

ORIGINAL ARTICLE

Establishing the sequential progression of multiple allergic diagnoses in a UK birth cohort using the General Practice Research Database

Y. S. Punekar¹ and A. Sheikh^{2,3}

¹Schering-Plough Ltd, Welwyn Garden City, UK, ²Allergy & Respiratory Research Group, Centre of Population Health Sciences, The University of Edinburgh, Edinburgh, UK and ³CAPHRI, University of Maastricht, Maastricht, The Netherlands

Clinical & Experimental Allergy

Summary

Background There is considerable international interest in understanding the sequential progression of multiple allergic conditions (also sometimes known as ‘the allergic march’).

Objectives To study the sequential progression of multiple allergic conditions in a national birth cohort throughout childhood.

Methods We constructed a birth cohort of 43 477 children born in 1990 and registered in UK general practices within a year of birth, using the national General Practice Research Database. Of these, 24 112 with complete follow-up until the age of 18 years were studied in order to understand disease progression and to estimate the absolute and relative risks of developing second and third allergic diagnoses following an index allergic condition.

Results 52.1% of children were diagnosed with at least one condition at some point in childhood. We were able to describe 15 different disease trajectories. Eczema was the most likely index condition with 60.7% [95% confidence interval (CI): 59.8–61.6] of allergy sufferers being diagnosed with this condition first. For those with a diagnosis of eczema, the relative risks of being diagnosed with asthma followed by rhinitis and rhinitis followed by asthma were 1.59 (95% CI: 1.32–1.91; $P < 0.0001$) and 0.54 (95% CI: 0.43–0.68; $P < 0.0001$), respectively. For those diagnosed with asthma first, the relative risks of being diagnosed with eczema followed by rhinitis and rhinitis followed by eczema were 1.27 (95% CI: 0.96–1.68; $P = 0.095$) and 0.27 (95% CI: 0.20–0.36; $P < 0.0001$), respectively. For those diagnosed with rhinitis first, the relative risks of being diagnosed with eczema followed by asthma and asthma followed by eczema were 0.64 (95% CI: 0.42–0.95; $P = 0.025$) and 0.47 (95% CI: 0.32–0.67; $P < 0.0001$), respectively.

Conclusions Among children diagnosed with multiple allergic diseases there is likely to be a number of variants of ‘the allergic march’. Of these, the diagnosis of eczema followed by asthma, which is in turn followed by rhinitis, is the most common trajectory. Surprisingly, some diagnoses indicate a possible strong protective effect of manifesting further likely allergic diagnoses.

Keywords allergic march, allergy, asthma, eczema, rhinitis

Submitted 30 March 2009; revised 17 August 2009; accepted 20 August 2009

Correspondence:

Aziz Sheikh, Allergy & Respiratory Research Group, Centre of Population Health Sciences, The University of Edinburgh, 20 West Richmond Street, Edinburgh EH8 9DX, UK.
E-mail: aziz.sheikh@ed.ac.uk

Introduction

‘The allergic march’, which refers to the sequential progression of multiple atopic conditions in terms of their development and symptomatic manifestations, has been an area of considerable interest over recent years. It is well recognized that individuals who develop an allergic disease are at a substantially increased risk of developing further allergic conditions [1]. The dominant pattern or

trajectory for the development of these co-morbid allergic disorders is believed to be eczema followed by rhinitis and then asthma, although the order of progression, where rhinitis or asthma is typically the second condition, is unclear [2, 3].

Several large international cross-sectional multi-centre studies have estimated the prevalence and co-prevalence of eczema, asthma and allergic rhinitis (AR), revealing that these conditions are common and that co-morbidity

affects a substantial proportion of people [4–6]. The natural history of disease is best studied using longitudinal designs and several birth cohort studies have now investigated patterns of disease in children with allergic disease [7–12]. These studies have, for obvious logistical and financial reasons, tended to be relatively small and underpowered, but these have nonetheless progressed our understanding of both the risk of developing these conditions and the importance of potentially avoidable environmental risk factors (such as allergen avoidance) in mediating disease risk [13].

Despite this recent focus of attention on the clustering of multiple allergic conditions in individuals, their progression relative to each other, remains relatively understudied [14, 15]. Thus, it is at present difficult accurately to estimate the risk of a child with eczema developing asthma or rhinitis, for example. This study aimed to describe the sequential progression of multiple allergic conditions based on their sequential diagnoses in children from birth up to the age of 18 years in real clinical practice and estimate the absolute and relative risks of a child developing a subsequent allergic disease following diagnosis of an index condition.

Methods

We constructed a birth cohort of children using the UK General Practice Research Database (GPRD). The GPRD is one of the largest healthcare databases in the world extracting data from 434 practices in England and Wales, comprising 3.68 million active individuals who contribute 32.77 million person-years of data. The records from this database have been validated in several studies [16–20]. Our study protocol was approved by the GPRD Ethics Committee.

Our cohort consisted of children born in the year 1990, who had a complete patient follow-up record until the age of 18 years. Thus, we selected children born between 1 January 1990 and 31 December 1990, who were registered with a GP practice within a year of their recorded date of birth and continued to be registered in the same practice until 31 March 2008. The registration at a GP practice within a year of birth was confirmed by at least one recorded consultation (for immunization) within 180 days of birth. It was also ensured that all selected children were still registered in the same practice by confirming their 'active' status in GPRD on 31 March 2008. This was done to ensure that they were not merely registered with the practice, but were still receiving care as ascertained by the stipulation that all selected children had to have at least one consultation between 31 March 2007 and 31 March 2008. This group was compared with other children born in the same year, but who were excluded from our cohort, on demographic variables to compare the characteristics of those children retained in

our cohort with those who transferred out of these practices.

We have focused on the three most common allergic diagnoses, namely eczema, asthma and rhinitis in this work. The diagnoses of eczema, asthma and rhinitis were identified using relevant: (1) Oxford Medical Information System (OXMIS) codes, which were derived from the International Classification of Disease (version, 8); and (2) Read codes, which are hierarchical codes commonly used in family practices in the United Kingdom. These medical condition codes were then verified using a separate list of eczema, asthma and rhinitis codes used in a previous study obtained by personal communication with the lead author [21]. This verified list of codes was then used to identify children diagnosed with one or more of these allergic conditions from our birth cohort and has been previously reported in this Journal [22].

Based on our previously reported approach, diagnosis of a condition was defined by the presence of two or more separate records of an OXMIS or a Read code relating to the same condition, <12 months apart [22]. For children with only one available mention of the condition, the diagnosis was confirmed only if there was a relevant prescription for the condition in question within 12 months following the diagnosis. The prescriptions used to confirm a diagnosis included a prescription of an emollient or a topical corticosteroid for eczema, a prescription of a β -2 agonist, an antimuscarinic bronchodilator or an inhaled corticosteroid for asthma and a prescription of an antihistamine or intranasal corticosteroid for rhinitis. A detailed list is provided in our previous report on this cohort [22]. In cases where a diagnosis was confirmed, the first record of the diagnosis was considered as the date of diagnosis of the condition. For every child, the date of diagnosis of each condition along with data on baseline characteristics such as gender, registered practice and date of registration were extracted.

The first recorded presumed allergic diagnosis was considered the index condition. In the absence of any literature reporting the minimum duration between two allergic diagnoses for these to be considered as independent, a 30-day period was deemed to be reasonable. For patients with an index condition, sequential progression was therefore defined as the diagnosis of the second condition at least 30 days after the diagnosis of the index condition. Similarly, patients suffering from two conditions were assumed to have a sequential progression only if their third condition was diagnosed at least 30 days after their second diagnosis.

The absolute risk of being diagnosed with the second or third allergic condition was calculated as the proportions of patients with second or third allergic diagnoses. Thus, in the sequential progression from eczema to asthma and then to rhinitis, for example, the absolute

risks of asthma and rhinitis, were the proportion of children diagnosed with asthma after eczema and the proportion of children diagnosed with rhinitis after eczema–asthma, respectively.

The relative risk of a second or a third allergic diagnosis conditional on the index condition was estimated by comparing with matched children who were not diagnosed with the index condition. Matching was carried out using age, practice and gender. A relative risk was defined as the ratio of the probability of developing second or third allergic diagnoses among children with an index condition compared with the general population i.e. the corresponding probability among children without the index diagnosis. Thus, in the sequential progression from eczema to asthma, for example, the relative risk was estimated as the ratio of the probability of being diagnosed with asthma (with or without rhinitis) after eczema to the probability of being diagnosed with asthma without ever being diagnosed with eczema. Similarly, for the sequential progression from eczema to asthma and then to rhinitis, the relative risk was the ratio of probability of being diagnosed with all three conditions in that sequence to the probability of being diagnosed with rhinitis without ever being diagnosed with eczema or asthma. The relative risks for other possible sequential progressions were also estimated in similar manner.

All data extraction and statistical analyses were conducted using STATA v9.2 [23].

Results

Overall characteristics of cohort

Our sample consisted of 43 477 children born in the year 1990 and registered with a general practice within a year of recorded date of birth. Of these children, 24 112 (55.5%) continued in the same practice for the next 18 years until 31 March 2008 and were used in our analysis. The cohort consisted of 12 322 (51.1%) boys and no more than 0.7% patients were included from a single practice. All the patients had at least one consultation during the first year and the last year of their patient record. Among the 19 365 children born in the same year, but lost to follow-up, 51.9% were boys and no more than 0.7% were from a single practice. Our cohort, thus, was not significantly different from children lost to follow-up. More details about this cohort have been reported previously in this Journal [22].

Overall findings

Of the 24 112 children studied, 8810 (36.5%) were diagnosed with eczema, 5514 (22.9%) were diagnosed with asthma and 2750 (11.4%) were diagnosed with rhinitis before reaching the age of 18 years. There was significant

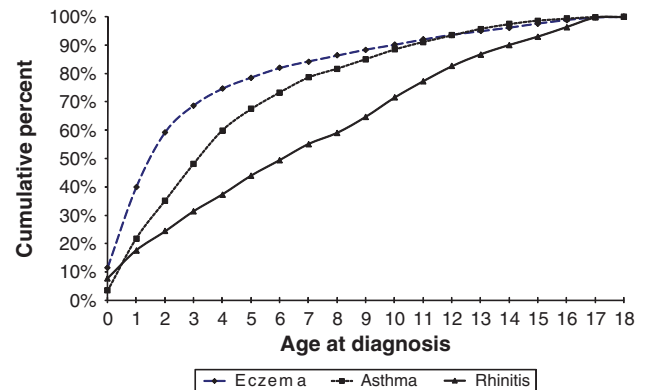


Fig. 1. Age at diagnosis of index conditions for eczema, asthma and rhinitis.

co-morbidity from allergic disease, with 12 545 (52.0%) patients diagnosed with at least one allergic condition, 3880 (16.1%) diagnosed with at least two and 613 (2.5%) diagnosed with all three conditions by the age of 18 years. The age distributions at diagnosis of the index conditions are presented in Fig. 1.

Allergic disease progression

Of the 12 545 children diagnosed with at least one allergic diagnosis, 7608 (60.7%) were diagnosed with eczema as their index condition, 3567 (28.4%) were diagnosed with asthma as their index condition and 1316 (10.5%) had rhinitis as their index diagnosed condition. The remaining 54 (0.4%) children were diagnosed with more than one condition during the same consultation.

We identified 15 sequential progressions as displayed in Fig. 2. We describe below in more detail the six trajectories among children diagnosed with all three allergic conditions.

1. Eczema–Asthma–Rhinitis

Diagnosis of eczema followed by asthma and then rhinitis was the most common sequential progression. Of the 7608 children who were diagnosed with eczema as their index condition, 1664 (21.9%) were diagnosed with asthma as their second allergic condition. The median duration between the two diagnoses was 3 years [inter-quartile range (IQR): 1–6]. Children diagnosed with eczema were at an increased risk of being diagnosed with asthma [relative risk (RR) 1.08; 95% confidence interval (CI): 1.02–1.15; $P = 0.0122$] compared with children without eczema. Two hundred and fifty-six (15.5%) of these patients were subsequently diagnosed with rhinitis. In half of the cases, rhinitis was diagnosed within 5 years (IQR: 2–8) of the diagnosis of asthma. Children diagnosed with eczema followed by asthma were at an increased risk of developing rhinitis (RR 1.59; 95% CI: 1.32–1.91; $P < 0.0001$) compared with children with neither of these conditions.

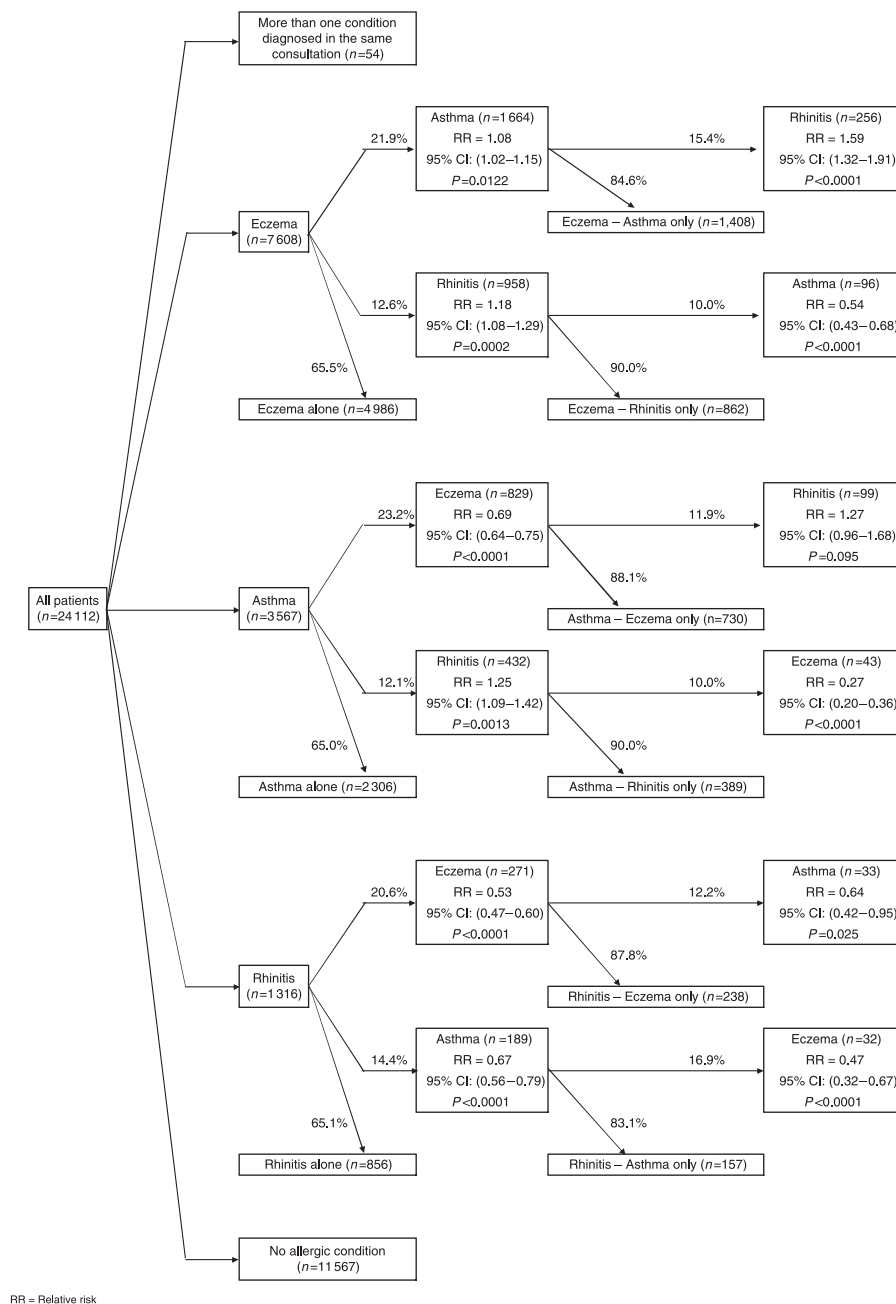


Fig. 2. Sequential progression of diagnoses of multiple allergic conditions.

2. Eczema–Rhinitis–Asthma

Of the 7608 children diagnosed with eczema, 958 (12.6%) were diagnosed with rhinitis as their second allergic condition. In half of these children rhinitis was diagnosed within 6 years (IQR: 3–10) of the diagnosis of eczema. Children diagnosed with eczema were at an increased risk of being diagnosed with rhinitis (RR 1.18; 95% CI: 1.08–1.29; $P=0.0002$) compared with children without eczema. Of these 958 children diagnosed with eczema and rhinitis, 96 (10.0%) were subsequently diagnosed with asthma. The median duration between the

rhinitis and asthma diagnoses was 2 years (IQR: 1–4). Children diagnosed with eczema followed by rhinitis were at a reduced risk of being diagnosed with asthma (RR 0.54; 95% CI: 0.43–0.68; $P<0.0001$) compared with children with neither of these conditions.

3. Asthma–Eczema–Rhinitis

Among 3567 children diagnosed with asthma as their index condition, 829 (23.2%) had eczema as their second allergic diagnosis. The median duration between the two diagnoses was 3 years (IQR: 1–7). Children diagnosed with asthma were at a reduced risk of being diagnosed with

eczema (RR 0.69; 95% CI: 0.64–0.75; $P < 0.0001$) compared with children without asthma. Of these 829 eczema and asthma sufferers, 99 (12.0%) subsequently developed rhinitis. In half of the children, rhinitis was diagnosed 4.5 years (IQR: 2–8) after the diagnosis of eczema. Among children diagnosed with asthma followed by eczema, the risk of being subsequently diagnosed with rhinitis was not significantly different (RR 1.27; 95% CI: 0.96–1.68; $P = 0.096$) compared with children without both these conditions.

4. Asthma–Rhinitis–Eczema

A total of 432 (12.1%) children developed rhinitis as their second allergic condition among 3567 children already diagnosed with asthma as their index condition. The median duration between the two diagnoses was 5 years (IQR: 2–8). Children diagnosed with asthma were at an increased risk of being diagnosed with rhinitis (RR 1.25; 95% CI: 1.09–1.42; $P = 0.0013$) compared with children without asthma. A total of 43 (10.0%) of them were subsequently diagnosed with eczema as their third allergic condition. In half of these children, eczema was diagnosed within 3 years (IQR: 2–6) after the diagnosis of rhinitis. Children diagnosed with asthma followed by rhinitis were at a reduced risk of being diagnosed with eczema (RR 0.27; 95% CI: 0.20–0.36; $P < 0.0001$) compared with children with neither of these conditions.

5. Rhinitis–Eczema–Asthma

Of the 1316 children who were diagnosed with rhinitis as their index condition, 271 (20.6%) were diagnosed with eczema as their second allergic condition. The median duration between the two diagnoses was 2 years (IQR: 1–5). Children diagnosed with rhinitis were at a reduced risk of being diagnosed with eczema (RR 0.53; 95% CI: 0.47–0.60; $P < 0.0001$) compared with children without rhinitis. Thirty-three (12.2%) of these 271 patients were subsequently diagnosed with asthma. In half of these patients, asthma was diagnosed within 3 years (IQR: 2–5) of the diagnosis of eczema. Children diagnosed with rhinitis followed by eczema were at a reduced risk of being diagnosed with asthma (RR 0.64; 95% CI: 0.42–0.95; $P = 0.025$) compared with children with neither of these conditions.

6. Rhinitis–Asthma–Eczema

Of the 1316 children diagnosed with rhinitis, 189 (14.4%) were diagnosed with asthma as their second allergic condition. Asthma was diagnosed in half of these children within 3 years (IQR: 1–5) of the diagnosis of rhinitis. Children with rhinitis were at a reduced risk of being diagnosed with asthma (RR 0.67; 95% CI: 0.56–0.79; $P < 0.0001$) compared with children without rhinitis. Of these 189 patients diagnosed with rhinitis followed by asthma, 32 (16.9%) were subsequently diagnosed with eczema. The median duration between the asthma and eczema diagnoses was 3 years (IQR: 1–8). Children diagnosed with rhinitis followed by asthma were

at a reduced risk of being diagnosed with eczema (RR 0.47; 95% CI: 0.32–0.67; $P < 0.0001$) compared with children with neither of these conditions.

Discussion

Our findings suggest that in those with multiple allergic diagnoses, there are likely to be multiple trajectories of disease progression. We have found that eczema is the most commonly diagnosed index condition followed by asthma and then rhinitis. Among all children diagnosed with at least one allergic condition, 60.7% were diagnosed with eczema first and of all the eczema sufferers, 86.0% had it as their index condition, suggesting that a relatively small proportion of patients developed eczema after asthma or rhinitis. Among the three conditions studied, rhinitis was the only condition to be diagnosed last in the sequence with a relative risk of greater than one. Overall, this work suggests that diagnosis of eczema followed by asthma and then rhinitis is the most plausible sequential progression. This work has also allowed us to estimate the absolute and relative risks of children developing subsequent allergic disease following an index diagnosis.

The median duration between the first and the second allergic diagnosis ranged from 2 to 6 years and that between the second and the third diagnosis ranged from 2 to 5 years. This may in part reflect possible delays in diagnosis, but may equally represent a genuine and important window of opportunity to prevent the development of other allergic conditions.

Of note in this respect is that those with a diagnosis of rhinitis were less likely to be diagnosed with asthma compared with those without diagnosis of rhinitis. This is contrary to some of the previous literature suggesting that rhinitis precedes and may in fact be causally associated with asthma as demonstrated in, for example, the Preventive Allergy Treatment (PAT) study [24]. Our sample had a relatively small proportion of those who were recorded as having rhinitis and then went on to acquire a diagnosis of asthma. This figure is lower than expected, but this may in part be attributable to the fact that rhinitis may have been under-diagnosed in this population [22]. Another possible explanation is that it may only be a subgroup of young people who develop rhinitis before developing asthma and in whom the PAT approach may thus be appropriate.

The major strengths of this work lies in the longitudinal design, national sample, length of follow-up and patient numbers available in GPRD. GPRD collects information from individual practices across the United Kingdom and our results are, thus, likely to be broadly generalizable to the UK population as a whole. The long follow-up period from birth allowed risks to be estimated throughout childhood and adolescence. A cohort with a long follow-up, such as this, may also be useful to investigate whether

effective treatments and control of the index condition can modify the risk of developing subsequent conditions and we are currently exploring the possibility of investigating this hypothesis.

This study also has a number of potential limitations. The allergic march analysis was based on patient records with clinician-diagnosed disease. No supplementary skin prick test, lung function or provocation test results were, for example, available and, thus, the diagnoses could not be verified apart from its repeated mention in the records and/or the associated issuing of a relevant prescription. This is perhaps of the greatest relevance in the context of the asthma diagnosis as a separate analysis of this same cohort has shown that asthma is possibly over-diagnosed in children under the age of 5 years [22]. In order to consider the impact of such diagnostic influences in relation to asthma, we therefore conducted a separate analysis (data not shown) in which we only considered the asthma diagnosis to be valid, if it was diagnosed in children aged 5 years or older or in whom a previous diagnosis was confirmed after the fifth year. The relative risks estimated were similar and the overall results confirmed an identical sequential progression from eczema to asthma and then to rhinitis.

Similar challenges may also occur in separating the diagnosis of infectious rhinitis from AR especially in children at a young age. Therefore, we conducted an additional analysis excluding all rhinitis diagnoses on or before the age of 6 years. The results were very similar (data not shown) confirming the sequential progression from eczema to asthma and then to rhinitis.

The possible under-diagnosis of eczema or rhinitis, particularly in those with less severe disease treated with over-the-counter medications, is also a possible limitation [25]. Although this may potentially bias the results, with this dataset we were not able to make further inroads into establishing the impact, if any, on our findings. However, it is important to note that the incidence and prevalence estimates from this cohort [22] are broadly in line with the previously published estimates [26, 27].

Potential limitations of this work also lie in the limited number of demographic variables available to explore the non-inclusion bias and also to match children with and without the index condition. It is also important to note that in presenting the co-morbid diagnoses results, we used 'allergic conditions' terminology to describe the presence of eczema, asthma and rhinitis alone or in combination. In the present study, we restricted our focus to the three most common likely allergic conditions; we now plan, however, to extend this work to also incorporate other potentially relevant conditions such as food allergy and anaphylaxis.

In conclusion, this study has found that allergic diseases are very common in childhood and that a significant minority of children affected by one condition go on to

develop co-morbid allergic disease. We have been able to characterize 15 different disease trajectories, but also to identify the most common of these, namely eczema followed by asthma and then rhinitis. We have furthermore also been able to estimate the risks of children being diagnosed with other relevant likely allergic conditions, which we hope will prove to be helpful both clinically and also for those planning trials aiming to halt progression of the allergic march.

Acknowledgements

The authors would like to acknowledge the statistical support provided by Carl Gibbons and manuscript review support provided by Karen Durkin.

Statement of interest: Yogesh Punekar is employed by Schering-Plough Ltd. Aziz Sheikh has served as a speaker, a consultant and an advisory board member for Schering-Plough Ltd, and has received research funding from Schering Plough Ltd for advice on this project.

This study was funded in full by Schering-Plough Ltd, and the writing of this paper was funded in full by Schering-Plough Ltd. Writing support was provided by Global Health Solutions and funded by Schering-Plough Ltd.

References

- 1 Wahn U. What drives the allergic march? *Allergy* 2000; 55:591–9.
- 2 Zeiger RS, Heller S, Mellon MH *et al.* Effect of combined maternal and infant food-allergen avoidance on development of atopy in early infancy: a randomized study. *J Allergy Clin Immunol* 1989; 84:72–89.
- 3 Bergmann R, Edenharter G, Bergmann K *et al.* Atopic dermatitis in early infancy predicts allergic airway disease at 5 years. *Clin Exp Allergy* 1998; 28:965–70.
- 4 Burney P, Chinn S, Jarvis D, Luczynska C, Lai E. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). *Eur Respir J* 1996; 9:687–95.
- 5 Kaur B, Anderson H, Austin J *et al.* Prevalence of asthma symptoms, diagnosis, and treatment in 12–14 year old children across Great Britain (international study of asthma and allergies in childhood, ISAAC UK). *Br Med J* 1998; 316:118–24.
- 6 Primatesta P, Stamatakis E. *Health survey for England 2001: respiratory symptoms, atopic conditions and lung function*. The Stationery Office, London, 2003.
- 7 Burney P, Chinn S, Jarvis D, Luczynska C, Lai E. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). *Eur Respir J* 1996; 9:687–95.
- 8 Kaur B, Anderson H, Austin J *et al.* Prevalence of asthma symptoms, diagnosis, and treatment in 12–14 year old children across Great Britain (international study of asthma and allergies in childhood, ISAAC UK). *Br Med J* 1998; 316:118–24.

- 9 Arshad S, Hide D. Effect of environmental factors on the development of allergic disorders in infancy. *J Allergy Clin Immunol* 1992; **90**:235–41.
- 10 Bergmann R, Bergmann K, Lau-Schadendorf S *et al*. Atopic diseases in infancy. The German multicenter atopy study (MAS 90). *Pediatr Allergy Immunol* 1994; **5**:19–25.
- 11 Brussee J, Smit H, van Strien R *et al*. Allergen exposure in infancy and the development of sensitization, wheeze, and asthma at 4 years. *J Allergy Clin Immunol* 2005; **115**:946–52.
- 12 Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995; **332**:133–8.
- 13 Sheikh A, Strachan DP. The hygiene theory: fact or fiction? *Curr Opin Otolaryngol Head Neck Surg* 2004; **12**:232–6.
- 14 Simpson CR, Newton J, Hippisley-Cox J, Sheikh A. Incidence and prevalence of multiple allergic disorders recorded in a national primary care database. *J R Soc Med* 2008; **101**:558–63.
- 15 Strachan DP, Sheikh A. A life course approach to respiratory and allergic diseases. In: Kuh D, Ben-Shlomo Y, eds. *A life course approach to chronic disease epidemiology*, 2nd Edn. Oxford: Oxford University Press, 2004.
- 16 Walley T, Mantgani A. The UK General Practice Research Database. *Lancet* 1997; **350**:1097–9.
- 17 Hansell A, Hollowell J, Nichols T, McNiece R, Strachan D. Use of the General Practice Research Database (GPRD) for respiratory epidemiology: a comparison with the 4th Morbidity Survey in General Practice (MSGP4). *Thorax* 1999; **54**:413–9.
- 18 Nazareth I, King M, Haines A, Rangel L, Myers S. Accuracy of diagnosis of psychosis on general practice computer system. *Br Med J* 1993; **307**:32–4.
- 19 Staa V, Abenheim L. The quality of information recorded on a UK database of primary care records: A study of hospitalisations due to hypoglycaemia and other conditions. *Pharmacoepidemiol Drug Saf* 1994; **3**:15–21.
- 20 Peng M, Jick H. A Population-Based Study of the incidence, cause, and severity of anaphylaxis in the United Kingdom. *Arch Intern Med* 2004; **164**:317–9.
- 21 McKeever T, Lewis S, Smith C *et al*. Siblings, multiple births, and the incidence of allergic disease: a birth cohort study using the West Midlands general practice research database. *Thorax* 2001; **56**:758–62.
- 22 Puneekar Y, Sheikh A. Establishing the incidence and prevalence of clinician diagnosed allergic conditions in children and adolescents using routinely collected data from general practices. *Clin Exp Allergy* 2009; **39**:1209–16.
- 23 StataCorp. *Intercooled Stata 9.2 for Windows*. College Station, TX: Stata Corporation, 1985–2006.
- 24 Jacobsen L, Niggemann B, Dreborg S *et al*. The PAT investigator group. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy* 2007; **62**:943–8.
- 25 Walker S, Sheikh A. Self reported rhinitis is a significant problem for patients with asthma. *Prim Care Respir J* 2005; **14**:83–7.
- 26 Simpson CR, Newton J, Hippisley-Cox J, Sheikh A. Trends in the epidemiology and prescribing of medication for eczema in England. *J R Soc Med* 2009; **102**:108–17.
- 27 Gupta R, Sheikh A, Strachan DP, Anderson HR. Burden of allergic disease in the UK: secondary analyses of national databases. *Clin Exp Allergy* 2004; **34**:520–6.