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Temporal trends of aeroallergen sensitization over twenty-five years

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Clinical and
Experimental
Allergy

Summary

Background Little is known about time trends of allergic respiratory disease in adults, in particular in older adults. Furthermore, few trend studies have used objective measurements of IgE sensitization against inhalant allergens.

Objectives To investigate time trends of aeroallergen sensitization in adults over a 25-year period.

Methods The study includes a total of 7820 persons, aged 30, 40, 50, and 60 years, who participated in three repeated cross-sectional studies of the general population of Copenhagen, Denmark, in 1976–1977, 1982–1984, and 1999–2001, respectively. Respiratory allergy was assessed by determination of specific IgE aeroallergen sensitization in stored serum samples.

Results Over this 25-year period, a marked and statistically significant increase in the prevalence of aeroallergen sensitization had occurred. This increase was seen in all age-groups challenging the notion that the allergy epidemic only affects generations born 1960 onwards. For example, in 40-year-olds the prevalence (with 95% confidence intervals) of aeroallergen sensitization was 14.9% (12.7–17.1), 19.7% (17.1–22.3), and 27.6% (25.1–30.1) in 1976–1977, 1982–1984, and 1999–2001, respectively.

Conclusions Our results support that the allergy epidemic has spread to older adults resulting in a continuing increase in the overall prevalence of aeroallergen sensitization and an increase in the mean age of allergic patients.

Keywords aeroallergen sensitization, allergy, epidemiology, specific IgE

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Introduction

It has been discussed whether the reported increase in allergic respiratory disease as assessed by questionnaire or interview surveys reflects a true increase or merely increased recognition of symptoms or changes in labelling of disease over time [1]. This has emphasized the need for the inclusion of objective measurements of allergic respiratory disease in time-trend studies.

In children and young adults, the overall balance of evidence supports that a significant increase in allergic respiratory disease has occurred in developed countries [2–10]. This increase appears to have started with genera-

tions born around 1960 or later that may have been subjected to early life risk factors increasing their susceptibility to allergic respiratory disease [3, 11]. Recent evidence suggests that in developed countries the increase in children has reached a plateau [12–14]. It is not known whether this trend is due to changes towards a more healthy risk factor profile or if it merely reflects a ceiling (saturation) effect, i.e. the majority of genetically susceptible individuals in the population now go on to develop allergic respiratory disease.

In cross-sectional studies, it has consistently been shown that the prevalence of allergic respiratory disease and aeroallergen sensitization decreases with increasing age. This has often been interpreted as if allergic patients tend to outgrow their allergy as they get older. However, it is increasingly being recognized that allergic respiratory disease is a reasonably chronic condition in adulthood, [3, 5, 6, 15] suggesting that the overall prevalence of

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allergic respiratory disease in the total population will continue to increase as the allergic generations (those born around 1960 or later) grow older. As a consequence, the mean age of patients with allergic respiratory disease is expected to increase due to an increasing prevalence of allergic respiratory disease among older adults [6, 16]. However, little is known about the trends of allergic respiratory disease in these age-groups.

In three cross-sectional population-based studies in 30–60-year-olds over a 25-year period, we investigated time trends of aeroallergen sensitization, a well-established objective measure of allergic respiratory disease.

Methods

Study populations

The study comprises three cross-sectional studies of age- and sex-stratified random samples drawn from the Danish Civil Registration System, in which all people living in Denmark are registered by a unique 10-digit number. In the 1982–1984 and 1999–2001 studies, the sampling frame represented all subjects living in 11 municipalities (Ballerup, Brøndby, Glostrup, Herlev, Albertslund, Hvidovre, Høje Taastrup, Ledøje-Smørum, Rødovre, Ishøj, and Vallensbæk) of Copenhagen County. In the 1976–1977 study, the sampling frame represented four of the above municipalities (Brøndby, Glostrup, Herlev, and Ledøje-Smørum).

In each of the studies, the randomly selected persons were invited by a standard letter for a health examination focusing on risk factors for cardiovascular disease. Enclosed was a questionnaire concerning medical history and health and lifestyle to be completed in advance. The wording of questions used for the present analyses were the same in the three studies. As part of the studies blood was drawn, left to coagulate, serum separated, and kept at -20°C until the analysis in 2004. Participants had no knowledge that their participation would later involve serological allergy testing as part of the present study.

The 1976–1977 study. A random sample of 1200 men and women born in 1936 (aged 40 years) was invited for the health examination. Between August 1976 and July 1977, a total of 1052 persons were examined (87.7% of the invited) [17].

The 1982–1984 study. The 1982–1984 study represents the Danish MONICA I study of the WHO MONICA project [18, 19]. A random sample of 4807 men and women, born in 1922, 1932, 1942, and 1952 (aged 30, 40, 50, and 60 years), was invited for the health examination. Between November 1982 and February 1984, a total of 3608 persons (78.8% of the invited) were examined.

The 1999–2001 study. The subjects were participants in the baseline study of the Inter99 study [20]. An age-

stratified random sample of persons born in 1939–1940, 1944–1945, 1949–1950, 1954–1955, 1959–1960, 1964–1965, and 1969–1970 (aged 30, 35, 40, 45, 50, 55, and 60 years) were invited for the health examination. Only the subjects aged 30, 40, 50, and 60 years born in 1939–1940, 1949–1950, 1959–1960, and 1969–1970 ($n = 6918$) were selected for the present study since these age-groups were included in the earlier studies (in 1976–1977 and 1982–1984). The health examinations took place between March 1999 and January 2001. A total of 3609 (52.2% of the invited) were examined.

Measurement of aeroallergen sensitization

Measurement of aeroallergen sensitization was performed using the ADVIA Centaur[®] allergy screen assay (Bayer HealthCare Diagnostics division, Tarrytown, NY, USA) [21, 22]. The assay is a multi-allergen one for the qualitative detection of specific IgE antibodies specific to common inhalant allergens in serum. The test encompasses the 19 most commonly encountered inhalant allergens: Two house dust mites (*Dermatophagoides pteronyssinus* and *D. farinae*), three animal danders (horse, cat, and dog), two grasses (*Phleum pratense* and *Cynodon dactylon*), three moulds (*Cladosporium herbarium*, *Aspergillus fumigatus*, and *Alternaria alternata*), four trees (*Betula verucosa*, *Quercus alba*, *Olea europae*, and *Cryptomeria japonica*), four weeds (*Ambrosia artemisifolia*, *Artemisia vulgaris*, *Plantago lanceolata*, and *Parietaria officinalis*), and finally one insect (*Blattella germanica*). Aeroallergen sensitization was defined as a positive result of the dichotomized assay output [22]. Serum samples were analysed consecutively in 2004. Analyses were performed at the *In Vitro* Business Unit, ALK-Abelló A/S, Stenløse, Denmark.

Statistical analyses

Ninety-five percent confidence intervals (CIs) for the estimated prevalence of aeroallergen sensitization were calculated using the normal approximation to the binomial distribution [23]. The increase in the prevalence of aeroallergen sensitization was evaluated by logistic regression analysis by including study year (1976–1977, 1982–1984, and 1999–2001) as the independent variable and sensitization as the dependent variable. Multivariable logistic regression models were performed separately for each age-group (30, 40, 50, and 60 years). The variables considered in these regression models are shown in Table 1. The strategy was to include these variables stepwise in groups observing changes in the odds ratio estimates for the study year. These groups were: (1) sex, alcohol, smoking, and season, (2) sex, alcohol, smoking, season, vocational training, BMI, and cholesterol. Table 2 shows crude estimates and estimates adjusted for sex, alcohol, smoking, and season (group 1). Changes in the odds ratio estimate for a specific study year may be calculated by

Table 1. Characteristics of the study populations

	Year of examination		
	1976–1977	1982–1984	1999–2001
Number of persons examined	1056	3785	3609
Participation rate (%)	87.7	78.8	52.2
Persons with available serum sample	989	3481	3350
Persons excluded due to missing serum sample	67 (6.3%)	304 (8.0%)	259 (7.2%)
Females	527 (53.3%)	1720 (49.4%)	1681 (50.2%)
Males	462 (46.7%)	1761 (50.6%)	1669 (49.8%)
Aeroallergen sensitization	147 (14.9%)	594 (17.1%)	865 (25.8%)
Current smoking	534 (54.0%)	2004 (57.6%)	1287 (38.4%)
Missing	0	0	17 (0.5%)
Age (years)			
30	–	946 (27.2%)	325 (9.7%)
40	989 (100%)	925 (26.6%)	1241 (37.0%)
50	–	819 (23.5%)	1304 (38.9%)
60	–	791 (22.7%)	480 (14.3%)
Vocational training (yes)	706 (71.4%)	2430 (69.8%)	2683 (80.1%)
Missing	1 (0.1%)	0	121 (3.6%)
Alcohol (drinks per week)			
0	201 (20.3%)	504 (14.5%)	321 (9.6%)
1–7	426 (43.1%)	1664 (47.8%)	1501 (44.8%)
8–14	170 (17.2%)	635 (18.2%)	692 (20.7%)
15–21	83 (8.4%)	297 (8.5%)	350 (10.5%)
≥ 22	109 (11.0%)	378 (10.9%)	334 (10.0%)
Missing	0	3 (0.1%)	152 (4.5%)
Body mass index			
≤ 22.5	373 (37.7%)	1123 (32.3%)	649 (19.4%)
22.5–26	381 (38.5%)	1292 (37.1%)	1187 (35.4%)
≥ 26	235 (23.8%)	1065 (30.6%)	1514 (45.2%)
Missing	0	1 (0.0%)	0
Serum cholesterol (mmol/L)			
< 4.5	37 (3.7%)	260 (7.5%)	641 (19.1%)
4.5–6.5	599 (60.6%)	2092 (60.1%)	2158 (64.4%)
≥ 6.5	353 (35.7%)	1128 (32.4%)	550 (16.4%)
Missing	0	1 (0.0%)	1 (0.0%)

dividing the odds ratio estimate for the study year in the adjusted model by the crude estimate obtaining the relative change in percent. For example, the crude and adjusted odds ratio estimate for the year 1999–2001 among 60-year-olds was 2.54 and 2.29, respectively (Table 2), yielding an approximately 10% relative change. Changes above 15% (arbitrarily chosen) were considered important.

Subsequently, all age-groups were included in the same model, but without the 1976–1977 participants (where only 40-year-olds were included). In this model, first-order interactions of study year with age and sex were examined.

Ethics

The three studies had previously been approved by the Ethical Committee for Copenhagen County. In 2002, the present study including measurement of specific IgE in

serum samples that had been kept in our biobank was approved by the Ethical Committee for Copenhagen County (KA 02136).

Results

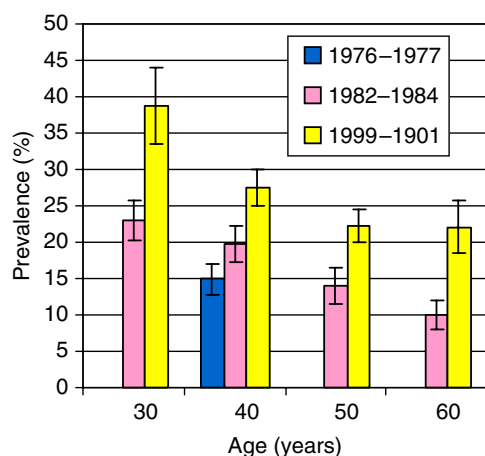
Characteristics of the study populations are shown in Table 1. The most evident changes in potential risk factors over time were increased prevalence of overweight (BMI > 26), and decreased prevalence of current smoking and decreased levels of serum cholesterol. The prevalence of aeroallergen sensitization increased in all age-groups (Fig. 1). The 95% CIs were not overlapping in any of the age-groups thereby emphasizing that the increases were highly statistically significant within each age-group. In multivariable logistic regression analyses, these increases remained statistically significant after adjustment for other factors, suggesting that the increase in aeroallergen sensitization was not fully explained by changes in the

Table 2. Odds ratios (ORs) (95% confidence intervals) comparing the prevalence of aeroallergen sensitization in 1999–2001 and 1976–1977 to the prevalence of aeroallergen sensitization in 1982–1984

Year of examination					
1976–1977			1999–2001		
Age (years)	Crude OR*	Adjusted OR*	1982–1984	Crude OR*	Adjusted OR*
30	†	†	1 (reference)	2.20 (1.67–2.90)	2.13 (1.58–2.87)
40	0.71 (0.56–0.90)	0.73 (0.57–0.93)	1 (reference)	1.55 (1.26–1.90)	1.51 (1.22–1.86)
50	†	†	1 (reference)	1.79 (1.41–2.27)	1.61 (1.26–2.06)
60	†	†	1 (reference)	2.54 (1.85–3.50)	2.29 (1.63–3.195)

*ORs has been obtained in four separate logistic regression models for each age-group. In the adjusted analyses, ORs were adjusted for sex, smoking, alcohol consumption, season of examination, and study year (year of examination).

†The 1976–1977 study included only 40-year-olds.

**Fig. 1.** Age-stratified prevalence (with 95% confidence intervals) of aeroallergen sensitization from 1976 to 2001 in Copenhagen, Denmark (total $n = 7820$).

risk factors included (Table 2). In these multivariable analyses, the odds ratio estimate for study year changed $<15\%$ relative to the crude estimates. The single factor that had the most marked influence on the estimates for study year was smoking status. Accordingly, smoking status was independently associated with a lower prevalence of aeroallergen sensitization (data not shown). In the analysis, where the 1976–1977 study was excluded (because this study only included 40-year-olds), there was no statistically significant interaction of study year with sex ($P = 0.663$) or age-group ($P = 0.055$). Thus, the increase in the prevalence of aeroallergen sensitization from 1982–1984 to 1999–2001 could be assumed to be similar across age-groups and sexes.

Discussion

We found evidence of a substantial increase in the prevalence of aeroallergen sensitization from 1976 to 2001 in all age-groups examined and in both sexes.

Few studies have examined time trends of aeroallergen sensitization in repeated cross-sectional population-based studies in adults. In London, England, Law *et al.* [5] investigated trends in three cross-sectional samples (500 persons in each sample) of 40–64-year-olds and found evidence of an increase in the prevalence of aeroallergen sensitization from 1975–1976 to 1996–1998. Consistent with this, the present results, which are based on data from 7820 persons, lend strong support to the hypothesis that a significant increase in allergic respiratory disease has occurred in adults over the last decades and supports the notion that the allergy epidemic has spread to older adults [16]. It has been suggested that the increase in allergic respiratory disease started with generations born around 1960 onwards, and that generations born before 1960 were largely unaffected [3]. Thus, it has been proposed that these ‘allergic generations’ born 1960 onwards have been exposed to novel environmental or lifestyle risk factors that mainly operate early in life. Inconsistent with this, we found a substantial increase in 60-year-olds (the 60-year-olds examined in 1999–2001 were born in 1940), suggesting that the allergy epidemic also affects generations born before 1960. This finding may even raise the question as to whether risk factors for respiratory allergy operate only in early life or also in adult life. In support of this view, we found evidence of an increase in sensitization from 40 to 60 years of age in persons belonging to approximately the same birth cohort. Thus, the prevalence of sensitization was 14.9 (95% CI 12.7–17.1) and 22.1 (95% CI 18.4–25.8) at the age of 40 years (born 1936 and examined in 1976–1977) and 60 years (born 1939–1940 and examined in 1999–2001), respectively. The non-overlapping 95% CIs clearly show that this increase was statistically significant. The above evidence suggests that allergy development in adulthood is relatively common and may challenge the notion that aeroallergen sensitization primarily develops in early life.

Although aeroallergen sensitization is a generally accepted biomarker of allergic respiratory disease, the

relationship between aeroallergen sensitization and allergic disease may vary with the population under study and possibly also over time. Thus, in another repeated cross-sectional study in Copenhagen, there was a significant increase in aeroallergen sensitization (specific IgE against inhalant allergens) and an increase in the strength of the association between aeroallergen sensitization and allergic respiratory symptoms from 1990 to 1998 [4]. Thus, the sensitivity, i.e. the proportion of sensitized persons reporting allergic symptoms, increased from 1990 to 1998 indicating increased morbidity among sensitized individuals or alternatively increased awareness of symptoms.

The present analyses comprise data from three large population-based studies that aimed at investigating risk factors for cardiovascular disease. There were no available data on symptoms or diagnoses of allergic respiratory diseases. However, the increase in aeroallergen sensitization observed in this adult Danish general population is consistent with previously reported increases in self-reported diagnoses of allergic respiratory disease from 1987 to 2000 [24] and symptoms of allergic respiratory disease from 1989 to 1998 [25] in Danish adults emphasizing that the increase in aeroallergen sensitization is of clinical significance. Furthermore, the increase in aeroallergen sensitization is in line with numerous questionnaire studies that have reported increases in self-reported symptoms and diagnoses of allergic respiratory disease in developed countries worldwide.

It should be considered whether persons with aeroallergen sensitization would be more likely to participate in the 1999–2001 study as compared with the earlier studies, thereby inducing selection bias. However, at the time the studies were performed, the hypothesis of the present article and the decision to analyse IgE antibodies were not known to either the study participants or the researchers responsible for the conduct of the studies. The aim of all three studies was to study risk factors of cardiovascular disease. Thus, it seems unlikely that sensitized persons would have been more likely to participate in the most recent study compared with the earlier studies. However, assuming that other factors, e.g. socioeconomic status, were strongly associated with both aeroallergen sensitization and participation, this might have influenced the results. Of note is that a marked increase in aeroallergen sensitization was also observed from 1976–1977 to 1982–1984, and both these studies had reasonably high-participation rates. Assuming that non-participants had a 25% lower prevalence of aeroallergen sensitization as compared with participants, it can be calculated that the prevalence of aeroallergen sensitization in the total sample (both participants and non-participants) in 1982–1984 and 1999–2001 would be 15.9% (95% CI: 14.9–16.9) and 22.5% (95% CI: 21.5–23.5), respectively. The decrease in participation rate over time is part of a steadily decreasing

trend of participation rates of population-based studies performed in Denmark during this period.

The diagnostic efficacy of the immunoassay used in the present study has been evaluated in another population-based study in Copenhagen and it proved to be a valid measure of allergic respiratory disease [22]. All serum samples were analysed consecutively by using the same immunoassay and at the same laboratory thereby minimising bias due to interobserver or laboratory variability and changes in diagnostic techniques over time. Moreover, we have previously confirmed the stability of specific IgE in serum samples stored at -20°C for 8 years in our biobank [4]. There was no evidence of degradation of specific IgE during this period. On the contrary, concentrations of specific IgE tended to be higher when samples were re-analysed after 8 years of storage as compared with the initial analysis 8 years earlier, indicating that evaporation during storage or thawing might have occurred. Assuming that evaporation increases with increasing storage time, this would tend to overestimate the concentrations of specific IgE in serum samples kept for the longest time in the biobank, thereby possibly underestimating the increase in the prevalence of aeroallergen sensitization.

In conclusion, over a 25-year period, we found strong evidence of a substantial increase in the prevalence of aeroallergen sensitization. This increase was equally present in 30, 40, 50, and 60-year-olds, thus challenging the notion that the allergy epidemic only affects generations born 1960 onwards and that allergy development primarily occurs in early life. Although, in many countries, the increase in allergic respiratory disease appears to be starting to level off in children, the present data suggest that the prevalence of allergic respiratory disease, as reflected by aeroallergen sensitization, continues its increase in adults resulting in a continuing increase in the overall prevalence of allergic respiratory disease and an increase in the mean age of allergic patients. The impact of these trends on public health and on the direct and indirect costs may be significant.

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