

The allergy epidemic extends beyond the past few decades

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Summary

Background Increased prevalence of allergic diseases in western societies has been described as an epidemic. The precise turning point for the epidemic and the antigens responsible for it remain obscure.

Objective To evaluate how the prevalence of atopic disease has changed in terms of detectable sensitization to aeroallergens and dietary allergens in a cross-sectional comparison of subjects from birth cohorts more than 60 years apart.

Methods We studied four groups of 100 subjects each (at ages 7, 27, 47 and 67 years), representing those born in 1990, 1963–66, 1943–46 and in 1923–26, respectively. Serum total and specific IgE concentrations against aeroallergens and dietary allergens were determined. A questionnaire elicited information on symptoms, allergic diseases and medication.

Results The proportion of subjects with detectable IgE antibodies against aeroallergens increased consistently from the oldest to the youngest birth cohorts; χ^2 trend = 56.809, $P < 0.0001$. Similar progression was not seen in sensitization to dietary allergens. The proportion of those with diagnosed asthma differed significantly ($\chi^2 = 13.45$, $P = 0.004$) across the birth cohorts. The lowest prevalence of asthma and sensitization to dietary allergens was detected in those born in 1943–46, i.e. during or immediately after World War II.

Conclusion Prevalence of sensitization to airborne allergens, unlike that to dietary allergens, has increased over a long period of time. Our results support the concept of the immune function being programmed by external factors early in life. They also call for caution when interpretations of the pace and possible causes of the allergy epidemic are made on the basis of short-term studies.

Keywords allergy, atopy, epidemiology, food allergy

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Introduction

Western societies are faced with an increase in the burden of atopic diseases [1–3]. Increased production of antigen-specific IgE antibodies constitutes the hallmark of atopic disease. It would thus be expected that this responder type now more frequently governs exposures to common environmental antigens, i.e. aeroallergens and food allergens. Indeed, increased prevalence of allergy in the young has been linked to an increase in allergen sensitization in successive birth cohorts [4, 5]. Consequently, such objective measurements can be applied in evaluating the allergy epidemic. Precise understanding of the turning-point of the progression and identification of the prevailing allergens responsible for the detrimental development may furnish new preventive meas-

ures. Simple objective measurements in subjects representing a wide range of birth cohorts may prove useful for these aims.

The mainstream explanatory theories link the predominance of atopic diseases to altered hygienic conditions: improved sanitation and living conditions, declining family size, vaccinations and antimicrobial therapy [2, 3]. People living in affluent hygienic environments are lacking the pressure of microbial stimulation. According to the hygiene hypothesis, this stimulation would be needed to hinder the consolidation of the atopic responder type [6]. The same holds true for human nutrition. A shift in food preservation from drying and natural fermentation to industrial pasteurization and sterilization has reduced the microbial exposure associated with food intake [7–9].

The objective of the present study was to assess, how the prevalence of atopic phenotype has changed over decades. For this end, we combined data from recent cross-sectional child and adult studies conducted within the same defined area in Southwest Finland. These included randomly selected people born before, during and after the World War II. The subjects studied had thus been exposed to markedly different diets and living conditions in their infancy, a critical period for the consolidation of the immune responder type [10, 11].

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A further aim of our study was to assess IgE production to aeroallergens and dietary allergens concomitantly, which has not been done before.

Methods

This study is a cross-sectional comparison of subjects representing four birth cohorts, one of children and three of adults, all dwelling in the city of Turku and surrounding rural and urban communities in Southwest Finland. The cohort studies were approved by the Ethics Committees of the University of Turku (child cohort) and the Social Insurance Institution Research Centre (adult cohorts).

Participants and design

The random child cohort, born in 1990, has previously been described in detail [12]. In brief, 131 children (60% of those contacted) attended for clinical examination between January and November 1997, i.e. when they were 7 years old. The parents were asked to fill a questionnaire adapted from the ISAAC (International Study of Asthma and Allergic Disease in Childhood) study [1]. Information was obtained on cow milk allergy and other allergic manifestations, including asthma and factors aggravating symptoms.

In 1990–93, adults of either sex, in five age strata, born between 1923 and 1966 were randomly drawn from the population register and contacted in the sampling order [13]. If no response was obtained, subjects further on the random list were contacted. Altogether, 2155 subjects (66% of those contacted) attended for examination. A questionnaire on previous diseases, symptoms, and medication during the past year was filled, including items on asthma and adverse reaction to foods, particularly cow milk. To distinguish between asthma and other diseases causing bronchial obstruction, separate items dealt with bronchitis and emphysema. Information was also separately elicited on lactose intolerance. Asthma and food hypersensitivity were taken into account only if diagnosed by a physician and if currently (during the past twelve months) in need for care.

For the present study, 100 (out of the 131) children and three subsets of 100 adults (about one in four) were randomly selected from the participants to represent those born in 1990, 1963–66, 1943–46 and in 1923–26, respectively. The random samples stratified by sex were selected by a random number generator, and those participants with the 50 highest random numbers were selected from each subgroup defined by sex and birth cohort. The study population thus comprised four birth cohorts of 100 subjects of either sex, examined at ages with 20 year intervals, i.e. at 7, 27, 47 and 67 years of age.

Assessment of sensitization Blood samples were collected and serum specimens frozen and stored at -70°C until analyses. The concentrations of total IgE in serum were determined with the Pharmacia CAP FEIA immunoassay on a Unicap 100 automatic analyzer (Pharmacia & Upjohn, Uppsala, Sweden) according to the manufacturer's instructions and reference values. Analyses for allergen-specific IgE antibodies were made using two mixtures of allergens; eight airway allergens (Phadiatop): grass, birch, mugwort, dog, cat,

horse, *Cladosporium herbarum* and house dust mite, and six food allergens (Code Fx5): egg white, milk, cod, wheat, peanut, soybean. In cases of detectable response to these food allergens, testing was continued for milk.

Statistics The 95% confidence intervals (CI) for the prevalences of binary responses were obtained using the exact binomial formula. χ^2 test was used to compare the binary response variables between cohorts. In case of a significant result, the Armitage test for trend was applied. Logistic regression analyses were performed to compare cohorts regarding the binary response variables with the cohort born in 1923–26 as the reference. Results are given with odds ratios (OR) with 95% CI. The logarithmically transformed IgE concentrations were compared between birth cohorts using ANOVA. The Fisher's LSD test was used for pairwise comparisons. Results are given as geometric means with 95% CI.

Results

Evidence for selective increase in the atopic responder phenotype

The geometric means for serum IgE were 57.1 kU/L (95% CI 40.9–79.6), 37.2 kU/L (27.5–50.2), 29.9 kU/L (22.6–39.7) and 31.0 kU/L (22.3–43.0), from the youngest (born 1990) to oldest (1923–26) birth cohort, respectively. The difference between birth cohorts was statistically significant (ANOVA, $P=0.014$) and comparisons of the adult cohorts to the youngest cohort were all significant (born 1963–66, $P=0.056$; born 1943–46, $P=0.004$; born 1923–26, $P=0.006$), whereas the levels of IgE between the adult cohorts were not significantly different (Fisher's LSD test).

The proportion of subjects with detectable IgE antibodies against aeroallergens increased consistently from the oldest birth cohort to the youngest; χ^2 trend = 56.809, $P<0.0001$, whereas no difference was found in the proportion of subjects with elevated serum total IgE concentrations between the four cohorts (Fig. 1).

Compared to the reference cohort (those born in 1923–26), the risk of sensitization to dietary allergens was elevated in the youngest birth cohort; OR = 9.64 (95% CI 4.5–20.67), $P<0.001$, comparable in those born in 1963–66; OR = 0.98 (0.38–2.52), $P=0.961$ and lower in those born in 1943–46; OR = 0.18 (0.04–0.86), $P=0.032$ (Fig. 1). Sensitization to milk, detected in 1–9% of subjects (Table 1), likewise showed no linear trend in successive birth cohorts (χ^2 trend = 0.849, $P=0.357$).

Clinical manifestations

The prevalence of asthma was 4.25% (95% CI 2.50–6.72) in the total study population. The proportion of subjects with current asthma diagnosed by a doctor differed significantly across the birth cohorts; $\chi^2=13.45$, $P=0.004$ (Table 1), although without any significant linear pattern (χ^2 trend = 2.765, $P=0.096$). Symptoms associated with milk consumption, lactose intolerance excluded, were reported by 10–14% of the subjects irrespective of birth cohort. However, sensitization to milk antigens tended to differ between the birth cohorts; $\chi^2=6.99$, $P=0.07$ (Table 1).

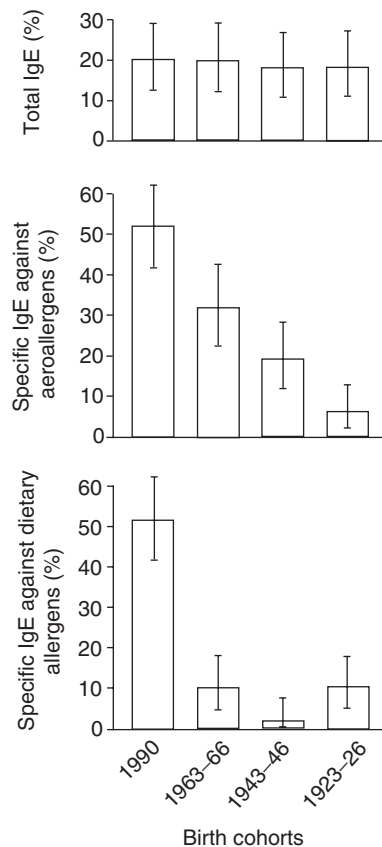


Fig. 1. Prevalences (%) (with 95% CI) of subjects with serum total IgE concentrations above reference values (upper panel), with detectable (>0.35 kU/L) IgE against aeroallergens (middle panel) and against dietary allergens (lower panel) in those born in 1990 (age 7 years), 1963–66 (27 years), 1943–46 (47 years) and in 1923–26 (67 years).

Discussion

Allergic diseases have been described as the epidemic of the 21st century. During the past few decades, increases of 75–100% for asthma [14] and 150% for atopy [15] have been reported in Western societies. However, because of the large number of factors involved, sound evidence for actually changing morbidity is difficult to obtain. For instance, the apparent increase in the prevalence of allergic disease may be due to better public and professional awareness of these conditions, better access to medical care, or altered diagnostic criteria.

Most scientific reports on the progression of allergy do not extend beyond one decade [16–21]. Nevertheless, self-reports on symptoms of atopic disease combined with relevant

measurements, such as peak expiratory flow rates [17], reactivity in skin prick tests [19], or concentrations of specific IgE and IgG4 antibodies in serum [20, 21] have consistently suggested a true increase in the prevalence of allergic diseases. We found that detectable antigen-specific IgE in serum has become more prevalent without simultaneous change in serum total IgE level. Our findings thus imply that the prevalence of the atopic phenotype indeed has increased.

Without sound evidence the prevalence of food allergy is assumed to increase along with increasing prevalence of atopic disease [22, 23]. The golden standard of food allergy diagnosis is double-blind, placebo-controlled challenge. For ethical and practical reasons, such procedures cannot be applied in epidemiological research. Anyhow, sensitization to aeroallergens and dietary allergens can be compared without blinded oral challenges as we did in the present study. Our results showed that the generation of IgE antibodies to dietary allergens does not follow the same progressive pattern as the generation of IgE antibodies to aeroallergens. Thus, we hypothesize that allergy may represent a constellation of diseases which respond differently to various environmental changes.

The proportions of children and young adults with detectable IgE antibodies against aeroallergens in the present study are comparable to those reported from other industrialized countries [5, 19, 20]. Sensitization is associated with age. The immune response patterns to allergens are imprinted within the first 5 years of life [24], and serum IgE concentrations stabilized by school age [25]. At old age, due to age-related immunological impairment, the reverse is thought to ensue [5]. Still, the concentrations of IgE in serum appear to remain rather stable in adults, including subjects even more than 60 years old [26]. In our study, the common sensitization to dietary allergens was therefore an expected finding in the children, but not expected in the adults, especially in the oldest age group.

Sensitization pattern in successive birth cohorts has been followed in an industrialized country (UK [5]) and in the Arctic (Greenland [27]). The UK cohort study indicated that the secular increase in the prevalence of sensitization was not due to reduced sensitization in older age cohorts over time but resulted from a true increase with successive younger birth cohorts. The same conclusion was made in a US study also evaluating child cohorts [4]. In contrast, a different pattern was reported in the Greenland study; there was an increase in the prevalence of sensitization in all age groups studied. Against these backgrounds, the results of the present study support the concept according to which the immune system is programmed by external factors [28]. Factors exerting their effect early in life may be particularly relevant in the Western industrialized countries.

Table 1. Prevalences (%) (with 95% CI) of asthma, cow milk hypersensitivity and detectable milk-specific serum IgE in subjects representing those born in 1990, 1963–66, 1943–46 and in 1923–26

Birth cohorts	1990 7 years <i>n</i> = 100	1963–66 27 years <i>n</i> = 100	1943–46 47 years <i>n</i> = 100	1923–26 67 years <i>n</i> = 100
Asthma	10 (4.9–17.6)	1 (0.03–5.5)	1 (0.03–5.5)	5 (1.6–11.3)
Cow milk hyper-sensitivity	14 (7.9–22.4)	10 (4.9–17.6)	14 (8.0–22.6)	13 (7.1–21.2)
Milk-specific IgE	9 (4.2–16.4)	4.4 (1.2–10.8)	1.0 (0.03–5.5)	7.1 (2.9–14.0)

In the present study we found a notch in the progression of sensitization. Sensitization to dietary allergens and asthma were less common in the wartime cohort born in 1943–46 as compared with those born in 1923–26. Our observation calls for caution when interpretations on the pace and possible causes of the alleged epidemic are made in short-term studies. The epidemic probably started long before World War II, a man-made environmental distortion that may have temporarily diverted the progression.

Exposure to various environmental stress factors can exert immunosuppressant effects [29]. During the war years 1939–45 environmental changes in Finland also encompassed such changes in dietary, hygienic and other living conditions that recent research has connected with reduced risk of sensitization [2]. During the wartime, Finnish children (and pregnant women) residing in population centres customarily took long-term refuge in the countryside thereby exposing themselves to unpasteurized milk. The practise of milk pasteurization became mandatory throughout the country only after the war.

In conclusion, the atopic phenotype, due to increasingly prevalent sensitization to aeroallergens, but not to dietary allergens, has steadily become more common over a long period of time. Environmental distortions, such as World War II, may temporarily divert the progression of atopy and allergic diseases. The human immune function appears to be programmed by external factors early in life. Better understanding of these factors and deeper insight into the mechanisms by which they exert their actions are needed in order to develop new strategies for the prevention of the impending allergy epidemic.

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