

Prevalence and predictors of atopy among young Danish adults

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Summary

Background The prevalence of atopic diseases is increasing in western countries, and environmental exposures in childhood may influence development of atopic sensitization.

Objective To investigate the prevalence and predictors of atopy among young Danish adults.

Methods Of 940 invited subjects, aged 19–29 years, complete data were obtained from 525 (56%) subjects. All completed a questionnaire concerning asthma, rhinitis, preschool nursery care, smoking habits, family size, education and employment. A skin prick test was performed, and pulmonary function was measured using standard techniques. Atopy was defined as a positive skin prick test.

Results The frequency of atopy was 32% (males 43% vs. females 23%, $P < 0.001$). We found a positive association between atopy and atopic dermatitis ($P < 0.05$), rhinitis ($P < 0.001$), itching when eating nuts ($P < 0.001$) and current asthma ($P < 0.001$). There was an inverse relation between atopy and having furred pets in childhood ($P < 0.05$), passive smoking in childhood ($P < 0.01$) and current passive smoking ($P < 0.05$). An increasing number of siblings was inversely related to atopy to grass ($P < 0.05$); however, only an increasing number of older siblings seemed to protect from atopy to grass ($P < 0.05$). Subjects who had never attended a day-care centre had significantly more atopy to grass ($P < 0.05$). No significant association was found between atopy and airway infections requiring hospitalization before the age of 5 years, or between atopy and bedroom sharing in childhood.

Conclusion Atopy is common among young Danish adults, especially in males. Participants were less likely to be atopic, especially to grass allergen, if they came from large families, had kept furred pets as children, and had been exposed to tobacco smoke.

Keywords adults, atopy, family size, prevalence, risk factor, siblings, skin prick test, smoking

Submitted 22 June 2001; revised 25 September 2001; accepted 5 October 2001

Introduction

In the past few decades numerous studies have reported a rise in the prevalence of atopic diseases, including allergic rhinitis, asthma and atopic dermatitis, in both children [1–4] and adults [5] in different parts of the world. The prevalence of rhinitis has doubled or tripled over a period of 10 to 25 years [1,4,6]. Newly reported frequencies of atopy range between 19% among adults in Tartu, Estonia [7], and 43% among teenagers in northern Sweden [8]. However, most studies report frequencies of atopy in adults around 30–35% [9–13]. Several reports seem to have revealed important factors associated with atopic diseases. An inverse relationship between family size and manifestations of allergy is described in many reports [14–19]. One hypothesis is that this is due to a protective effect of early childhood infections, as they selectively enhance differentiation of Th cells to the Th1 subtype, suppressing the Th2 subtype, which is implicated in IgE-mediated allergy [18,20]. Others conclude that this is not the case [14,17,21,22]. Other suggested explanations for the increase in allergic diseases are increasing exposure to allergens [23] and an increased population

susceptibility as a consequence of reductions in dietary intake of antioxidants [24].

Conflicting results and sometimes unexpected correlations emphasize that we are facing a multifaceted health problem and that the explanation for the rise in atopic disorders is not straightforward.

This study investigates factors associated with atopy in a random population sample of young adults from the city of Copenhagen, Denmark.

Methods

Subjects

All subjects included in the study took part in a prospective study of asthma, allergy and airway hyper-responsiveness initiated in 1986 [25]. A random sample of 983 children and adolescents living in the area surrounding Rigshospitalet in the city of Copenhagen was drawn from the civil registration list. All subjects were born between 1969 and 1979.

In 1998 all subjects in the original sample were invited by letter to participate in the present study. Seven had died prior to the study in 1998 and 36 subjects were living outside Denmark. Of the 940 eligible subjects, 624 (66%) participated in the present study (345 females and 279 males), aged

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18–29 years (mean age 23.9), of whom 90 subjects only completed a written questionnaire. All data used in this analysis were taken from the examination in 1998. Only data for the 525 participants with complete data were included in the analyses (nine subjects did not answer all the questions in the questionnaire). The discussion of potential non-responder bias has been published previously [26]. Briefly, stayers, drop-outs and newcomers were compared in two previous examinations of this population. No differences were found between the groups with respect to anthropometric data and prevalence of atopy.

Exclusion criteria

In case the participants were taking medication for asthma or allergy, they were asked not to use theophylline or an antihistamine for at least 24 h, astemizole for 6 weeks, an oral β_2 -agonist for 18 h, an inhaled short acting β_2 -agonist for 6 h, and a long acting β_2 -agonist for 12 h, before the tests. They were allowed to continue use of any inhaled or oral corticosteroid they had been taking. In case of recent respiratory infection, the examination was postponed for 6 weeks.

In case of pregnancy, histamine challenge test and skin prick test were not performed and, furthermore, breast-feeding mothers were excluded from the histamine challenge test.

Case history

All participants filled in a written questionnaire concerning respiratory and allergic symptoms as related to themselves and their parents, current and former smoking habits, drinking habits, education, family size and sports activities.

The questions concerning allergy and allergy-related factors were as follows:

1. Have you ever experienced allergy in your nose or eyes [27]?
2. Have you ever had atopic dermatitis?
3. Do you have carpets in your bedroom?
4. Did you have pets in your home as a child?
5. Do your parents suffer from allergy? If yes, do they suffer from allergy towards pollen, animal dander, house dust mites or moulds?
6. How old are your siblings, and did you grow up together with them?
7. Where were you taken care of in your pre-school years?
8. Is there moisture on the inside of the windows at your home in the wintertime, and how far up?
9. Is there mould on the walls at your home?
10. Did you share a bedroom with any older siblings before the age of 5?
11. Did you have a serious hospital-requiring airway infection before the age of 5?
12. Does eating nuts cause itching in your mouth?

Disposition to allergic disease was defined as a positive answer to either maternal or paternal allergy, or both.

Furthermore, all participants reported whether they were current smokers, ex-smokers or never smokers. The duration of smoking and the daily tobacco consumption were registered, and an estimate of their lifetime tobacco exposure was calculated as pack-years: current tobacco consumption (g/day) $\times$ duration of smoking (years). Passive maternal and paternal smoke exposure during childhood and/or from a present

partner, if any, was also noted. Based on the available data it was not possible to quantify the extent of tobacco exposure during childhood. Current passive smoking was quantified as hours of daily tobacco exposure.

Skin prick test

Subjects were tested on the volar surface of the distal forearm, using standard dilutions (10 HEP) of allergens in 50% glycerol (ALK, Hørsholm, Denmark). Skin prick tests (SPTs) were done in duplicate according to the EAACI guidelines [28] with a histamine standard of 10 mg/mL and the diluent as a negative control. The allergens used were birch, grass, mugwort, horse, dog, cat, house dust mite (HDM) (*Dermatophagoides pteronyssinus* and *D. farinae*) and two moulds (*Alternaria iridis* and *Cladosporium herbarum*). The positive control was read after 10 to 15 min, and the remaining weals were read after 12 min. Weal reactions were outlined with a fine marker and transferred to paper with transparent tape. The reaction to each of the allergens was regarded as positive if the mean weal diameter $[(d1 + d2)/2]$ was at least 3 mm [29]. In case of reaction to the negative reference, a positive result was recorded when the difference between the mean weal diameter of the reaction to the allergen and to the negative reference exceeded 3 mm. A positive SPT was defined as a positive reaction to at least one of the allergens [29].

Atopy was in the present paper defined as a positive skin prick test, whereas atopic diseases were defined as self-reported symptoms and a positive skin prick test.

Pulmonary function test

The forced expiratory volume in 1 s (FEV₁) and forced vital capacity (FVC) were measured with a 7-L dry wedge spirometer (Vitalograph®) that was calibrated weekly. Each measurement consisted of at least two maximal expiratory manoeuvres from total lung capacity to residual volume with a variation of less than 5%. The highest FEV₁ and FVC were used in the analyses. Data on pulmonary function were also expressed as a percentage of predicted values (%pred), using prediction equations based on age, sex and height in non-smoking white individuals [30].

Blood samples

Venous blood was taken (before the histamine challenge test) into both a dry glass and a tube containing EDTA. From the EDTA blood the number of total leucocytes and eosinophilic leucocytes was counted.

Statistics

The data were analysed using the statistical package SPSS 10.0. Differences in mean (SD) values between atopics and non-atopics were tested with non-parametric analysis. Prevalence rates were calculated for the entire group and the subgroups, and differences were tested using chi-square analysis. Logistic regression analysis was used to assess potential risk factors primarily for the presence of atopy. Non-significant variables were deleted by backward elimination using the Wald statistic. A *P*-value < 0.05 was considered significant.

The study was approved by the local ethical committee of Copenhagen, Denmark.

Results

Complete data were available for 525 subjects, 229 males and 296 females. Characteristics of the examined subjects are given in Table 1. Eighty per cent of the participants had pets in childhood and 80% were passive smokers as children. A total of 13% never attended day-care in their pre-school years and 7% lived in moistured homes. Subjects with disposition to allergic disease (27%) were less often exposed to tobacco smoke (70% vs. 82%, $P < 0.01$), whereas no difference was found in pet ownership.

The point prevalence of atopy to at least one specific inhalant allergen was 31.8%, of whom 63.5% had ever experienced allergic symptoms from the nose and/or the eyes.

A very pronounced gender difference was observed as 43.2% males and 23.0% females were found to be atopic ($P < 0.001$).

The frequency of atopy to pollen allergens accounted for 19.8%, followed by atopy to mite allergen with a frequency of 16.2%. The gender specific prevalences are visualized in Fig. 1. Among the atopics, 86.2% had a positive reaction to grass, cat or mite allergen. One-third reacted to only one allergen, and only one single person had a positive reaction to all 10 allergens.

In univariate analysis the following factors were inversely associated with atopy (Table 1): having a cat or other furred pet (apart from a dog) in childhood ($P < 0.05$); passive smoking in childhood ($P < 0.01$); current passive smoking ($P < 0.05$); and the total leucocyte count ($P < 0.05$). The difference in height between atopic and non-atopic subjects is most likely due to the higher proportion of males in the former group.

The type of current occupation was also associated with atopy as both the skilled workers and the independent own-office workers had significantly more atopy ($P < 0.05$). Unskilled workers had significantly less atopy ($P < 0.05$) (Table 2) when compared with students, unemployed participants and housewives. The type and length of education was not associated with atopy.

When analysing data in a multiple logistic regression model the following factors were found to be significantly related to

atopy (Table 3): rhinitis (OR 9.0, CI 5.5–14.6); current asthma (OR 2.9, CI 1.4–6.2); skilled worker (OR 1.3, CI 1.0–1.5); passive smoking in childhood (OR 0.5, CI 0.3–1.0); and the total leucocyte count (OR 0.8, CI 0.7–0.9). The data are adjusted for gender, and the question of whether eating nuts caused itching in the mouth is not included as the relation must be regarded as a cross-reaction rather than a potential risk factor. No significant association was found between AHR (OR 1.0, CI 0.9–1.0), day-care centre attendance (OR 1.0, CI 0.6–1.6), current active smoking (OR 0.9, CI 0.6–1.3), disposition to allergic disease (OR 1.2, CI 0.8–1.8), hospital requiring airway infections before the age of 5 (OR 0.9, CI 0.4–2.2), or bedroom sharing in childhood (OR 1.1, CI 0.7–1.8), and the presence of atopy.

Further analysing data with regard to factors potentially associated with atopy to grass, which in our study was the most prevalent form of atopy, showed that an increasing number of siblings was inversely related to atopy to grass ($P < 0.05$) (Table 4). After dividing the siblings into older and

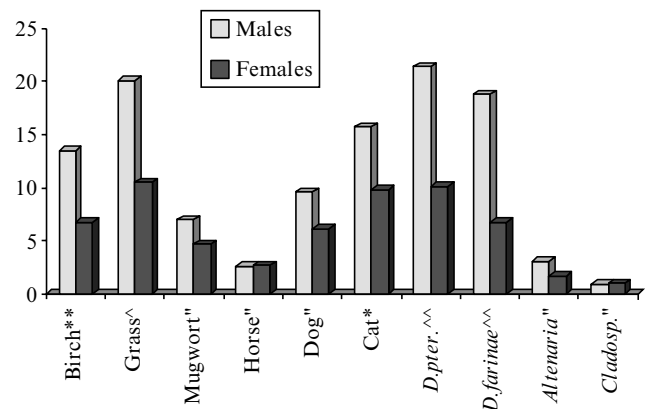


Fig. 1. Gender-specific prevalences of atopy to 10 different aeroallergens in a sample of young Danish adults, aged 19 to 29 years ($n = 525$). * $P < 0.05$, ** $P < 0.01$, ^ $P < 0.005$, ^^ $P < 0.001$, 'NS.

Table 1. Baseline characteristics (mean and (SD)) and factors associated with atopy in a population sample comprising 525 subjects, aged 19 to 29 years (% of column)

	Atopic	Non-atopic	Total	P-value
<i>n</i>	167	358	525	
Males/females	99/68	130/228	229/296	< 0.001
Age (yr)	24.0 (2.9)	23.9 (3.0)	23.9 (2.9)	= 0.56
Height (cm)	176.6 (9.5)	173.3 (9.2)	174.3 (9.3)	< 0.05
Weight (kg)	74.6 (17.0)	69.6 (14.2)	71.1 (15.4)	= 0.53
BMI	23.8 (4.7)	23.1 (4.0)	23.3 (4.3)	= 0.40
Atopic dermatitis	15.6%	8.9%	11.1%	< 0.05
Rhinitis ever	63.5%	17.0%	31.6%	< 0.001
Nuts itching	15.4%	2.8%	7.4%	< 0.001
Current asthma	19.2%	5.3%	9.3%	< 0.001
Cat in childhood	33.5%	43.9%	39.7%	< 0.05
Furred pets in childhood	26.3%	36.6%	32.5%	< 0.05
Passive smoking in childhood	73.1%	83.2%	78.7%	< 0.01
Current passive smoking	44.3%	54.5%	51.0%	< 0.05
Leucocyte count	6.37 (1.7)	7.27 (3.1)	6.97 (2.8)	< 0.05

Table 2. Occupational pattern in atopic and non-atopic subjects, % of subgroup (non-atopic or atopic)

	Non-atopic	Atopic	P-values
<i>n</i>	358	167	
Education (%)			
No education	10.6	9.6	NS
Apprentice	14.5	18.6	NS
Short school education	11.7	13.2	NS
Intermedian school education	36.3	28.1	= 0.065
Long school education	30.7	35.9	NS
Occupation (%)			
Unemployed	11.7	10.8	NS
Unskilled worker	22.9	14.4	< 0.05
Skilled worker	17.3	25.1	< 0.05
Housewife	1.4	1.8	NS
Independent own office worker	2.0	6.0	< 0.05
Salaried employees	10.3	10.8	NS
School/university	33.0	29.3	NS

Table 3. Factors associated with atopy in a population sample (*n* = 525). Multiple logistic regression model. Adjusted for sex

	OR	95% CI	P-value
Rhinitis	9.0	5.5–14.6	< 0.001
Passive smoking in childhood	0.5	0.3–1.0	< 0.05
Current asthma	2.9	1.4–6.2	< 0.005
Skilled worker	1.3	1.0–1.5	< 0.05
Leucocyte count	0.8	0.7–0.9	< 0.005

younger siblings, only an increasing number of older siblings seemed to protect from atopy to grass ($P < 0.05$). We have only included siblings whom the participants had mainly grown up with in order to avoid bias by including a lot of siblings and half-siblings the participants didn't have any contact with in childhood.

Subjects who were solely looked after at home in their pre-school years had significantly more atopy to grass ($P < 0.05$), as well as a significantly higher prevalence of ever having had rhinitis ($P = 0.02$).

Moistured homes, defined as mould spots on the walls in the subjects present homes, were negatively associated with atopy to grass ($P < 0.05$).

The eosinophil count was associated with atopy to grass, mugwort, dog and moulds.

Analysing data with regard to factors potentially associated with atopy to house dust mites – another common form of atopy in our study, and in Denmark – did not reveal any new statistically significant associations.

Discussion

This population study of unselected young adults from Copenhagen, Denmark, shows that atopy is common among young adults, especially in males. We found that subjects (i) from large families, especially with more older siblings, (ii) who

Table 4. Factors specifically associated with atopy to grass in a population sample comprising 525 subjects. Multiple logistic regression. Adjusted for sex

	OR	95% CI	P-value
Number of siblings	0.6	0.4–1.0	< 0.05
Older siblings	0.5	0.3–0.9	< 0.05
Never attended day-care centre	2.6	1.2–5.6	< 0.05
Moisture at home	0.1	0.0–0.7	< 0.05
Eosinophil count	16.1	2.2–118	< 0.01

had cats or other furred pets in their household as children, and (iii) had been exposed to smoke, had less atopy, especially to grass allergen. Furthermore, subjects who had never attended a day-care centre were more atopic to grass.

It is known that boys run a higher risk for atopy than girls [23], and although this sex difference tends to decrease in adulthood, most authors report a higher total IgE and a higher prevalence of specific IgE antibodies and of skin test positivity in men than in women [31,32]. We found a remarkably higher frequency of atopy in males than in females, which correlates to earlier findings of atopy in unselected adults in Denmark [10] and England [12], while the prevalence of positive skin prick tests was equal among the sexes in teenagers in northern Sweden [8]. In our study, a higher sensitization rate in males for house dust mite, birch, grass and cat epithelium accounted for the gender difference, and it didn't change significantly if a weal diameter of 2 mm was regarded as positive reaction, which some authors use as standard (data not shown). This is in contrast to the equal prevalence of self-reported rhinitis among the males and females (31% vs. 32%), suggesting either differential symptom recognition by the two sexes or a higher frequency of non-allergic rhinitis among the females.

In univariate analysis we found a protective effect of cat ownership in childhood on adult atopy. All furred pets except dog were negatively associated with atopy. The association disappeared in multivariate regression analysis. In our study no difference in pet ownership in subjects with and without parental allergy was seen, so the hypothesis that families with allergy less often keep pets in their household is not likely to explain the association. Earlier studies have also found a protective effect of dog and cat ownership in childhood on adult atopy. The protective effect of cat ownership was in one study only seen in subjects with parental allergy [33]. In children no such association was found by the age of 4 years [34].

It is well documented that passive smoking is an important risk factor for asthma [35] but its association with allergic sensitization is less clear. In Denmark smoking is socially acceptable, in contrast to many other countries. This could explain the relatively high prevalence of passive smokers during childhood in our cohort. We found that passive smoking in childhood and present passive smoking was significantly associated with a lower prevalence of atopic sensitization, of which only passive smoking in childhood was an independent factor. This can partly be explained by the fact that the allergic parents in our study were less likely to smoke. Current smokers or ex-smokers were not associated with atopy. This is in contrast to other studies that have found that current smokers are less likely than non-smokers to be skin-reactive [10,12,32]. On

the other hand Plaschke et al. found a higher frequency of sensitization to mite and a higher total IgE level among smokers [11]. The explanation of why tobacco smoke in some studies seems to protect from atopic sensitization is not fully understood, and one should be careful in drawing conclusions. A plausible explanation could be that tobacco smoke has some kind of immunosuppressive effect that makes the individual more susceptible to infections, which again might prevent the development of atopic disease. The seemingly protective effect of a higher leucocyte count might also reflect a higher prevalence of virus infections in these individuals.

We found an almost equal pattern of education among atopics and non-atopics. The atopics tended more often to have an apprentice education or long school education and work as skilled workers or have their own business, and they were less likely to be unskilled workers (Table 2). Atopic diseases have earlier been regarded as an upper class disease [36]. In our study we didn't obtain information concerning parents' education or the participants' living conditions in childhood and are therefore unable to see whether atopy is still more frequent in the higher social layers in our cohort. Although disposition to allergic disease is a well-known risk factor for development of atopy, we didn't find any statistically significant correlation. The parents were not skin prick tested or interviewed themselves, and the information regarding whether parents were allergic was based on interviewing the participants, which might be an imprecise method and cause a misclassification and underestimation of the connection between heredity and atopy in our study.

One of the strongest and most consistent risk factors for atopic disease relates to sibship size [12,14–19,33]. We found that the prevalence of skin prick test positivity to grass was inversely related to number of siblings, and that only the number of older siblings had independent effect on the prevalence of atopy to grass. This is consistent with other findings [12], while some studies do not find any difference in the protective effect of younger and older siblings [15,33]. Some authors describe a stronger protective effect of brothers than sisters [33]. In keeping with our findings, Jarvis et al. reported a negative association between family size and sensitization to grass allergen in young adults, and no relation to atopy to any other allergen [15].

Whether this protective effect of a large household size is due to an increased exposure to infections and thereby a stimulation of Th1 cell response with mutual down-regulation of the Th2 cell response, or/and the socioeconomic status of large families, nutrition, household amenities and hygiene, is widely debated [16]. It has been hypothesized that the decreased impact of infection through social changes and preventive measures may contribute to the rise in atopic disease in industrial countries [23]. We didn't find any relation between serious hospital-requiring airway infections or bedroom sharing before the age of 5, and atopy. Day-care centre attendance, which also promotes early infections, was in our study not related to adult atopy, but subjects who had never attended any day-care centre (13%) had significantly more atopy to grass and ever symptoms, which might point towards the trend that a too protective environment in childhood may predispose to the development of atopic diseases.

In summary, this population study of a sample of young adults from Copenhagen, Denmark, has shown a high fre-

quency of atopy. We found factors associated with a lower prevalence of atopy, such as large households, pets and tobacco smoke. Taken together this supports the hygiene theory, that a too clean environment may enhance the sensitization to aero-allergens. The fact that subjects who had never attended a day-care centre had significantly more atopy to grass supports this notion.

We cannot from this study conclude that early childhood infections explain the association between number of siblings and future risk of atopy. Although many authors have already tried to solve the riddle of the increase in allergic diseases, more epidemiological studies are needed to learn more about the relative importance of the various environmental factors that may enhance the sensitizing effects of early allergen exposure.

Acknowledgements

The Danish Lung Association has financially supported this study. GlaxoWellcome, Brøndby, Denmark, donated salbutamol and ALK-Abello, Hørsholm, Denmark, allergen solutions. The authors wish to thank all the young adults for their participation.

References

- 1 Burr ML, Butland BK, King S, Vaughan-Williams E. Changes in asthma prevalence: two surveys 15 years apart. *Arch Dis Child* 1989; 64:1452–6.
- 2 Burney PGJ, Chinn S, Rona RJ. Has the prevalence of asthma increased in children? Evidence from the national study of health and growth 1973–86. *BMJ* 1990; 300:1306–10.
- 3 Robertson CF, Heycock E, Bishop J et al. Prevalence of asthma in Melbourne schoolchildren: changes over 26 years. *BMJ* 1991; 302:1116–8.
- 4 Ninan TK, Russell G. Respiratory symptoms and atopy in Aberdeen schoolchildren: evidence from two surveys 25 years apart. *BMJ* 1992; 304:873–5.
- 5 Shaw RA, Crane J, O'Donnell TV, Porteous LE, Coleman ED. Increasing asthma prevalence in a rural New Zealand adolescent population: 1975–89. *Arch Dis Child* 1990; 65:1319–23.
- 6 Aberg N. Asthma and allergic rhinitis in Swedish conscripts. *Clin Exp Allergy* 1989; 19:59–63.
- 7 Jøgi R, Janson C, Björnsson E, Boman G, Björkstén B. Atopy and allergic disorders among adults in Tarsu, Estonia compared with Uppsala, Sweden. *Clin Exp Allergy* 1997; 28:1072–80.
- 8 Norrman E, Rosenhall L, Nyström L, Jönsson E, Stjernberg N. Prevalence of positive skin prick tests, allergic asthma, and rhinoconjunctivitis in teenagers in northern Sweden. *Allergy* 1994; 49:808–15.
- 9 Nowak D, Heinrich J, Jörres R et al. Prevalence of respiratory symptoms, bronchial hyperresponsiveness and atopy among adults: West and East Germany. *Eur Respir J* 1996; 9:2541–52.
- 10 Nielsen NH, Svendsen UG, Madsen F, Dirksen A. Allergen skin test reactivity in an unselected Danish population. *Allergy* 1994; 49:86–91.
- 11 Plaschke P, Janson C, Norrman E et al. Skin prick tests and specific IgE in adults from three different areas of Sweden. *Allergy* 1996; 51:461–72.
- 12 Strachan D, Harkins L, Johnston I, Anderson R. Childhood antecedents of allergic sensitization in young British adults. *J Allergy Clin Immunol* 1997; 99:6–12.

- 13 D'Souza W, Lewis S, Cheng S et al. The prevalence of asthma symptoms, bronchial hyperresponsiveness and atopy in New Zealand adults. *NZ Med J* 1999; 112:198–202.
- 14 Bodner C, Godden D, Seaton A. Family size, childhood infections and atopic diseases. *Thorax* 1998; 53:28–32.
- 15 Jarvis D, Chinn S, Luczynska C, Burney P. The association of family size with atopy and atopic disease. *Clin Exp Allergy* 1996; 27:240–5.
- 16 von Mutius E, Martinez FD, Fritzsche L et al. Skin test reactivity and number of siblings. *BMJ* 1994; 308:692–5.
- 17 Pekkanen J, Remes S, Kajosaari M, Husman T, Soininen L. Infections in early childhood and risk of atopic disease. *Acta Paediatr* 1999; 88:710–4.
- 18 Paolo M, Franzinelli F, Franco A et al. Sibship size, birth order, and atopy in 11,371 Italian young men. *J Allergy Clin Immunol* 1998; 101:439–44.
- 19 Nicolai T, Mutius E. Respiratory hypersensitivity and environmental factors: East and West Germany. *Toxicol Lett* 1996; 86:105–13.
- 20 Strachan D. Socioeconomic factors and the development of allergy. *Toxicol Lett* 1996; 86:199–203.
- 21 Ponsonby A, Couper D, Dwyer T, Carmichael A, Kemp A. Relationship between early life respiratory illness, family size over time, and the development of asthma and hay fever: a seven year follow up study. *Thorax* 1999; 54:664–9.
- 22 Bodner C, Anderson W, Reid T, Godden D. Childhood exposure to infection and risk of adult onset wheeze and atopy. *Thorax* 2000; 55:383–7.
- 23 De Swert L. Risk factors for allergy. *Eur J Pediatr* 1999; 158:89–94.
- 24 Seaton A, Soutar A, Mullins J. The increase in hay fever: pollen, particulate matter and SO₂ in ambient air. *Q J Med* 1996; 89:279–84.
- 25 Backer V. Bronchial hyperresponsiveness in children and adolescents. Thesis. *Dan Med Bull.* 1995; 42:397–409.
- 26 Ulrik CS. Comparison of stayers, dropouts, and newcomers in a longitudinal population study of asthma and bronchial hyperresponsiveness: introduction of bias? *J Asthma* 1995; 32 (4):295–300.
- 27 Dirksen A. Clinical vs. paraclinical data in allergy. *Dan Med Bull* 1982; 29 (Suppl. 2):5.
- 28 Dreborg S. Skin tests used in type I allergy testing (position paper). *Allergy* 1989; 44 (Suppl. 10):22–30.
- 29 Dreborg S. The skin prick test. Methodological studies and clinical applications. Medical dissertation, 239. Sweden: Linköping University, 1987.
- 30 Nysom K, Ulrik CS, Hesse B, Dirksen A. Published models and local data can bridge the gap between reference values of lung function for children and adults. *Eur Respir J* 1997; 10:1591–8.
- 31 O'Connor G, Sparrow D, Taylor D et al. Analysis of dose-response curves to methacholine. An approach suitable for population studies. *Am Rev Respir Dis* 1987; 136:1412–7.
- 32 Omenaas E, Bakke P, Elsayed E, Hanoa R, Gulsvik A. Total and specific IgE levels in adults: relationship to sex, age and environmental factors. *Clin Exp Allergy* 1994; 24:530–9.
- 33 Svanes C, Jarvis D, Chinn S, Burney P. Childhood environment and adult atopy: results from the European Community Respiratory Health Survey. *J Allergy Clin Immunol* 1999; 103:415–20.
- 34 Tariq S, Matthews S, Hakim E et al. The prevalence of and risk factors for atopy in early childhood: a whole population birth cohort study. *J Allergy Clin Immunol* 1998; 101:587–93.
- 35 Halken S, Høst A, Nilsson L, Taudorf E. Passive smoking as a risk factor for development of obstructive respiratory disease and allergic sensitization. *Allergy* 1995; 50:97–105.
- 36 Emanuel M. Hay fever, a post industrial revolution epidemic: a history of its growth during the 19th century. *Clin Allergy* 1988; 18:295–304.