

Atopy and Asthma in Migrants

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Key Words

Allergy · Immigrants · Migrants · Atopy · Asthma · Vaccination

Abstract

Atopy and asthma result from the effects of environmental factors on genetically susceptible persons, and different prevalence rates have been documented worldwide. In developed and industrialized countries a higher prevalence of atopy and asthma is observed as compared with undeveloped and less affluent countries. Migration involves exposure to a new set of pollutants and allergens. In addition, it involves several socioeconomic and cultural issues such as housing conditions, diet and accessibility to medical services, all of which are likely to affect migrants' health. Migration studies provide information on the role of environmental factors in the development of atopy and asthma. Immigration to allergy-prevalent countries causes more allergies and asthma in immigrants as compared to the prevalence of atopy in their countries of origin. The increase in allergy and asthma is usually not related to ethnicity, but in certain populations may play an important role. Studies on migrants support the notion that lifestyle and environmental factors in western industrialized countries facilitate atopy and asthma. The effect is time-dependent. Acquiring al-

lergy is influenced by the age at the time of immigration. Migrants, in general, are more prone to the development of allergies than the local population. Low hygiene prior to immigration does not seem to protect against the development of atopy or asthma. Vaccinations do not affect the development of atopy or asthma in the general population and in migrants. Migrants should be aware of the potential of developing allergies and/or asthma. Strategies for primary prevention in high-risk atopic individuals and secondary prevention guidelines should be developed both for populations in developing countries as well as for immigrants from such countries to atopy-prevalent developed countries.

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Introduction

Nearly 3% of the world's population are migrants. Over the past 35 years the number of international migrants has more than doubled to 175 million – 1 of every 35 people. Although this increase partially reflects the population growth over the same period, globalization, the gap in living standards between rich and poor countries, and aging societies in the rich world, all fuel greater labor mobility. Migration involves social as well as interesting and intriguing medical issues.

Atopy and asthma result from the effects of environmental factors on genetically susceptible persons [1]. For asthma, a wide range of risk factors have been identified including family history of asthma, prematurity, early viral respiratory infections, indoor-, outdoor- and workplace-inhaled pollutants, allergens, and urban living [1]. The prevalence of atopy and asthma varies markedly throughout the world, being more prevalent in affluent and developed countries than in less affluent and developing countries [1]. Migration involves not only exposure to a new set of pollutants and allergens, but it also involves several socioeconomic and cultural issues such as housing conditions, diet and accessibility to medical services. Migrants from developing to industrialized countries seem to be at an increased risk for atopy and asthma development. Environmental factors and lifestyle in western industrialized cities seem to be associated with this increased risk. In addition, longitudinal studies on the prevalence of asthma conducted in the US revealed that the prevalence of asthma varies among racial and ethnic groups, reflecting differences in genetic, as well as environmental, social and cultural influences among population groups [2].

Migration studies provide information on the role of environmental factors on the development of atopy and asthma. As asthma prevalence varies throughout the world, studying the effects of migration may help identify the reasons for this geographic variation. Studying the incidence and prevalence of atopy and asthma in immigrants can be utilized as a model to understand the interplay between genetic and environmental effects on the development of these diseases.

Several important questions are discussed: Does immigration to allergy-prevalent countries cause more allergies in immigrants compared to the prevalence of atopy in their countries of origin? What is the effect of ethnicity on such changes? What is the effect of time since immigration on such changes. Are immigrants more prone to the development of allergies than the local population and why? What can be learned from migrant studies on the pathophysiology of atopy and asthma? Who is at high risk for the development of allergies upon immigration?

Trends in the Prevalence of Atopic Diseases among Immigrants and Relevant Risk Factors

The prevalence of atopy and allergy in immigrants has been studied in different countries throughout the world, and similar patterns have been described. Studies per-

formed in Australia revealed that children born outside Australia tended to have less asthma and bronchitis than Australia-born children, and immigrant children tended to first develop asthma several years after arriving in Australia [3]. In a similar way, adolescents who migrated to Australia reported increased asthma symptoms, as compared to their peers in their country of origin, and asthma symptoms increased for every year of residence in Australia [4]. Among these adolescents, a 17% prevalence of wheeze was described in recent arrivals, 20% in adolescents having lived in Australia for more than 2 years, and 36% in those having lived all their life in Australia. For every year of residence in Australia there was an 11% increase in the prevalence of current wheeze [4]. The relationship between respiratory symptoms and time since arrival in Australia was demonstrated in an additional study, where residence in Australia for 5–9 years was associated with a 2.1-fold increase in the odds of self-reported wheeze, and after 10–14 years, this risk increased 3.4-fold [5]. This time effect on the prevalence of asthma symptoms was independent of age and country of birth. In addition, no difference was found in the severity of wheeze, as measured by the reported frequency of attacks, between Australian-born and non-Australian-born subjects [5], and at least in one study, the development of wheeze after migration to Australia was independent of eosinophilic inflammation and consistent with noneosinophilic asthma mechanisms [4]. Additional data was reported by Leung et al. [6, 7], who compared the prevalence of asthma, hay fever and atopy in three distinctive subpopulations of Australians: Asian immigrants, Australian-born Asians and Australian-born non-Asians. In patients under 20 years of age, the prevalence of wheeze or asthma ever was significantly higher in Australian-born non-Asians and Australian-born Asians than in Asian immigrants. In contrast, the prevalence of hay fever was significantly higher in Asian immigrants and Australian-born Asians than in Australian-born non-Asians. Similarly, in those older than 20 years, hay fever was almost twice as common in Asian immigrants than in Australian-born non-Asians. In this study, the prevalence of hay fever and, to a lesser degree, asthma in Asian immigrants, increased significantly with the length of stay in Australia, independent of age at arrival, sex and atopic status, and after 10 years in Australia, up to 60% of South East Asian immigrants developed hay fever and 15% had symptoms of asthma [8]. Taken together, these studies found substantial differences in the prevalence of asthma and hay fever between immigrants and the local population in Australia, but somewhat different trends were ob-

Table 1. Trend of atopy and/or asthma rate that developed in migrants compared to country of origin or country of immigration

Investigator	Year	Country	Patients surveyed	Country of origin	Trend ¹	Reference
Kalyoncu and Stalenheim	1992	Sweden	134	Asia, Africa, Middle East, South America	↑	14
Kalyoncu and Stalenheim	1993	Sweden	205	Turkey	↑	13
Leung et al.	1994	Australia	1,169	Asia	↑	6
Asseyr and Businco	1994	Italy	52	Somali	↑	15
Williams et al.	1995	UK	693	Caribbean	↑	22
Geller-Bernstein	1997	Israel	159	Ethiopia	↑	17
Powell et al.	1999	Australia	9,794	Various	↑	5
Hjern et al.	1999	Sweden	1,901	Adopted children from various countries	↑	24
Kabesch et al.	1999	Germany	7,445	Turkey	↑	25
Rosenberg et al.	1999	Israel	906	Ethiopia	↑	11
Tobias et al.	2001	Europe	19,516	Various	↑	10
Dervaderics et al.	2002	Hungary	880	Various	↑	16
Tedeschi et al.	2003	Italy	243	Extra-European	↑	9
Gibson et al.	2003	Australia	211	Asian, South Pacific, Middle East, Europe	↑	4

¹ Trend of atopy or asthma rate with time compared to country of immigration or country of origin.

served. For asthma, a higher prevalence was observed in Australians, either from Asian or non-Asian origin, as compared to recent immigrants. As the length of stay in Australia increases, a gradual increase in the prevalence of asthma is observed. These dynamic changes suggest that either a prolonged environmental exposure or other additional risk factors are required for the development of asthma in immigrants. In contrast, hay fever was more prevalent among immigrants or their offsprings than non-Asian Australians, stressing the effects of recent environmental exposure on its development.

A similar trend of progressive allergic and asthma symptoms developing after immigration has been reported among other ethnic groups of immigrants to industrialized countries. In a study on extra-European immigrants to Milan, Italy, 84% of immigrants declared they were healthy before immigrating, and allergy and asthma symptoms started to appear an average period of 4 years and 7 months after immigration [9]. One of the largest studies performed on the trends in the prevalence of atopic disorders was the European Community Respiratory Health Survey [10]. This study had potential advantages due to the number of countries involved, standardized collection of information, assessment of directionality of migration, and availability of physiological data on bronchial responsiveness and atopy. Prevalence rates of symp-

toms associated with asthma were compared for immigrants, emigrants and nonimmigrants living in centers, mostly in Western Europe. Similar analyses were carried out for bronchial responsiveness and atopy. Medication and use of health services were also evaluated. Overall, 1,678 (8.6%) of 19,516 participants were immigrants in the 18 countries participating in the study, of whom 581 were emigrants from one of the participating countries. Rates of asthma symptoms were higher in immigrants and emigrants compared to nonimmigrants after controlling for area, sex, age and smoking status. However, bronchial responsiveness and atopy were equally distributed between immigrants, emigrants and nonimmigrants. One of the disadvantages of this large study stems from the diversity of the populations studied. As several ethnic groups and different environments have been analyzed, these could have led to a dilution of environmental effects. As opposed to this multiethnic and international study, several studies conducted in Israel on Ethiopian immigrants reveal a more uniform picture. The past 20 years have seen a large immigration of Ethiopian Jews to Israel, primarily in two airlifts, one in 1984–1985 and the other in 1991. This enabled investigators to look at a relatively large but very discrete population of immigrants, which moved from one specific environment to a totally different one. Infections and parasitic diseases were the

dominant health problems in the early years. With time, a change in health patterns in this population was observed, particularly an increase in clinic visits for asthma, which contrasted with asthma rates of 2.5% reported at the time of immigration to Israel [11]. This gradual increase was observed in the time period of 8–17 years after immigration. The prevalence of asthma among Ethiopians was 17% compared with 6% in the control group (local population). Thirty-three percent of the Ethiopian asthmatics and 37% of the control group suffered from various allergic diseases. The prevalence of eosinophilia was 44% among Ethiopians, with no significant difference between asthmatics and nonasthmatic patients (49 vs. 43%) as compared to 8.4% eosinophilia in the control group. Asthma was more prevalent among patients with eosinophilia (22%) than without eosinophilia (6.4%). In this study, asthma was found to be 3 times more prevalent in adults of Ethiopian origin, living in Israel 8–17 years, than the general Israeli population, and markedly increased above the rate reported for newly immigrated Ethiopian Jews. The move from the rural hills of Ethiopia to the more urban and industrialized setting of Israel probably contributed to the increased prevalence of asthma in this population.

Finally, a meta-analysis of studies on the epidemiological aspects of asthma was conducted, in order to support or reject the clinical impression of an increased rate of asthma among immigrants [12]. Particular emphasis was given to data on populations with a very high or a very low rate of asthma. The prevalence of asthma in China and in Africa is 1–2 and 0.5–5%, respectively, similar to the prevalence in other indigenous populations (range 0.5–12%). In contrast, a statistically significantly higher prevalence (20–25%) is found in Australia and in New Zealand, where peoples' ancestors immigrated from distant countries ($p < 0.001$).

Allergic Status and IgE Levels

Several studies evaluated the allergic status and IgE levels of immigrants. In the studies on immigrants to Australia mentioned above, atopy was more common in Asian immigrants and Australian-born Asians than in Australian-born non-Asians, and was very strongly associated with both hay fever and asthma, irrespective of the length of stay. Pollen and mite sensitivities were significantly more common in Asian than non-Asian subjects [6, 7]. Asian immigrants had higher levels of IgE (>100 IU/ml), which were strongly associated with a his-

tory of hay fever, wheeze or asthma ever, atopy and the presence of specific IgE antibodies to grass pollen, dust mite, cockroach and *Ascaris* antigens [6, 7]. In another study involving 205 Turkish immigrants, aged between 16 and 76 years, living in Sweden, the atopy prevalence was 32.4% [13]. Clinical symptoms were significantly associated with positive skin prick test (SPT) reactivity. IgE levels in the atopic group were significantly higher than those of the nonatopic group. However, the difference in IgE levels was significant only between nonatopic and atopic patients residing in Sweden longer than 10.5 years, but not significant between those residing there less than 4.5 years. Among the Turkish immigrants, the allergic spectrum changed with residence time spent in Sweden, as SPT positivity to birch, cat, and dog increased with time. In another study conducted in Sweden, the allergy status of immigrants from Asia, Africa, the Middle East and South America was evaluated throughout a 10-year period [14]. IgE levels of nonatopic immigrants were significantly higher than the levels of the nonatopic local population. While there was no significant difference in IgE levels between atopic and nonatopic immigrants, this difference was significant in Swedish patients. In general, IgE levels of immigrants showed a decline with time, and reached approximately the same levels as for the Swedish population after 10.5 years. In Swedes and immigrants, pollen was the most common group of allergens. As with the Turkish immigrants, the spectrum of allergy changed during residence in Sweden, and gradually became more similar to the Swedish spectrum, with skin and/or RAST positivity to birch increasing from 16% within 2.5 years to 53% after more than 10.5 years in Sweden. An additional study among children of Somali immigrants in Italy revealed similar trends. Among 52 children, aged 0–14 years, who were examined during the spring season, 37% had atopic symptoms, and 15% of those without symptoms were positive to *Dermatophagoides pteronyssinus* [15]. This change in the reactivity to environmental allergens is probably related to the changes in lifestyle and habits, such as indoor contact with pets, and intensive environmental birch pollen exposure, and suggests that environmental factors rather than hereditary differences determine the IgE status.

Not only can allergy become as prevalent in immigrants as in the local population, but in some studies, immigrants seem to be more prone to the development of allergy than the local population. In a study from Hungary, the percentage of people sensitized against common allergens (ragweed, grass, *D. pteronyssinus*) was similar among natives and immigrants. However, when the

strength of sensitivity to ragweed was determined by quantitative SPT and specific IgE, significantly more immigrants (69%) than native workers (20%) exhibited high sensitivity to ragweed, and the titers of specific IgE antibodies were also significantly higher in the former group. Similar differences were found in the occurrence and type of allergic symptoms. Seasonal symptoms alone occurred in 69 and 38% of the immigrant and native workers [16]. This difference was mostly due to those with late summer symptoms characteristic of ragweed allergy. These symptoms occurred in 57% of the immigrant workers, much more frequently than in the natives (18%). Again, these results highlight the differential tolerance of natives and immigrants to environmental allergens.

Another interesting aspect of the IgE levels in immigrants is described in a study on Ethiopian immigrants having lived for at least 7 years in Israel [17], where blood IgE levels were compared in mothers, fathers and newborns (cord). A linear relationship was found between mother and newborn IgE levels, whereas the father's IgE levels had no correlation to the newborn IgE. This finding is in agreement with several studies that have demonstrated the genetic and particularly the maternal pattern of inheritance of IgE levels, even though the environment was completely different between the Ethiopian parents and their Israeli firstborn.

In conclusion, data from several studies indicate that the immunological status of immigrants is influenced by the new milieu, and within a few years the allergic status of immigrants adapts and/or reacts to the new environment.

Country of Origin

The effects of the country of origin on the prevalence of respiratory symptoms was evaluated in 1,299 adult Israelis, aged 30–65 years of age, who were referred for the evaluation of pulmonary disease [18]. The lowest peak flow values and an excess of reported respiratory symptoms and chronic obstructive airway diseases, especially asthma, were found among subjects and their parents, immigrants from Iraq-Iran. In contrast, among immigrants from Morocco, reported respiratory symptoms, pulmonary diseases and impaired peak flow values were relatively uncommon. The different distribution of reported respiratory symptoms, pulmonary diseases and impaired peak flow values by the country of origin could not be explained by environmental factors, such as smoking habits and socioeconomic background. The higher

prevalence of reported asthma among immigrants from Iraq-Iran in this study was most probably due to a genetic factor.

The Effect of Age on Development of Atopy in Migrants

Epidemiological and laboratory studies have implied that during early childhood, the environment plays an important role as regards the risk of developing atopic disorders. In a study on the prevalence of asthma, hay fever and eczema among 1,901 internationally adopted young men in Sweden, those who came to Sweden younger than 2 years of age suffered from these diseases significantly more often than those who came to Sweden between 2 and 6 years of age (risk ratios 1.6, 2.5 and 2.1, respectively) [19]. Adopted children originating from the Far East were particularly susceptible to the development of hay fever and eczema with risk ratios of 1.3 and 1.7. This study demonstrated that the environment during the first 6 years of life has a profound influence on the risk of suffering from atopic disorders as young adults.

Atopic Dermatitis in Migrants

Environmental factors may influence the expression of atopic dermatitis (AD) in genetically susceptible persons. The risk of AD has been found to be greater for Asian children born in Australia when compared with recently immigrated Asian children [20]. Polynesian immigrants in New Zealand had a higher prevalence of AD compared with similar ethnic groups in their country of origin [21]. London-born black Caribbean children also had a higher risk of AD than their white counterparts [22]. This data supports the notion that environmental factors seem at least as important as genetic factors in determining the expression of AD [23].

Conflicting data on the prevalence of atopic diseases has been reported in some studies. In a study performed in Sweden [24], which evaluated hospital admissions for asthma, children born outside Western Europe, the USA and Australia were less commonly admitted to hospital because of asthma than other children in the population. Moreover, Swedish-born children, with mothers born in Eastern and Southern Europe, were also at lower risk for admission to hospital with a diagnosis of asthma [24]. These findings suggest a possible protective ethnic effect acting on the immigrant children. In addition, from these

results, the true prevalence of asthma among the immigrant children cannot be inferred, as immigrant children might have had milder symptoms of asthma not requiring hospitalization. In another study conducted in Germany, a significantly lower prevalence of atopy, as assessed by SPT and bronchial hyperresponsiveness, and asthma was found among Turkish immigrant children, as compared to their German peers [25]. Again, these results may reflect a lower prevalence of asthma in specific ethnic groups. Alternatively, the lower prevalence of asthma and allergy among immigrant children in the above study may result from a selection bias affecting the parents of these children, as healthy individuals may have decided to immigrate.

Atopy and Hygiene Hypothesis: The Immigrants' Perspective

Several lines of evidence suggest that infants residing in agricultural environments and farms are relatively protected from the development of atopy and to a lesser extent of asthma [26]. This protective effect has been associated with early life exposure to endotoxin, a component of gram-negative bacteria. Numerous studies have supported the hygiene hypothesis, but whether endotoxin by itself confers the protection, or whether it acts as a marker for another environmental exposure is still unclear. The strongest arguments in favor of the 'hygiene hypothesis' are the numerous studies relating early life daycare attendance to a significantly reduced risk of atopy and asthma, and the strong association demonstrated between sibship size and the occurrence of atopy. In addition, serological immune responses to certain infections such as hepatitis A and *Toxoplasma gondii* suggest a role of such infections, or alternatively of the lack of hygiene, as protection from the development of allergic immune responses. Surprisingly therefore, the data on atopic disorders among immigrants is not in agreement with the hygiene hypothesis. As discussed above, immigrants from developing or undeveloped and poor countries are not protected from atopy, and, in fact, they tend to develop more allergies and atopic disorders than the local populations. In an attempt to reconcile these conflicting findings, an integrating approach to these issues is suggested: living in third-world countries or in a rural environment confers protection from atopic disorders, as suggested by the hygiene hypothesis. But, moving to industrialized centers in developed countries adds a new and completely different environmental exposure, to which immigrants do not seem to be protected. Continuous exposure to new aller-

gens, pollutants, changes in diet and housing conditions lead to the gradual emergence of atopic disorders. The protection conferred by the past rural environment does not apply to the new environment, making immigrants more susceptible to atopic disorders.

Vaccination and Allergy in Immigrants

Vaccines have had a major impact on controlling the spread of infectious diseases, but certain vaccines have been linked to potential allergic and autoimmune side effects in healthy and in certain high-risk populations [27]. As such, there is a growing interest in the potential interactions between infant vaccination, and the risk of developing atopic disease. In addition, there is a concern that the genetic risk for atopy may influence the capacity to respond to vaccination during infancy. In general, there is no evidence that vaccines such as BCG, pertussis, influenza, MMR or smallpox have an effect on the risk of developing atopy later in life. A German atopy risk-enhanced birth cohort of 1,314 neonates, born in 1990, and followed for up to 5 years of age, demonstrated that the cumulative vaccine dose was inversely related to AD and asthma. Children with a higher vaccination coverage seemed to be transiently better protected against the development of atopy in the first years of life [28]. Although BCG vaccination had none or merely a marginal suppressive effect on the development of atopy, differences were observed in the response between Germans and immigrants to Germany. Non-German origin or ethnicity was found to have a stronger protective effect against atopic manifestations among preschool children [29]. In another study, Strannegard et al. [30] examined whether previous BCG vaccination or infection with atypical mycobacteria may protect against the development of atopic disease. The study, which involved 6,000 children and included skin testing for mycobacteria and a questionnaire, revealed a low prevalence of allergy among BCG-vaccinated children, who immigrated or were adopted from other countries. However, Swedish-born vaccinated children did not have a significantly lower allergy prevalence than age-matched, unvaccinated children, suggesting that early mycobacterial infections do not confer a protective effect on the development of atopic disease.

In summary, vaccination does not affect the development of atopy or asthma in the general population and in immigrants. Childhood vaccination remains an essential part of children's health programs, and should not be withheld, even from children predisposed to allergy.

Conclusions

Immigration to allergy-prevalent countries is associated with a higher prevalence of allergies and asthma in immigrants, as compared to the prevalence of atopy in their countries of origin. The increase in allergy and asthma prevalence is usually not related to ethnicity, but in selected populations genetic factors may play an important role. Studies on immigrants support the notion that in western industrialized countries, lifestyle and environmental factors facilitate atopy and asthma. The effect is time-dependent, and the development of allergy is influenced by the

age at the time of immigration. Compared with the local population, recent immigrants have higher levels of IgE, which gradually decrease to the levels of the general population, and higher prevalence of atopy and allergies. Vaccination does not affect the development of atopy or asthma in the general population and among immigrants. Immigrants should be aware of the potential risk of developing allergies and/or asthma. Strategies for primary prevention in high-risk atopic individuals and secondary prevention guidelines should be developed both for populations in developing countries, as well as for immigrants from such countries to atopy-prevalent developed countries.

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