

ORIGINAL ARTICLE

The increase in allergy and extended challenges

A. Linneberg

Research Centre for Prevention and Health, Glostrup University Hospital, the Capital Region of Copenhagen, Copenhagen, Denmark

To cite this article: Linneberg A. The increase in allergy and extended challenges. *Allergy* 2011; **66** (Suppl. 95): 1–3.

Keywords

Copenhagen allergy study; epidemiology; exposure; respiratory disease.

Correspondence

Allan Linneberg, Research Centre for Prevention and Health, Glostrup University Hospital, the Capital Region of Copenhagen, Copenhagen, Denmark.
E-mail: allin01@glo.regionh.dk

Accepted for publication 17 March 2011

DOI:10.1111/j.1398-9995.2011.02619.x

Abstract

The prevalence of allergic diseases shows a well-documented increase in developed countries over several decades. Currently, 20–25% of European adults are affected. Westernisation, urbanisation, and affluence contribute to allergy development, so allergy is expected to increase in developing countries in the future. Identifying primary causes, developing new therapies, and increasing treatment access may interrupt the allergic epidemic.

In developed countries, allergic respiratory disease (ARD) has shown an increasing trend over the past five decades. This was first observed in self-reported studies using questionnaires and interviews about symptoms of allergic rhinitis and asthma. The rise in ARD was particularly dramatic in the 1990s, as seen in three large questionnaire-based studies, conducted from 1989 to 2006 in adults in Copenhagen, Denmark (1, 2). The increase in allergic rhinitis was not attributed to an increase in awareness of ARD in the general population or among doctors, or to changes in diagnosis criteria, because the findings were confirmed by objective measures in clinical studies on the general population in Denmark. These studies defined allergic rhinitis as a combination of relevant symptoms and objective allergy IgE sensitivity determined by skin prick test and blood tests against aeroallergens. The 1998 report found that 21.2% of young adults in Copenhagen had allergic rhinitis. The most recent survey from 2006, conducted in the same manner and using the same criteria, shows a continued increase in allergic rhinitis that is possibly beginning to plateau (3, 4).

The 20% prevalence of allergic rhinitis was confirmed by a similar study in eight European countries (5) that indicated that allergic rhinitis is probably the most common disease in young adults. The study also demonstrated that allergic rhinitis is underdiagnosed, with 31% of young adults unaware of their allergic status. The condition is also undertreated, with 47% of allergic subjects receiving no treatment in the previ-

ous 2 years. Although the increase in ARD prevalence may be becoming less dramatic in Europe, the prevalence in developing countries is predicted to increase, based on factors discussed later.

Impacts and implications of the allergy epidemic

Globally, ARD has an enormous societal and individual impact. The direct costs of moderate-to-severe allergic rhinitis were estimated at 343 Euros per year per patient (6), for services such as primary and secondary health care and prescription medicines. Indirect costs such as sick days from work were estimated to be even greater, at 547 Euros per patient per year.

A study of 47 occupational settings and covering more than 8000 employees in the United States found that employees reporting allergic rhinitis symptoms had an average of 52 days per year of symptoms, resulting in 3.6 days per year of absence from work. In terms of productivity loss, allergic rhinitis was estimated as the most costly disease, above other candidates including stress and cardiovascular disease (7).

At the patient level, ARD also has serious implications. Although doctors may tell patients they may 'outgrow' their allergy, a study following children to age 22 found that the rate of sensitization increased throughout childhood (8). A prospective followup study in Copenhagen that followed 174 ARD patients with pollen sensitivity for 8 years found a

remission rate of only 15%, with 98% of patients still having a positive pollen allergy test at the end of the follow-up period (9). Therefore, for a majority of people with allergic rhinitis, the disease takes a chronic course.

Allergic rhinitis is strongly linked to asthma. The 8-year Copenhagen study found that people with allergic rhinitis who were asthma free at the beginning of the study had a risk of developing asthma over the 8 years of the study that was 8–46 times higher than in people without allergic rhinitis (10). People with one allergy had an increased risk of developing additional sensitivities. For example, patients with grass allergy were found to have a 12 times higher risk of cat allergy over the 8-year study than patients with no other allergies. A similar pattern was seen for other allergens.

Why is allergy increasing?

With decades of questionnaire-based and objectively assessed data on ARD, the trend of increasing prevalence is clear, and the economic and clinical effects are documented. Many hypotheses have attempted to explain the rise in ARD and atopic diseases such as allergic rhinitis, asthma and atopic dermatitis. Genetics and environment and their interaction are clearly important, but lifestyle changes also contribute to the development of allergy. Although the exact causes are unknown, worldwide epidemiological observations show that three factors are consistently associated with high atopic disease prevalence: westernization, urbanization, and affluence. For example, Greenland has a native Inuit population that until recently lived a traditional lifestyle with fishing and hunting as the main occupations, in an environment with no industry and few cars. As a more western lifestyle was adopted in this population, diseases associated with globalization increased, such as diabetes, cardiovascular disease, asthma, and allergy (11). Thus, from a global perspective, a continuing increase in ARD may be expected, especially in countries in Eastern Europe and Asia that are undergoing westernization and urbanization and increasing affluence. This suggests that, among other populations, 1.3 billion Chinese may be entering the allergic march.

The factors that underlie the association of westernization, urbanization, and affluence with allergic disease are under investigation. Urbanization has the ability to induce large differences in allergy prevalence, even in populations that are very genetically homogeneous. For example, a study in Greece (12) found that although rural area homes have indoor cats and dogs at more than twice the rate of urban area homes (58.8% rural prevalence vs 27.4% urban prevalence for cats; 50.3% rural prevalence vs 18% urban for dogs), positive skin prick tests for cat and dog allergens were more than twice as frequent in the urban areas than the rural areas (5.2% urban prevalence vs 2.1% rural for cats; 3.2% urban prevalence vs 1.5 rural for dogs).

How are these findings reconciled with the notion that increasing doses of allergen increase the risk of allergy? Environmental exposure is known to contribute to the development of IgE sensitization and this has been the basis for allergen avoidance recommendations for IgE-mediated aller-

gic disease. However, this policy seems to be contradicted by the finding that cat and dog allergies are more common in urban areas, where homes have fewer indoor cats and dogs than in rural areas, and similar results for other allergens such as house dust mites were also obtained (2).

The bell-shaped curve

A plausible explanation for why exposure to allergens is involved in IgE sensitization, yet lower pet allergy prevalence appears to be associated with higher exposure to indoor pets, is that the dose response between allergen exposure and risk of allergy is not linear but bell-shaped (Fig. 1). This bell-shaped curve hypothesis, also proposed by Dr. Patrick Holt (13), states that the risk of sensitization is low when exposure is in the lower allergen concentration range. At a certain level of allergen, allergy begins to be induced, but at higher levels of allergen, tolerance results. The level at which tolerance occurs is determined by individual factors, including genetic makeup. An individual with a higher personal risk of developing ARD requires a lower dose of allergen to develop allergy (individual B in Fig. 1). Relevant to allergen-specific immunotherapy according to this hypothesis, this person would also require a higher dose of allergen to induce tolerance.

This hypothesis may explain many of the conflicting results obtained in epidemiological and allergy avoidance studies. It also suggests several areas of future research to determine why individuals have different responses to allergen-specific immunotherapy and what discriminates between the levels at which tolerance is induced in individuals. This approach is also known as personalized medicine.

In summary, more than 20% of adults in Europe suffer from allergic rhinitis and the trends suggest that prevalence will increase on a global basis. In the majority of allergic rhinitis cases, the disease is chronic and confers greater risk of asthma and additional allergies. This obviously poses both a substantial challenge to the field of allergy research and treatment development, to change the course of the disease. Accessibility and diagnosis are key issues, with the need to

Dose-response curve for allergen exposure and risk of sensitization ?

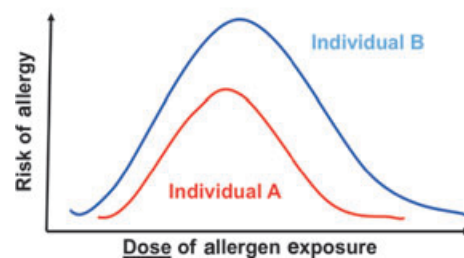


Figure 1 Hypothetical dose-response curve for allergen exposure and risk of sensitization. The red line shows the relationship for a low-risk individual (A) and the blue line shows the relationship for a high-risk individual (B).

better identify those in need of treatment and introduce treatments to broader populations. Currently, allergen specific immunotherapy is the only treatment capable of changing the course of allergic disease. Nonetheless, recent findings on the epidemiology of allergic rhinitis provide an opportunity to change the course of the allergy epidemic, by investigating novel risk factors within urbanization, westernization, and

affluence that may open new avenues for treatment, accessibility, and diagnosis.

Conflict of interest

Allan Linneberg has received lecture fees from ALK-Abelló and MSD.

References

1. Linneberg A, Nielsen NH, Madsen F, Frolund L, Dirksen A, Jorgensen T. Secular trends of allergic asthma in Danish adults. The Copenhagen Allergy Study. *Respir Med* 2001;**95**:258–264.
2. Linneberg A. Are we getting enough allergens? *Int Arch Allergy Immunol* 2008;**147**:93–100.
3. Linneberg A, Jorgensen T, Nielsen NH, Madsen F, Frolund L, Dirksen A. The prevalence of skin-test-positive allergic rhinitis in Danish adults: two cross-sectional surveys 8 years apart. The Copenhagen Allergy Study. *Allergy* 2000;**55**:767–772.
4. Linneberg A. Unpublished data. 2006.
5. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. *Eur Respir J* 2004;**24**:758–764.
6. Petersen KD, Gyrd-Hansen D, Dahl R. Health-economic analyses of subcutaneous specific immunotherapy for grass pollen and mite allergy. *Allergol Immunopathol (Madr)* 2005;**33**:296–302.
7. Lamb CE, Ratner PH, Johnson CE, Ambegaonkar AJ, Joshi AV, Day D et al. Economic impact of workplace productivity losses due to allergic rhinitis compared with select medical conditions in the United States from an employer perspective. *Curr Med Res Opin* 2006;**22**:1203–1210.
8. Rhodes HL, Thomas P, Sporik R, Holgate ST, Cogswell JJ. A birth cohort study of subjects at risk of atopy: twenty-two-year follow-up of wheeze and atopic status. *Am J Respir Crit Care Med* 2002;**165**:176–180.
9. Bodtger U, Linneberg A. Remission of allergic rhinitis: an 8-year observational study. *J Allergy Clin Immunol* 2004;**114**:1384–1388.
10. Linneberg A, Henrik Nielsen N, Frolund L, Madsen F, Dirksen A, Jorgensen T. The link between allergic rhinitis and allergic asthma: a prospective population-based study. The Copenhagen Allergy Study. *Allergy* 2002;**57**:1048–1052.
11. Krause T, Koch A, Friberg J, Poulsen LK, Kristensen B, Melbye M. Frequency of atopy in the Arctic in 1987 and 1998. *Lancet* 2002;**360**:691–692.
12. Priftis KN, Anthracopoulos MB, Nikolaou-Papanagiotou A, Matziou V, Paliatsos AG, Tzavelas G et al. Increased sensitization in urban vs. rural environment – rural protection or an urban living effect? *Pediatr Allergy Immunol* 2007;**18**:209–216.
13. Holt PG, Thomas WR. Sensitization to airborne environmental allergens: unresolved issues. *Nat Immunol* 2005;**6**:957–960.