

Is the increase in allergic respiratory disease caused by a cohort effect?

A. Linneberg, N. H. Nielsen*, F. Madsen†, L. Frølund‡, A. Dirksen‡ and T. Jørgensen

Centre for Preventive Medicine, Glostrup University Hospital, Glostrup, *Department of Dermatology, Gentofte University Hospital, Gentofte, †Department of Internal Medicine B, Frederiksberg University Hospital, Frederiksberg and ‡Department of Respiratory Medicine Y, Gentofte University Hospital, Gentofte, Denmark

Summary

Background Changes in lifestyle or environmental factors are responsible for the increasing prevalence of allergic respiratory disease. Establishing the time at which the increase began may provide a clue as to what factors possibly could have contributed to the increase. Many cross-sectional studies have shown that the prevalence of allergic sensitization decreases with increasing age. This could reflect the natural course of allergic sensitization. Alternatively, this could reflect that the increase in sensitization is caused by a cohort effect, i.e. an increase among subjects born during recent decades.

Objective The aim was to investigate age-specific changes in the prevalence of allergic sensitization in a cohort of adults.

Methods A total of 599 subjects aged 15 to 69 years participated in a cross-sectional general population study in 1990. In 1998 they were invited to a follow-up, and 64.4% (386/599) were re-examined. Serum samples obtained from the participants in 1990 and 1998 were analysed for specific IgE to six common inhalant allergens with the same assay.

Results The prevalence of allergic sensitization (specific IgE to at least one allergen) increased among subjects who were less than c. 30 years at baseline (1990), i.e. subjects born during the 1960s or later, while the prevalence was unchanged among subjects who were more than c. 30 years at baseline.

Conclusions The results support the notion that the increasing prevalence of allergic respiratory disease is caused by a cohort effect. Thus, changes in lifestyle or environmental factors that occurred around or after 1960 may have contributed to this increase.

Keywords adult, atopy, cohort effect, epidemiology, respiratory hypersensitivity, specific IgE

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Introduction

There is evidence that the prevalence of allergic respiratory disease has increased among children in westernized European countries during recent decades [1]. We have recently reported a significant increase in the prevalence of allergic respiratory disease among 15 to 41-year-olds during the 1990s in Copenhagen, Denmark [2]. The causes of this increase are not known, but it is likely that recent changes in lifestyle or environment are responsible. Establishing the time at which the increase began may provide a clue as to what factors possibly could have contributed to the increase.

Many cross-sectional studies in adult populations have reported that the prevalence of allergic sensitization tends to decrease with increasing age [3–5]. This may reflect the natural course of allergic sensitization. Alternatively, this trend may reflect a cohort effect, i.e. an increase in the prevalence of allergic sensitization among the youngest birth cohorts. However, it is difficult to discriminate from cross-sectional data

between an age-effect and a cohort effect. This issue may be further elucidated in prospective studies of age-specific changes in prevalence of allergic sensitization in general population samples.

We investigated age-specific changes in the prevalence of allergic sensitization to common inhalant allergens in a general population cohort of 15 to 69-year-olds examined at two time points in 1990 and 1998.

Methods

Participants

The baseline study comprised a cross-sectional sample of the general population of Copenhagen, Denmark. The study population has previously been described in more detail [6]. Briefly, a questionnaire on respiratory symptoms was mailed to a random sample of 15 to 69-year-olds living in the western part of Copenhagen. A random sample of the responders ($n = 793$) was invited to a health examination, including blood sample drawing. A total of 599 subjects (participation rate 75.5%) were examined between February 1990 and January 1991. The participants in the health examination in 1990 were invited to a

Correspondence: Allan Linneberg, Centre for Preventive Medicine, Glostrup Hospital, 57 Ndr. Ringvej, Entrance 8, 7th floor, DK-2600 Glostrup, Denmark. E-mail: Linneberg@dadlnet.dk

follow-up examination 8 years later. Thus, a total of 386 subjects (participation rate 64.4%) were re-examined between October 1997 and November 1998.

Specific IgE measurements

In both the 1990 and 1998 study, venous blood was taken on the day of examination. The serum was then separated and kept at -20°C without thawing until the analysis in 1999. The serum samples were analysed for specific IgE to birch, grass (timothy), mugwort, dog, cat and *Dermatophagoides pteronyssinus* with the ADVIA[®] Centaur[™] Specific IgE assay system (Bayer Corporation, New York, NY, USA) [2]. The stability of specific IgE in serum samples stored at -20°C has previously been confirmed [2]. The analysis for specific IgE was judged to be positive if the measurement was in excess of 0.35 kU/L. Allergic sensitization was defined as a positive test for specific IgE to at least one of six allergens.

Statistical analysis

The age of participants was categorized by 8-year intervals (Table 1). Comparison of groups was performed with chi-square or Fisher's exact test. A *P*-value of less than 0.05 was considered statistically significant. Multivariable analysis was performed by using a logistic regression model with the generalized estimation equation (GEE) option to take into account repeated measurements. The dependent variable was allergic sensitization and the independent variables were sex, age at examination (as a continuous variable), and study year (1998

vs. 1990). A possible change in the age-dependency of the prevalence of sensitization from 1990 to 1998 was examined by testing for interaction between study year and age at examination. Analyses were performed with SAS (release 8.01).

Results

Table 1 shows rates of participation to follow-up by age, sensitization at baseline, sex, and familial predisposition to hayfever.

Figure 1 shows the age-specific prevalences of allergic sensitization in 1990 and 1998. The prevalence of allergic sensitization tended to increase from 1990 to 1998 among subjects who were less than approximately 30 years at baseline, while there was no apparent change in the prevalence of sensitization among subjects who were older than approximately 30 years at baseline.

Table 2 shows the age-specific prevalence of sensitization by birth cohort. It appears that the prevalence of sensitization at the age of 31 to 38 years was significantly higher among subjects born in 1959 to 1966 compared with subjects born in 1951 to 1958. Similarly, the prevalence of sensitization at the age of 23 to 30 years was higher among subjects born in 1967 to 1974 compared with subjects born in 1959 to 1966, although this difference was not statistically significant.

In the multivariable analysis, there was a significant (odds ratio 1.47, 95% CI 1.06 to 2.05) increase in the prevalence of sensitization from 1990 to 1998 when taking into account sex

Table 1. Rates for participation in the follow-up study in percentages (number of subjects participating in the follow-up study) by age group and allergic sensitization at baseline, sex, and familial predisposition to hayfever

Age at baseline (year)	Sensitization at baseline			Sex			Familial predisposition to hayfever		
	Yes	No	Difference†	Men	Women	Difference†	Yes	No	Difference†
15–22	64.3 (18)	64.0 (32)	0.3	71.0 (22)	62.0 (31)	9.0	71.4 (15)	63.3 (38)	8.1
23–30	76.9 (20)	72.6 (45)	4.3	74.5 (35)	72.1 (31)	2.4	66.7 (10)	74.7 (56)	– 8.0
31–38	66.7 (14)	62.4 (53)	4.3	62.3 (33)	64.2 (34)	0.1	70.8 (17)	60.5 (49)	10.3
39–46	82.4 (14)	67.4 (58)	15.0	73.3 (33)	66.7 (40)	6.6	77.8 (14)	68.8 (59)	9.0
47–54	55.0 (11)	69.3 (52)	– 14.3	68.6 (35)	62.2 (28)	6.4	76.2 (16)	61.6 (45)	14.6
55–62	60.0 (6)	55.7 (34)	4.3	66.7 (26)	43.8 (14)	22.9	64.7 (11)	53.7 (29)	11.0
63–69	50.0 (2)	47.8 (22)	2.2	53.1 (17)	38.9 (7)	14.4	40.0 (2)	51.2 (22)	– 11.2
Total	67.5 (85)	63.7 (296)	3.8	67.4 (201)	61.5 (185)	5.9	70.2 (85)	63.1 (298)	7.1

†Difference in percentage points.

Table 2. Age-specific prevalence of allergic sensitization in percentages (number of sensitized subjects) by birth cohort

Year of birth	Age-group (year)							
	15–22	23–30	31–38	39–46	47–54	55–62	63–70	71–77
1919–26							8.0 (4)	8.3 (2)
1927–34						14.1 (10)	12.5 (5)	
1935–42					21.1 (20)	17.5 (11)		
1943–50				16.5 (17)	16.7 (12)			
1951–58			19.8 (21)	20.9 (14)				
1959–66		29.5 (26)	36.9 (24)					
1967–74	35.9 (28)	42.3 (22)						
<i>P</i> -value*	–	0.176	0.022†	0.602	0.607	0.765	0.724	–

*Chi-square test evaluating age-specific differences in the prevalence of sensitization between birth cohorts (vertical comparison). †Significant.

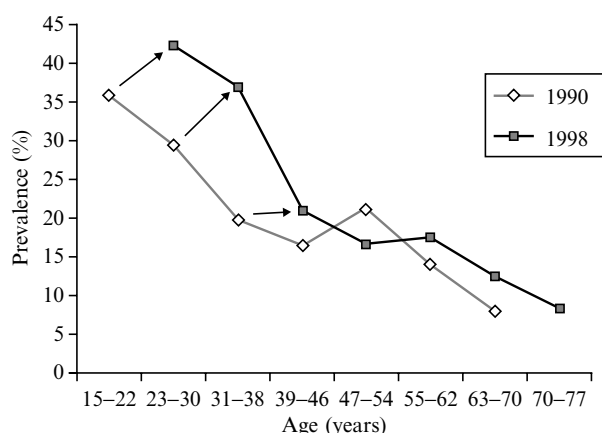


Fig. 1. Changes in the prevalence of allergic sensitization by age-group in a general population cohort between 1990 and 1998.

and age at examination. The *P*-value for test for interaction between study year and age at examination was 0.051. Thus, there was no statistically significant change from 1990 to 1998 in the effect of age on the prevalence of sensitization, which would imply a cohort effect.

In both studies the prevalence of allergic sensitization decreased with increasing age (chi-square test for trend: $P < 0.001$ in both studies).

Discussion

In this general population cohort the prevalence of allergic sensitization showed an increasing trend only among subjects who were less than *c.* 30 years in 1990, i.e. among subjects who were born around 1960 or thereafter.

The prevalence of sensitization tended to increase only in the two youngest age groups. Although subjects who were sensitized at baseline tended to participate at a higher rate than those who were not sensitized at baseline, this was not particularly seen in the two youngest age groups (Table 1). Of note is that the highest participation rate was found among subjects who were sensitized and 39 to 46 years at baseline. Nevertheless, the prevalence of sensitization did not change in this age group. The prevalence of sensitization tended to increase among subjects who were 23 to 30 years at baseline, but not among subjects who were 31 to 38 years at baseline. However, the difference in participation to follow-up in percentage points between those sensitized and those not sensitized at baseline was the same in these two age-groups, i.e. 4.3% (Table 1). Similar arguments could be applied for the difference in participation to follow-up by sex and familial predisposition to hayfever (both male sex and familial predisposition to hayfever were significantly associated with sensitization). Furthermore, essentially similar results were obtained when the analysis was restricted to those subjects who participated in both studies (data not shown). However, we cannot exclude the possibility that differences between age groups in participation to follow-up may have influenced the results.

It would have been of interest to have information on sensitization status in our cohort at earlier ages. In particular, it would have been interesting to know whether the curve of sensitization by age group in Fig. 1 would some decades ago have been horizontal, i.e. without any association between the

prevalence of sensitization and age. This would favour the interpretation that the decrease in the prevalence of sensitization with increasing age observed in many cross-sectional studies is due to a cohort effect. A second future follow-up of our study population may further elucidate this issue. However, if the observed distribution of the prevalence of sensitization by age in 1990 was solely due to an age-effect, we would expect a decline in the prevalence of sensitization among those less than 30 years at baseline. On the contrary, we observed an increase in these age groups (Fig. 1).

In multivariable analysis we found a significant increase in the overall prevalence of sensitization in this cohort when taking into account the effect of sex and age. A change in the distribution of the prevalence of sensitization by age from 1990 to 1998 would imply the occurrence of a cohort effect. In the multivariable analysis this change was only borderline significant. Thus, we cannot make any definitive conclusion on whether the relationship of age to the prevalence of sensitization reflects a cohort effect, an age effect, or a combination of both effects. Nevertheless, in our opinion these data support the suggestion that a cohort effect underlies the increasing trend of sensitization in our background population.

It has been discussed whether an individual's susceptibility to sensitization is primarily influenced by risk factors in early childhood, and whether risk factors also operate later in life. These two notions are not mutually exclusive, and the influence of risk factors may furthermore vary with age. Our data seem to suggest that the increase in sensitization in our study population is caused by a cohort effect. This finding is consistent with the idea that the youngest generations in our cohort have been exposed to risk factors in early childhood (or *in utero*) that have changed their susceptibility to IgE sensitization. However, changes in risk factors that operate in childhood and adolescence among the youngest generations in our cohort could also potentially explain the observed increase.

We speculate that the responsible factors became ubiquitous in western societies before or during the 1960s. Nevertheless, many changes in lifestyle and environment occurred at that time. Establishing the time period at which the increase began may provide a clue as to what factors could, and could not, have contributed to this increase. For instance, vaccination against measles has been suggested as a contributing factor to the rising prevalence of allergic respiratory disease [7]. In Denmark, however, a vaccination programme in children against measles, mumps and rubella was not launched until 1987. Thus, our study population has not been vaccinated as part of this programme. Therefore, it is unlikely that vaccination against measles, mumps and rubella has had a major influence on prevalence rates of allergic respiratory disease in Denmark. Many other factors have been put forward to explain the increasing prevalence of respiratory allergy, e.g. increased intake of *trans* fatty acids [8], increased body weight [9], decreased exposure to infections [10], and decreased microbial pressure on the gut-associated lymphoid tissue [11]. As regards the latter hypothesis, it could be of interest that the microbial content of foods has probably decreased substantially as the use of antimicrobial preservatives in foods, pasteurization of milk products and refrigerators became widespread in western societies.

Heinrich et al. compared age-specific prevalences of allergic sensitization to inhalant allergens among 20 to 44-year-olds in an eastern (Erfurt) with a western (Hamburg) German city [12].

They found that subjects aged 20 to 30 years born in the period 1962 to 1971, but not earlier, were responsible for the higher prevalence of sensitization in Hamburg as compared with Erfurt. This finding suggests that the increase in the prevalence of allergic respiratory disease in western Germany is caused by a cohort effect. Jögi et al. reported age-specific prevalences of allergic respiratory disease and allergic sensitization to common inhalant allergens in Tartu (Estonia) and Uppsala (Sweden) [13]. In Uppsala the prevalence of allergic respiratory disease was inversely related to age, whereas this was not the case in Tartu. Although the same age-dependency of the difference in the prevalence of allergic sensitization between the two cities was not so evident, this may suggest that a cohort effect underlies the increasing prevalence of allergy in Sweden. In Switzerland, the prevalence of self-reported hayfever doubled from 1958 to 1986 (5% vs. 10%), while in 1928 the prevalence of self-reported hayfever in Switzerland was rare, i.e. less than 1% [14]. In a Danish cross-sectional study, Schultz-Larsen et al. investigated the prevalence of atopic eczema in the twin population of Fyn County. The cumulated prevalence up to age 7 increased steadily from 3.2% among those born between 1960 and 1964 to 11.5% among those born between 1975 and 1979 [15]. Moreover, data from examinations of Finnish military conscripts between 1921 and 1989 indicates that the increase in the prevalence of asthma among Finnish men began around 1960, and showed a linear increasing trend thereafter [16]. Thus, there seem to be some evidence that the increase in atopic diseases in Europe began during the 1950s to 1960s.

In conclusion, the results support the notion that the increasing prevalence of allergic respiratory disease is caused by a cohort effect, i.e. an increase associated with being born around 1960 or thereafter. This suggests that changes in lifestyle or environmental factors that occurred around or after that time are at least partly responsible for the recent increase in allergic respiratory disease.

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References

- 1 von Mutius E. The rising trends in asthma and allergic disease. *Clin Exp Allergy* 1998; 28 (Suppl. 5):45–9.
- 2 Linneberg A, Nielsen NH, Madsen F, Frølund L, Dirksen A, Jørgensen T. Increasing prevalence of specific IgE to aeroallergens in an adult population: two cross sectional surveys 8 years apart. The Copenhagen Allergy Study. *J Allergy Clin Immunol* 2000; 106:247–52.
- 3 Weeke ER. Epidemiology of hay fever and perennial allergic rhinitis. *Monogr Allergy* 1987; 21:1–20.
- 4 Sibbald B. Epidemiology of allergic rhinitis. *Monogr Allergy* 1993; 31:61–79.
- 5 Mygind N, Dahl R. Epidemiology of allergic rhinitis. *Pediatr Allergy Immunol* 1996; 7:57–62.
- 6 Nielsen NH, Svendsen UG, Madsen F, Dirksen A. Allergen skin test reactivity in an unselected Danish population. The Glostrup Allergy Study, Denmark. *Allergy* 1994; 49:86–91.
- 7 Shaheen SO, Aaby P, Hall AJ et al. Measles and atopy in Guinea-Bissau. *Lancet* 1996; 347:1792–6.
- 8 Weiland SK, von Mutius E, Husing A, Asher MI. Intake of trans fatty acids and prevalence of childhood asthma and allergies in Europe. ISAAC Steering Committee [Letter]. *Lancet* 1999; 353:2040–1.
- 9 Huang SL, Shiao G, Chou P. Association between body mass index and allergy in teenage girls in Taiwan. *Clin Exp Allergy* 1999; 29:323–9.
- 10 Strachan DP. Hay fever, hygiene, and household size. *Br Med J* 1989; 299:1259–60.
- 11 Matricardi PM, Rosmini F, Riondino S et al. Exposure to foodborne and orofecal microbes versus airborne viruses in relation to atopy and allergic asthma: epidemiological study. *Br Med J* 2000; 320:412–7.
- 12 Heinrich J, Nowak D, Wassmer G et al. Age-dependent differences in the prevalence of allergic rhinitis and atopic sensitization between an eastern and a western German city. *Allergy* 1998; 53:89–93.
- 13 Jögi R, Janson C, Björnsson E, Boman G, Björkstén B. Atopy and allergic disorders among adults in Tartu, Estonia compared with Uppsala, Sweden. *Clin Exp Allergy* 1998; 28:1072–80.
- 14 Wuthrich B. Epidemiology of the allergic diseases: are they really on the increase? *Int Arch Allergy Appl Immunol* 1989; 90 (Suppl. 1):3–10.
- 15 Schultz LF. Atopic dermatitis: a genetic-epidemiologic study in a population-based twin sample. *J Am Acad Dermatol* 1993; 28:719–23.
- 16 Haahtela T, Lindholm H, Björkstén F, Koskenvuo K, Laitinen LA. Prevalence of asthma in Finnish young men. *Br Med J* 1990; 301:266–8.