but overall there was no difference in prevalence of allergic rhinitis between the early food-avoidance and control groups at 7 yr of age (43).

Another study with longer follow-up of 236 infants born in Helsinki, Finland in 1975 did disclose a protective effect of avoidance of cow milk (42). Infants divided into three groups by duration of breastfeeding (at least 6 mo, 1–6 mo, and less than 1 mo) were examined periodically during their first year and at 3, 5, 10, and 17 yr of age,

with examination of 150 children at 17 yr of age. Atopy (allergic rhinitis, asthma, atopic eczema, or food allergy) was found in 20% at 1 yr of age and 47% at 17 yr of age with cumulative prevalence of atopy in 67% by 17 yr of age.

Prevalence of atopy was significantly greater in the group assigned to little or no breastfeeding. Food allergy at 1–3 yr of age was highest in that group, and respiratory allergy was most frequent in that group (65% at 17 yr of age compared with 43% or less in those breastfed for at least 1 mo) (42).

Although sensitization to food in infancy usually is transient and often elicits no symptoms, persistent sensitization may increase risk of allergic rhinitis and asthma (44). In a prospective study of 460 German children, followed their first 5 yr and selected for increased risk of allergy by elevated cord-blood IgE concentrations or at least two atopic family members, serum samples were obtained at 1, 2, and 5 yr of age (44). Determinations of specific IgE to egg, cow milk, soy, and wheat by CAP-RAST-FEIA permitted division into three groups depending on sensitization to none of the foods within the first 2 yr, sensitization to at least one of the foods once (transient sensitization), or sensitization at both 1 and 2 yr of age (persistent sensitization). Allergic rhinitis at 5 yr of age was defined by physician diagnosis or a report of nasal congestion and rhinorrhea for 2–8 consecutive months not related to infection. Prevalence of allergic rhinitis at 5 yr of age was 18.1%, including 15% of those never sensitized to any of the four foods, 19% of those transiently sensitized, and 44% of those sensitized persistently (at both 1 and 2 yr of age). Prevalence of asthma also was increased in this persistently sensitized group (36% compared with 5% in those never sensitized). Those with persistent sensitization had a 4.7-fold higher risk of allergic rhinitis at 5 yr of age compared with those never sensitized and a 3.4-fold higher risk than those with transient sensitization to food. Sensitization to inhalant allergens (Der p 1, Fel d 1, mixed grasses, and birch pollen) at 5 yr of age varied from 18% in those never sensitized to foods to 67% in those with food sensitivity at both 1 and 2 yr of age. Prevalence of allergic rhinitis at 5 yr of age was 12% in those with no atopic parent, 23% in those with one atopic parent, and 37% in those with both parents atopic (44).

Thus, although it may be uncertain whether avoidance of cow milk and other highly allergenic foods in early infancy prevents subsequent allergic rhinitis, persistent food allergy or sensitization during the first 2 yr is strongly predictive of subsequent allergic respiratory disease (44).

Increased prevalence of allergic rhinitis, asthma, atopic sensitization, and bronchial hyperresponsiveness in West Germany as compared with East Germany has invited investigation of possible causes

(45). Questionnaires completed by the parents of 9–11-year-old children and allergy prick testing disclosed hay fever in 8.6% of the children in West Germany compared with only 2.7% in East Germany, and positive skin tests to at least one of six allergens in 36.7% of the children in West Germany but only 18.2% in East Germany (45).

Data from ISAAC questionnaires collected in 1994 and 1995 in Munster, West Germany, and Greifswald, East Germany, have disclosed significantly higher lifetime prevalence of hay fever in Munster than Greifswald (5.7% compared with 2.8% among 5–8-year-old children, 21.5% compared with 11.9% among 12–15-yr-old children) (46). Cumulative prevalence of asthma and eczema also was higher in Munster. Both allergic rhinitis and asthma were more common in boys than girls and associated with parental histories or allergy. Heating with wood or coal and use of feather bedding were associated significantly with fewer symptoms of allergic rhinitis. Active smoking, frequent or constant truck traffic on a residential street, and parental school education of at least 11 yr increased the risk of allergic rhinitis (46). An earlier survey of 9–11-year-old schoolchildren in Bavaria also had disclosed significant reductions in risk of hay fever (OR 0.57, 95% CI 0.34–0.98) and at least one positive skin test to a panel of common aeroallergens (OR 0.67, 95% CI 0.49–0.93) in homes where coal or wood was used for heating (47). Heating with coal or wood reportedly increases the risk of respiratory infections for reasons that remain uncertain.

It is noteworthy that the ISAAC questionnaire data disclosed no significant difference in symptoms of allergic rhinitis during the previous 12 mo among children 12–15-yr of age between Munster and Greifswald (46). Other data also suggest convergence of atopic diseases between East and West Germany within 5 yr of re-unification (48). Two independently drawn random samples of more than 3000 adults 20–44 yr of age from Hamburg, West Germany and Erfurt, East Germany completed screening questionnaires of the European Community Respiratory Health Survey from 1990–1992 and 1994–1995. Prevalence of symptoms of allergic rhinitis did not change significantly between the two periods in Hamburg (22.9% and 24.6%, respectively) but increased significantly in Erfurt from 13.3% to 15.9% (48). Prevalence of asthma and wheezing also remained stable in Hamburg, but increased significantly in Erfurt, approaching prevalence in Hamburg. Over the same period there was substantial reduction in ambient air pollution owing to sulfur dioxide, nitrogen dioxide, and particulates in Erfurt as a result of reduced dependence on coal for heating (48). It remains uncertain, however, whether there were true changes in morbidity or only changes in perception of symptoms.

Questionnaire surveys completed by parents of 9–11-yr-old schoolchildren in Munich, West Germany, from 1989–1990, and in Leipzig, East Germany, in 1991 disclosed significantly higher prevalence of hay fever and symptoms of allergic rhinitis in Munich (19.7%) than Leipzig (16.6%) (49). Physician-diagnosed hay fever was reported for 8.6% (95% CI 7.8, 9.4) of the children in Munich and 2.4% (95% CI 1.4, 3.3) if those in Leipzig. Prevalence of bronchitis was significantly greater in Leipzig, where sulfur dioxide and particulate air pollution was much greater than in Munich, but there were no significant differences in frequency of asthma, wheezing, or nocturnal coughing between the two cities (49).

Hygiene Hypothesis

Strachan inferred a protective effect of respiratory infection in early childhood against allergic rhinitis from the decreased prevalence of hay fever with increasing family size, an effect greater with increased number of older siblings than younger siblings in the British cohort studies (14,15). Survey of a randomly selected sample of 1159 British adults 20–44 yr of age also disclosed a negative association of prevalence of hay fever with family size and birth order as well as a negative association between symptoms of asthma and family size (50). Prevalence of physician-diagnosed hay fever as reported by a questionnaire survey of parents of 11–16-yr-old adolescents in Sheffield, UK, for whom information about neonatal illness was available from interviews when they were 1-mo old also was associated negatively with family size (51). The number of older siblings had a significantly greater effect than the number of younger siblings. Prevalence of hay fever was 16.4% in the 11,765 adolescents, ranging from 11.3% for those with three or more older siblings to 17% for firstborn children (51). Current prevalence of hay fever also was associated with increasing maternal age, varying from 12.9% for maternal age less than 20 yr at the time of birth to 17.7% for those with mothers at least 30 yr of age. There was no significant association with either personal or family history of infection during the first month of life (51).

Self-reported inhalant allergy to grass, dust, or cats also was associated with increasing maternal age at time of birth in a survey of 11,042 pregnant women 14–45 yr of age (52). Prevalence of inhalant allergy decreased with increasing sibship size owing to a significant effect only on the number of brothers.

Completion of questionnaires by parents of 2766 16-yr-old Finnish twins disclosed a significantly lower cumulative prevalence of physician-diagnosed hay fever in those with three or more older siblings (3.9%, 95% CI 1.2, 6.5%) compared with those with none (12.3%, 95% CI

10.4–14.2), or one (13.1%, 95% CI 11.0–15.2) or two (12.8%, 95% CI 9.4–16.1) older siblings (53).

Five different studies have disclosed significant inverse relationships between allergic sensitization and sibship size (50,51,54–56). Prevalence of positive allergy prick tests to grass pollen in 723 British children 11–16 yr of age varied from 11% in those with at least three siblings to 20% in those with none (51). In vitro determination of specific IgE to grass pollen in 907 British adults 20–44 yr of age disclosed a significant negative association with family size ranging from positive in 20.8% of those with at least four siblings to 29.9% of those with one sibling and 25.6% of those with no siblings (50). Allergy prick testing of 2335 9–11-yr-old school children in East Germany and 4451 in West Germany with six common aeroallergens disclosed a significant decrease in prevalence of sensitization with increasing number of siblings from 38.0% of those with one sibling to 25.0% of those with five or more siblings in West Germany and 19.4% of those with no siblings to 11.1% of those with five or more in East Germany (54). In vitro determination of specific IgE to four inhalant allergens in sera of 11,371 Italian men 18–24 years of age also disclosed an inverse relationship between sensitization and the number of siblings from 25% of those with no siblings to 9% of those with five or more siblings (55). Allergy prick testing of 1369 British adults 34–35 yr of age with extracts of grass pollen, house-dust mite (Der p 1), and cat fur elicited at least one positive reaction in 38.3% of those with no older sibling but only 23.1% of those with three or more older siblings (56).

Review of the medical records of 1934 children followed in a British medical practice at least until 12 yr of age disclosed no significant relationship between atopic disease and sibship size, although there were significant positive associations with immunization with whole-cell pertussis vaccine (OR 1.76, 95% CI 1.39–2.23) and treatment with oral antibiotics during the first 2 yr of life (OR 2.07, 95% CI 1.64–2.60) whether for respiratory infection or urinary tract infection (57).

Retrospective analysis of data collected in 1964 from the parents of 2111 Scottish children 10–14 yr of age disclosed a significant inverse relationship between risk of hay fever and having had three or more older siblings (OR 0.2, 95% CI 0.1–0.8), but a significant trend in the odds ratios toward greater risk of hay fever with increasing exposure to rubella, mumps, and varicella (58).

If the protective effect of a large family were owing to transmission of respiratory infections from older siblings, one would anticipate a protective effect of attendance at daycare facilities. A survey of 8387 schoolchildren in Finland, 13–14 yr of age, revealed a significantly increased risk of having had hay fever at some time in the past for those

with no siblings as compared with three or more siblings ($p < 0.001$), but no significant effect of sibship size on symptoms of hay fever within the previous 12 mo and an increased risk of current symptoms of hay fever for attendance at a daycare center at 1–3 yr of age (OR 1.34, 95% CI 1.12–1.60) (59). A 1992–1993 study of 2430 children 5–14 yr of age in eastern Germany did indicate decreased prevalence of allergenic sensitization and cumulative prevalence of hay fever for those who entered daycare at 6–11 mo of age compared with those who entered only at older ages but only for the 669 children in small families (no more than three people) (60). Age of entry to daycare facilities had no effect on risk for hay fever or sensitization in the 1761 children from larger families. In 1995 a questionnaire study of 6378 Australian schoolchildren 7 yr of age indicated no effect on prevalence of hay fever of any regular child care during the first 5 yr of life (61). There was a significant protective effect of increasing numbers of siblings, especially older siblings (61). Allergy skin testing at 34–35 yr of age of 1369 members of the British cohort followed from birth in 1958 also disclosed no relationship between allergenic sensitization and attendance at a preschool playgroup or nursery (56).

In 1994 allergy prick testing of 262 adolescents and young adults 14–21 yr of age with seven aeroallergen extracts disclosed sensitization in 12.8% of those who had survived measles infection 14–16 yr earlier and 25.6% of those who had never had measles owing to protective vaccination (62). Sensitization was almost entirely to house-dust mites in this study in a semirural area of West Africa. Although 25% of the children younger than 3 yr of age who contracted measles in the epidemic of 1978–1980 survived by participants in this study died, these observations have suggested a protective effect of measles for allergic sensitization (63). Analysis of prevalence of hay fever at 16 yr of age in 6888 adolescents in a 1970 British birth cohort indicated reduced prevalence in those who had had measles (OR 0.86, 95% CI 0.76–0.96) and increased prevalence in those vaccinated for measles (OR 1.16, 95% CI 1.03–1.31) (64). There was a strong interaction with birth order, however, and prevalence of hay fever was reduced in both those who had had measles and those vaccinated who also had multiple older siblings. A nationwide study of 547,910 subjects in Finland, however, did not support any protective effect of measles on atopic disease (65). Self-reported physician-diagnosed allergic rhinitis or hay fever was slightly but not significantly greater among those 1370 6-yr-old children who had had measles than the 22,145 at that age who had not. The age of onset of the hay fever as related to the measles was not known, however (65).

Study of 867 Japanese children 12–13 yr of age disclosed no association between “atopic symptoms” and measles infection or vaccination, but here was a significant inverse relationship to delayed

hypersensitivity to *Mycobacterium tuberculosis* (66). Intradermal partial protein derivative (PPD) skin testing within the first 3 mo of life and at 6 and 12 yr of age was considered positive whenever it elicited at 48 hr an area of induration at least 10 mm in diameter. At each of these ages all negative responders (less than 5-mm induration) received immunization with attenuated bovine *M. tuberculosis*. At 12 yr of age prevalence of current "atopic symptoms" in positive tuberculin responders was one-third that in negative responders, and remission of atopic symptoms between 7 and 12 yr of age was six to nine times as likely in positive tuberculin responders (66). Geometric mean total serum IgE concentration was lower for those who were positive tuberculin responders at any of the three times of testing as compared with those who always were negative responders. Positive tuberculin responders also had significantly lower serum concentrations of interleukin (IL)-4, IL-10, and IL-13 and higher levels of interferon- γ (IFN- γ) at 12 yr of age than negative tuberculin responders (66).

How might infection in early childhood or delayed hypersensitivity to *M. tuberculosis* afford protection against atopic allergy? Those lymphocytes known as T lymphocytes are distinguished by CD4 and CD8 cell-surface molecules. The T lymphocytes expressing CD4, T helper (Th) cells, are divided into Th1 cells and Th2 cells. The main Th1 cytokine is IFN- γ , whereas Th2 cells release IL-4, IL-5, IL-10, and IL-13. IL-4 promotes isotype switching of B cells to synthesis of IgE, enhanced also by IL-5, whereas IL-10 can inhibit production of IFN- γ . IFN- γ , on the other hand, can inhibit IL-4-dependent IgE synthesis. Intrauterine production of high levels of IL-4 and IL-10 polarize the cytokine milieu at the fetomaternal interface towards the Th2 profile, possibly to provide protection against IFN- γ , which can cause fetal loss (67). This polarization toward the Th2 profile continues for variable periods after birth. The decreased Th1 cytokine-production capacity of cord-blood mononuclear cells (MNCs) from newborn infants with atopic family histories as compared with that of infants with no family history of atopic allergy suggests there may be an unusually extreme intrauterine Th2 profile for infants with an atopic genotype (67). Holt proposes that microbial stimulation in early infancy may enhance Th1 immunity to promote a Th1/Th2 balance that might minimize risk of atopic allergy (67). Although public-health and immunization programs and widespread use of antibiotics in infants have greatly reduced morbidity and mortality from infectious diseases in children, these undeniable gains may have been realized at the expense of increased susceptibility to atopic disease.

The Bacille Calmette-Guérin (BCG) vaccine is a potent adjuvant for induction of cell-mediated immunity, which induces production of IFN- γ . Observations of its effects in Japanese children suggested a pos-

sible role in prevention of atopic allergy (66). Two Swedish studies do not favor such a possibility (68,69). Skin testing with mycobacteria and completion of questionnaires by parents of more than 6000 children in Sweden to identify those with atopic allergy and those immunized with BCG disclosed no significant association of mycobacterial infection or BCG immunization with protection against atopic allergy (68). Furthermore, a retrospective cohort study of 216 children with positive family histories for atopic diseases born in Stockholm between 1989 and 1992 and vaccinated with BCG vaccine by 6 mo of age disclosed no difference in prevalence of atopy from 358 age-matched controls who had not been vaccinated as determined by history, examination, and allergy skin testing and in vitro determination of specific IgE at 3–7 yr of age (69). Some have inferred from these observations need for a better vaccine for protection against tuberculosis and prevention of atopic allergy (70). Others urge caution because of continued uncertainty of the effects of such an attempt to stimulate Th1 activity (71).

Holt suggested that the normal gastrointestinal microflora might be the source of the stimulus to a Th1 profile in infancy protective against atopic allergy (67). Study of 1659 Italian men 17–24 yr of age disclosed an inverse relationship between hepatitis A seropositivity and atopic allergy as determined by allergy prick testing, in vitro determination of specific IgE, and cumulative prevalence of allergic rhinitis or asthma (72). The authors inferred hepatitis A seropositivity may have been a marker for unhygienic living conditions in childhood. Lifetime prevalence of allergic rhinitis or asthma was 8.4% in the 443 men seropositive for hepatitis A and 16.7% in those who were seronegative.

Study of 240 Italian men with atopic allergy and 240 nonatopic controls provided further evidence of importance of the orofecal route for microbial protection against atopic allergy (73). Prevalence of serum antibodies to *Toxoplasma gondii* as well as hepatitis A was significantly more frequent in the nonatopic than the atopic group, while there was no significant difference in presence of antibodies to measles, mumps, rubella, varicella, Cytomegalovirus, or Herpes simplex (73). After adjustment for relevant sociodemographic confounders, the odds of having atopic allergy decreased linearly with cumulative exposure to *Helicobacter pylori*, *T. gondii*, and hepatitis A virus, but not with cumulative exposure to the other virus infections

Increased exposure to microbial antigens in early childhood conceivably could account for reported decreased prevalence of allergic rhinitis, asthma, and atopic sensitization among children reared on farms (19,74,75).

Significantly decreased cumulative prevalence of allergic rhinoconjunctivitis, asthma, and allergic sensitization was found in 295 children 5–13 yr of age at anthroposophic school near Stockholm, Sweden,

as compared with 380 children of the same age attending neighboring schools (76). The anthroposophic life style includes immunization usually only against tetanus and poliomyelitis, with the result that in Sweden measles occurs mostly in such families. Their physicians restrict use of antibiotics. Vegetables are preserved by spontaneous fermentation. Children from the anthroposophic schools had less often received antibiotics than those from the control schools (52% compared with 90%) and had less frequently been immunized against measles, mumps, and rubella (18% compared with 93%). As a result 61% of them had had measles. Fermented vegetables containing live lactobacilli had been consumed by 63% of these children, compared with 4.5% of those at the control schools. For children at the anthroposophic schools cumulative prevalence of asthma was 5.8% compared with 17%, prevalence of allergic rhinoconjunctivitis was 7.1% compared with 14%, at least 1 of 13 allergy prick tests was positive in only 7.2% compared with 13%, and there was an inverse relationship between the number of anthroposophic life-style characteristics and risk of atopy. No single lifestyle characteristic was identifiable as primarily responsible for the reduced frequency of atopy (76).

Questionnaire surveys completed by the parents of 12,601 German schoolchildren 5–7 and 9–11 yr of age indicated a significant association between physician-diagnosed hay fever and six or more courses of treatment with antibiotics for more than three consecutive days during the first 3 yr of life (OR 1.58, 95% CI 1.1–2.51)(77). The association with asthma was much stronger (OR 7.95, 95% CI 6.02–10.50 for six or more courses of treatment; OR 3.27, 95% CI 2.51–4.26 for three to five courses of treatment). Among the asthmatic children the number of episodes of fever during the first year of life and courses of treatment with antibiotics during the first 3 yr were strongly inversely related to prevalence of atopic sensitization as determined by allergy prick testing and RAST (77).

Whatever the effect of infection in early childhood upon risk of atopic allergy, daycare attendance can increase the risk of infection in some children. A 1987 survey of a nationwide representative sample of children less than 5 yr of age in the United States identified risk of respiratory illness in the previous 2 wk associated with daycare attendance (78). Daycare attendance was defined as enrollment in daycare with at least one unrelated child for at least 10 h per week in each of the 4 wk before the interview. Risk of respiratory illness was increased significantly for children 6 wk through 17 mo of age attending daycare (OR 1.6, 95% CI 1.1–2.4) as compared to children not attending daycare and who also had no siblings less than 5 yr of age in regular daycare (78). Risk of respiratory illness associated with daycare attendance also was increased significantly for children 18 through 35 mo of age who had no

older siblings (OR 3.4, 95% CI 2.0–6.0), but not for children in this age group with older siblings.

The U.S. Bureau of the Census reports enrollment in organized childcare facilities of the youngest three preschool children of employed mothers increased from 1,886,808 in 1985 to 3,024,672 in 1994. A slight increase in prevalence of hay fever overall (Fig. 1) and little if any change in prevalence at less than 18 yr of age (Fig. 3) have occurred with this substantial increase in daycare attendance.

There also have been small decreases in average family size in the United States from 3.58 in 1970 to 3.29 in 1980 and 3.19 in 1995 and 1997.

Perinatal Risk Factors

A retrospective cohort study of 149,398 males conscripts born in Sweden from 1973–1975 linked information from the Military Service Enrollment Register to the national Medical Birth Register (79). Univariate analyses identified several significant associations with decreased risk of current allergic rhinitis at 18 yr of age: number of older siblings, multiple gestation, young maternal age, prematurity, low-birth weight, growth retardation, and perinatal asphyxia, defined as Apgar score less than 7 at 5 min. Prevalence of current allergic rhinitis varied from 11.8% for those with four or more older siblings to 16.2% for those with none and from 11.1% for multiple gestation to 15.1% for none. Prevalence varied from 13.2% for maternal age less than 20 yr to 15.5% for maternal age greater than 29 yr. It varied from 11.0% for birth weight less than 1500 Gm (OR 0.69, 95% CI 0.49–0.97) to 15.5% for weight 3500–3999 Gm. Prevalence varied from 13.7% for infants small for gestational age (OR 0.89, 95% CI 0.84–0.95) to 15.1% for those not more than 2 standard deviations (Sds) below expected weight for gestational age. Prevalence of allergic rhinitis was 12.9% for those with low Apgar scores, but 15.2% for those with scores of at least 7 (OR 0.84, 95% CI 0.73–0.96). Prevalence varied from 11.6% for those with gestations of less than 33 wks to 15.2% for those with gestations greater than 36 wk. Older siblings, multiple gestation, and young maternal age were highly significant independent determinants of allergic rhinitis (79). No associations were found with neonatal infection or neonatal respiratory disorders. This association of increasing susceptibility to allergic rhinitis with increasing prenatal maturation is consistent with progressive intrauterine influence of Th2 cytokines (80).

Disproportionate fetal growth has been associated with increased total serum IgE concentrations at 47–55 yr of age in British men and women born from 1935–1943 (81). Forty-one men and 21 women of a total of 280 men and women studied had serum IgE concentrations greater than 80 IU/mL. Mean head circumference at birth was 0.3 inch

larger ($p = 0.004$) and mean weight was 5.6 ounces greater for those with the elevated serum IgE concentrations, whereas crown to heel lengths were similar for both groups. Prevalence of elevated IgE increased from 14% in those with head circumferences at birth of 13 inches or less to 37% in those with circumferences greater than 14 inches. The association was independent of gestational age at birth and maternal pelvic size and parity (81). The authors sought no associations with atopic disorders or sensitization, but a prospective, 16-yr longitudinal study of 1265 New Zealand children disclosed a significant association of head circumference of 37 cm or more at birth with asthma but not with other atopic disorders (82).

Prospective study of 8088 children born in Finland from 1985–1986 disclosed an association between allergic rhinitis by 7 yr of age and low parity, febrile infection during pregnancy, especially during the first trimester, bleeding during the first trimester, and greater weight gain during pregnancy, as well as use of intrauterine contraceptive devices before the pregnancy (83). It is possible some of these factors might affect intrauterine Th1 to Th2 balance.

Air Pollution

Although ambient air pollution has been associated with increased symptoms of rhinitis and asthma it has not been associated with increased incidence of either allergic rhinitis or asthma nor with increased allergic sensitization (84,85). Associations between vehicular traffic and allergic rhinitis as well as asthma have been found, however. Prevalence of Japanese cedar pollinosis has been associated with intensity of exposure to automobile exhaust fumes (86). Prevalence of allergic rhinitis and wheezing has correlated with exposure to truck traffic in Germany (46,87). There is evidence that polyaromatic hydrocarbons in diesel exhaust particles can enhance production of IgE and increase expression of Th2-type cytokines with allergen challenge (88,89).

Environmental Tobacco Smoke

Although a few studies have indicated positive associations between environmental exposure to tobacco smoke (43,90), others have found significant negative associations between maternal smoking during pregnancy and allergenic sensitization as determined by allergy skin testing (56,91). A systematic smoking review of 36 studies disclosed no overall significant association of passive smoking with skin-test positivity, total serum IgE concentrations, or allergic rhinitis or eczema (92).

Socioeconomic Status

Increased prevalence of allergic rhinitis has been found in association with higher socioeconomic status in some (15,93) but not all population studies (94). Prevalence of hay fever at 23 yr of age in the 1958 British cohort study varied from 13.2% among those whose fathers at their births had been semi-skilled or unskilled laborers to 20.8% for those whose fathers had been in professional or managerial positions (15). Follow-up at 5, 10, and 16 yr of age of a 1970 British Birth Cohort disclosed significant increases in prevalence of hay fever by 16 yr of age (OR 1.48, 95% CI 1.12–1.96) and prevalence at 16 yr of age (OR 1.68, 95% CI 1.28–2.19) for the most advantaged as compared with the most disadvantaged social classes (93). Low birth order also was a significant risk factor for hay fever (93). On the other hand, the ISAAC questionnaire survey of 3948 children 6–7 yr of age in Valencia, Spain disclosed no significant association between socioeconomic stature and prevalence of hay fever or allergic rhinitis (94).

Allergy prick testing of 1369 members of the nationwide 1958 British birth cohort at 34–35 yr of age with three aeroallergens revealed significant associations with the fathers' social classes at their birth (56). Presence of at least one positive skin test varied from 24.5% for those with fathers who were semi-skilled laborers to 47.1% for professional and executive fathers. There was no significant association with the social class of the participants themselves. Current cigarette smoking and maternal smoking during pregnancy were associated independently and significantly with reduced prevalence of skin-test positivity (56).

Here in the United States prevalence of allergic rhinitis also has been associated with family income (Fig. 5). The Tucson Children's Respiratory Study indicated increased prevalence of physician-diagnosed allergic rhinitis by 6 yr of age was more common among children whose mothers had more than a high-school education and children with at least one positive skin test elicited by prick testing with seven aeroallergens were more likely to be of higher social class as measured by maternal education (10). Whatever the reason for the association with socioeconomic status, increasingly affluent lifestyles may in part account for increases in prevalence of allergic rhinitis across time as well as disparities of prevalence among countries.

Month of Birth

Several studies have indicated significant associations between allergic rhinitis and season of birth (95–98). A Swedish study of school-children and a cohort of 18-year-old young men born in 1863 disclosed increased prevalence of allergic rhinitis among those born in Novem-

ber through May although there was no significant effect of season of birth in a cohort of 18-yr-old young men born in 1953 (95). Increased prevalence of hay fever was found in 10-yr-old children born in May in Munich and Southern Bavaria with decreased prevalence for those born in November (96). Birth in May through August was associated with increased risk of allergic rhinitis or asthma among children and adolescents in Greece (97). Another Swedish study disclosed 11% of 12–15-yr-old children born from March through May had allergic rhinoconjunctivitis compared with 29–34% in each of the other three quarters of the year (98).

Allergy prick testing indicated increased prevalence of sensitization to grass pollen in Munich and Southern Bavaria for children born in February, May, or June; grass pollination there is heaviest in May, June, and July (96). In Greece significant associations were found for sensitization to *D. pteronyssinus* with birth in May to August; for grass pollen, with March to August; and for *Olea europaea*, with March (97). Peak concentrations of mites are found in Greece between August and December. *O. europaea* pollinates from March through June (97).

In one of the Swedish studies, sensitization to egg white and cow milk was significantly more frequent in children born in September to February (98). Sensitization to egg white and cow milk has been more frequent in children born from November to January in the Netherlands. Risk of sensitization to cat or dog was also greatest for those born from November to January, and sensitization to birch pollen, grass pollen, and dust mites was most frequent for those born up to 3 mo before the peak season for each of those (99).

Association of sensitization to birch pollen with birth in February to April in Finland suggested pollen exposure within the first 6 mo of life increased risk (100). Others have reported association of sensitization with pollens prevalent at the month of birth in Greece (101) and India (102).

On the other hand, multivariate analysis disclosed no significant association between month of birth and prevalence of allergic rhinitis in children and adolescents in Singapore, conceivably because of the relatively constant environment throughout the year (103). However, no significant association was found between month of birth and allergic rhinitis in Japanese schoolchildren (104). A significant association was found between birth during the winter and sensitization to cockroach in 159 asthmatic children in Chicago (105). In 1998 and 1989, allergy prick testing of 1066 Bavarian children 5–6 yr of age with extracts of *Dermatophagoides pteronyssinus*, cat allergen, grass pollen, and birch pollen disclosed no significant associations of specific sensitization or allergic rhinitis, atopic eczema, or asthma with month of birth (106). Contrasting results of studies of effects of the months of births

suggest importance of other variables, including age and possibly intensity of allergenic exposure.

Allergenic Exposure

Prospective study of children with at least one atopic parent confirmed an association during their first 5 yr of sensitization to grass pollen, dust mite allergen, egg, and cow milk and atopic dermatitis and recurrent wheezing (107). Allergy prick testing at 13 yr of age of a cohort of children in New Zealand indicated a significant association between hay fever and sensitization to grass pollen, dust mites, and cat allergen, but a closer relationship to grass sensitivity than to mite or cat sensitivity (108). Asthma, on the other hand, was associated primarily with sensitization to house dust mite or cat (108).

Determination of concentrations of the major allergens of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* in mattress dust samples from the beds of atopic and nonatopic children and young adults indicated an increased risk of sensitization at concentrations of at least 2000 ng/gm of dust (109). Prospective study of a cohort of German infants followed for their first 36 mo of life confirmed the interaction between heredity and environmental exposure (110). Sensitized children had been exposed to significantly higher concentrations of dust-mite allergen (median 868 ng/gm compared with 210 ng/gm) and cat allergen (median 150 ng/gm compared with 64 ng/gm) in carpet dust in their homes than the children without elevated serum-specific IgE. For those with positive family histories of atopy, mite-allergen exposures of less than 750 ng/gm elicited a 3% sensitization rate, but for those with negative family histories, exposure to concentrations up to 25,000 ng/gm resulted in sensitization of 3%. Similar disparity in rates of sensitization to cat was determined by family history of atopy (110).

Exposure to high concentrations of dust-mite allergen also can increase risk of sensitization in older children. Allergy prick testing of primary schoolchildren three times at 12-mo intervals with seven inhalant allergens and sampling of mattress dust disclosed a significantly increased risk of sensitization for those exposed to more than 2 µg Derp I per gram of dust if they already had sensitization to a nonmite allergen (111). Avoidance of dust mites is of potential benefit for allergic children whether or not they are already sensitive to mites.

Prognosis

Prognosis for allergic rhinitis is not good. In the Tucson Children's Respiratory Study, 23% of children with onset of allergic rhinitis in their first year of life experienced remission by 6 yr of age (10), but Pedvis et al. observed remission within 12 yr in only 18% of 143 children with

allergic rhinitis (114). Linna et al. found complete resolution of allergic rhinitis within 8–11 yr in only 10% of 154 children 3–17 yr of age at the time of initial diagnosis (115). Asthma or wheezing had occurred in 19% by the time of follow-up (115).

In a 10–23-yr follow-up of adults with hay fever, Greisner et al. reported 23% of 306 to be symptom-free (116). Of 168 who had had hay fever when initially examined as college freshmen, the percent reporting improvement in symptoms 23 yr later was inversely associated with age of onset of symptoms.

Association with Asthma

Allergic rhinitis in college freshmen was a risk factor for subsequent asthma at follow-up 23 yr later (34). Asthma had appeared in 10.5% of 162 who had had allergic rhinitis as freshmen compared with 3.6% of 528 who had had no allergic rhinitis as freshmen. Questionnaire surveys have disclosed allergic rhinitis in as many as 99% of adults with asthma and 92.5% of 116 adolescents with asthma (117). The symptoms of rhinitis reportedly began either before or simultaneously with those of asthma in 81.3% of these adults and 72% of these adolescents with rhinitis (117). Rhinitis preceded asthma in 43% to 64% of the cases (118).

The longitudinal Tucson Children's Respiratory Study disclosed physician-diagnosed asthma by 6 yr of age in 10% of nonatopic children with physician-diagnosed allergic rhinitis and 25% of atopic children with allergic rhinitis as well as physician-diagnosed "bronchitis" in an additional 18% of nonatopic children with allergic rhinitis and 23% of atopic children with allergic rhinitis (10). The 8–11-yr follow-up of 154 children 3–17 yr of age revealed onset of wheezing or asthma in 19%, including 15 of 44 with perennial allergic rhinitis and 14 of 110 with seasonal allergic rhinitis (115).

A 20-yr follow-up of asthmatic children indicated associated rhinitis increased severity and persistence of asthma (119). Furthermore, effective treatment of allergic rhinitis can reduce symptoms of asthma (120).

Asthma had been reported earlier in as many as 44–58% of adults with allergic rhinitis (121,122). In a British study of adults with rhinitis, wheezing was reported by 23% of those with seasonal rhinitis, 26% of those with perennial rhinitis, and 44% of those with both seasonal and perennial rhinitis (123). Among adults with rhinitis, the risk of asthma was increased by allergic sensitization to indoor allergens, elevated serum IgE concentrations, increased blood eosinophil counts, and maternal asthma.

Much earlier study of allergic rhinitis and asthma in Tecumseh, MI had confirmed their frequent association, but the two conditions had begun within the same year or asthma had preceded hay fever in 75% of the affected population (124). For the others who could time the onset of hay fever and asthma, asthma followed hay fever in only 5–10% of people.

Complications

Sinusitis

Whatever the mechanism, allergy has been identified as the most common risk factor for chronic sinusitis in children (125–128). There was evidence of allergic rhinitis or asthma in 38% of children evaluated for suspected sinusitis with radiographic confirmation in 96% (129). Allergy skin testing and serum IgE supported suspicions of allergy in 39% of 61 children with chronic sinusitis (130).

A survey of 104 adults undergoing surgery for chronic sinusitis disclosed an association between allergic sensitization and peripheral eosinophilia with the most extensive sinus disease (131). Extensive disease was evident in 87% of those with peripheral eosinophilia (at least $0.3 \times 10^6/\text{L}$). Review of records of 92 patients enrolled in two studies of effects of antibiotics on recurrent sinusitis disclosed 92% had allergy (132).

Sinusitis may be a frequent complication of allergic rhinitis. Computed tomography of the paranasal sinuses of 40 adults with perennial allergic rhinitis and sensitization to *Dermatophagoides* disclosed “sinus abnormalities” in 67.5% compared with 33.4% of 30 control subjects who underwent cranial computed tomography (CT) for evaluation of dizziness (133).

Responses to nasal provocation with allergen have provided further evidence of the association between allergic rhinitis and sinusitis. Rhinometry before and after nasal challenge with allergens in 37 adults with chronic maxillary sinusitis disclosed 41 positive responses in 29 patients, including 13 immediate responses, 18 late phase responses at 4–12 h after challenge, and 10 responses that were both immediate and late (134). Maxillary sinus radiographs at baseline, 2 h, and 6 or 12 h disclosed changes after provocation in 32 of the 41 positive responses, consisting usually of increased mucosal thickening or increased opacification of the sinus.

If allergic rhinitis can cause sinusitis, one might expect resolution of sinusitis after effective treatment of the rhinitis, but this does not necessarily occur, at least immediately. Evaluation of 10 adults with seasonal allergic rhinitis owing to ragweed allergy disclosed mucosal

thickening of paranasal sinuses by CT scan in six at the peak of the ragweed season (135). Treatment with intranasal beclomethasone dipropionate elicited symptomatic improvement, but repeat CT scans in five of these six after the season indicated no significant change in CT scores, although an air-fluid level resolved in one patient.

Chronic Middle-Ear Disease

There have been many studies of the possible association of otitis media with effusion with allergic rhinitis; results have been contradictory. There have been several reviews of the subject (118,128,136). Some have found allergic rhinitis in as many as 40–50% of children more than 5 yr of age who have chronic otitis media with effusion (128). Natural exposure to allergen has been associated with eustachian tube obstruction (137) and negative middle-ear pressure that might lead to effusion (118). Intranasal challenge with allergen can cause eustachian tube dysfunction (118). Although infection is the most common cause of middle-ear effusion, allergic rhinitis is a likely contributing factor for chronic middle ear effusion at least beyond 5 yr of age.

Sleep Disorders

Nasal obstruction owing to allergic rhinitis also can cause disordered sleep. Of 100 children with perennial allergic rhinitis, 88% reported sleep disorders, including 22% with “sleep apnea,” 24% with enuresis, 33% with nightmares, 30% with sleep talking, and 26% with restless sleep (138). Estimates of the prevalence of obstructive sleep apnea in the general population have varied in part with the definition because episodes of apnea with or without decreases of more than 3% or 4% in SaO_2 may average from 1 to more than 10 per hour of sleep and may or may not be associated with daytime sleepiness that may or may not interfere with usual activities (139). Home monitoring of Australian men disclosed 26% had at least 5 episodes per hour of sleep and 10% had at least 10 episodes per hour (140). The Wisconsin Sleep Cohort Study disclosed episodes of apnea lasting at least 10 s or reduced airflow with decreases of at least 4% in oxyhemoglobin saturation at least 5 times per hour of sleep in 9% of women and 24% of men (141). There was associated self-reported hypersomnolence in 22.6% of the women and 15.5% of the men, leading to estimates of sleep-apnea syndrome in 2% of women and 4% of the men (141).

Authors of a study of 996 children 4–5 yr of age estimated prevalence of significant sleep disorders at 1.1% (142), but 12% snored on most nights, 22% had daytime sleepiness, and mouth-breathing was evident in 17.5%. At follow-up 2 yr later, more than half those who originally snored often no longer snored, but others had begun to snore,

so the prevalence of snoring still was 11.4% (143). Daytime sleepiness had decreased to a prevalence of 10% at follow-up. Daytime sleepiness, hyperactivity, and restless sleep were all significantly more common among those who snored frequently than those who never snored (143).

A population-based study of children 6 mo to 6 yr of age in Iceland indicated a prevalence of sleep-apnea syndrome of at least 2.9% (more than three respiratory events per hour of sleep with decreases in oxygen saturation of at least 4%) (144).

Some children, however, may have abnormal increases in upper-airway resistance during sleep causing increased respiratory effort and periodic arousals without apnea or decreased arterial oxygen saturation (145). This sleep fragmentation owing to upper airway-resistance syndrome has been associated with snoring, nightmares, sleep walking, daytime mouth-breathing, fatigue, daytime hyperactivity, oppositional behavior, sleepiness, poor growth, and "repetitive airway infections" (145). These symptoms and "chronic rhinorrhea" also are common in children with obstructive sleep apnea (146). Other complications of obstructive sleep apnea include poor growth (147), systemic hypertension (148), cor pulmonale with pulmonary hypertension (149), and poor school performance (150,151). The adverse effect of nasal obstruction on quality of sleep may explain impairment of learning in children with allergic rhinitis even when not receiving sedating antihistamines (152).

Severe sleep-disordered breathing has been reported to be 1.8 times more likely in adults who reported nasal congestion owing to allergy (153). Patients with seasonal allergic rhinitis owing to allergy to ragweed experience more frequent and longer-lasting episodes of obstructive apnea associated with increased nasal resistance during the ragweed season as compared with 6–8 wk later (154). Furthermore, treatment of nasal congestion owing to perennial allergic rhinitis with a topical corticosteroid to relieve nasal congestion can reduce reported "sleep problems" (155).

Disordered sleep and consequent daytime sleepiness are common in patients with asthma (156,157), but allergic rhinitis, which is associated frequently with asthma (157), has been related independently to both difficulty in inducing sleep and daytime sleepiness (157). "Sinus problems" and persistent wheeze were identified as independent risk factors for sleep disorders in children and adolescents in a study that also identified obesity and African-American race as risk factors (158). Allergic sensitization was found in 36% of 39 children referred to a sleep laboratory for polysomnography because of habitual snoring, and obstructive sleep apnea was significantly more frequent in those with allergic sensitization (159).

Obesity is the most common cause of obstructive sleep apnea in adults (141), and hypertrophy of tonsils and adenoids is the most common cause in children (146,149,151), but nasal obstruction owing to allergic rhinitis can be a contributing factor and is probably the most common cause of less extreme disorders of sleep (153,154,157,158). Symptoms often have been overlooked or disregarded (151,160).

Conclusion

Prevalence of allergic rhinitis has probably nearly doubled in the United States from 1970–1992 and doubled in much of Europe over the same period. The much higher prevalence in “developed” as compared with less-developed countries, an association with higher socioeconomic status, and the possible protective effect of large family size and daycare attendance in infancy are consistent with microbial induction of a shift in infancy to a Th1 profile that may have been lost in more hygienic environments. Family size has been decreasing in the United States, but daycare attendance for young children has been increasing, so it is not obvious that this is an explanation for recent changes in prevalence of allergic rhinitis here.

The prognosis is not good, with rates of remission of only approx 10–20% in 10–20 yr (114–116). Asthma is a frequent complication, appearing in 10–20% within 10–20 yr, and many if not most patients with asthma also have allergic rhinitis. Other complications include sinusitis, chronic middle-ear disease, and sleep disorders, all often unrecognized. Management affects prognosis of course; avoidance of allergen (161) and immunotherapy when appropriate (162,163) can eliminate symptoms and prevent complications.

Despite some epidemiologic evidence suggesting a role for better sanitation in increased prevalence of allergic rhinitis, most will opt not to feed their children dirt or return to the devastating morbidity and mortality of infectious diseases of the not-too-distant past.

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