

Out of Africa: what can be learned from the studies of allergic disorders in Africa and Africans?

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Purpose of review

Allergic diseases have only recently gained serious attention in Africa. This review discusses recent studies that have focused on allergy among Africans and people of African ancestry.

Recent findings

Time trend studies of the prevalence of allergies in Africa show a consistent increase over a period of 7–10 years. Recent studies have reported that the link between IgE, skin reactivity to allergens and allergic symptoms increases with increasing gross national income of the country. Association between helminth infections, and allergies seem contradictory, which may be attributed to differences in the length of infection and species studied. Importantly, researchers have identified an ‘urban diet’ component, which is associated with increased skin reactivity to allergens. Finally, whereas Africans in rural Africa seem to suffer less from allergies, people of African ancestry in affluent countries have higher prevalence and greater severity of allergic symptoms than natives of these host countries, raising important issues on genetic control of allergic diseases.

Summary

Mechanisms underlying the development of allergy are a complex interaction of genetic susceptibility and environmental exposures. Identification of specific environmental factors, mechanistic pathways and genetic risk factors in sufficiently powered studies will be necessary to better understand and control the allergic march in Africa and elsewhere.

Keywords

Africa, allergy, asthma, environment, epidemiology, genetics, infections

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Introduction

Though widely prevalent in Europe and America, allergy has not been given the same focus on the African continent. The general perception tends to be that allergic diseases are not a major health problem in Africa. Owing to limited health facilities and the relative prominence of infectious diseases with high virulence, like malaria and tuberculosis in Africa, allergy may not often be reported. The definition of allergic conditions such as rhinitis or atopic dermatitis can be mistaken for common colds or infection-related dermatoses, respectively. Moreover, the tools currently available for allergy research and diagnostics are developed mainly for Europe and America and thus based on populations with a different biological profile than those from Africa. In addition, allergens commercially available for skin prick tests (SPTs) or IgE determinations may not be of local relevance. Despite these hindrances to allergy research in Africa, studies have successfully indicated that in general, Africa

typically has lower prevalence of allergy than higher income regions such as Europe and Northern America. Recent studies have suggested that allergy is increasing in the African continent, particularly within upper to middle income countries such as South Africa [1]. In the poorer countries with low to middle income, however, an interesting dichotomy has been observed between rural and urban centers, with the latter usually showing higher prevalence than the former [2,3]. This has been linked to the presence of protective factors associated with a rural lifestyle and exposure to infections and the same reasoning has been used to explain the difference between the developing countries and the higher income countries. In fact, a similar rural–urban difference has been observed in some European studies [4] highlighting the importance of environmental factors in the development of allergic symptoms.

Given that allergic disorders are increasingly becoming a public health problem on the African continent,

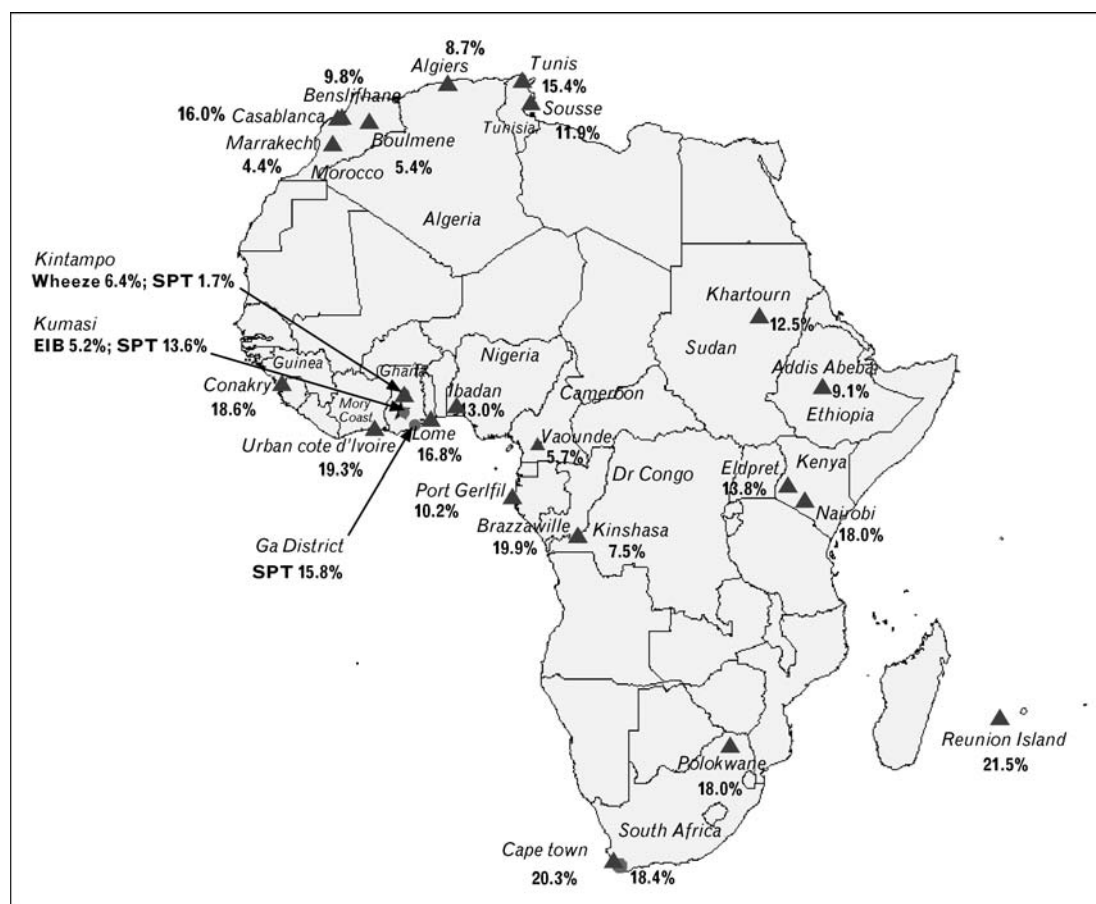
identification of risk factors responsible for the rise would be an important step towards harnessing the problem. Conversely, the identification of protective factors and the underlying mechanisms that have kept, and are still in some environments keeping, the prevalence of allergies at a low level might help the design of medical interventions to prevent allergic diseases worldwide.

Recent epidemiological studies

A number of recent epidemiological studies in Africa have used questionnaire-based data either alone or in combination with objective measurements to estimate the prevalence of allergic disorders (Fig. 1 [7,8^{••},9]). Of these, a study conducted in South Africa [1] compared the cross-sectional prevalence of asthma, allergic rhinitis and eczema in South African adolescents using questionnaire data of the International Study of Asthma and Allergies in Childhood (ISAAC) collected during phase I and then 7 years later, phase III surveys. From over 5000 schoolchildren in each of the surveys within the same areas, they

found allergic disease to be not only common, but also significantly increased in prevalence over the 7-year period. Prevalence of reported wheeze in the past 12 months had increased from 16% in 1995 to 20.3% in 2002, the latter being higher than in Germany (17.5%) and close to reports from the UK (24.7%). In fact, results from the ISAAC study from several centers in Africa generally showed relatively high asthma symptom prevalences, similar to those in Western Europe. However, considerable variation between the various African centers and between centers within the same country in the prevalence of wheeze (4–22%), allergic rhinoconjunctivitis (7–27%) and eczema (5–23%) was observed [9]. In the ISAAC phase II surveys, one African site, Kintampo in Ghana, reports prevalence of wheeze in the last 12 months to be 6.4% and considering the objective measurement of skin prick testing very low prevalence of allergic sensitization of 1.7% [8^{••}]. Another recent study set up in Kumasi, Ghana [2^{••}], collecting data on objective measurements of SPT and exercise-induced bronchospasm (EIB) and reported time trends over a 10-year period in schoolchildren. The

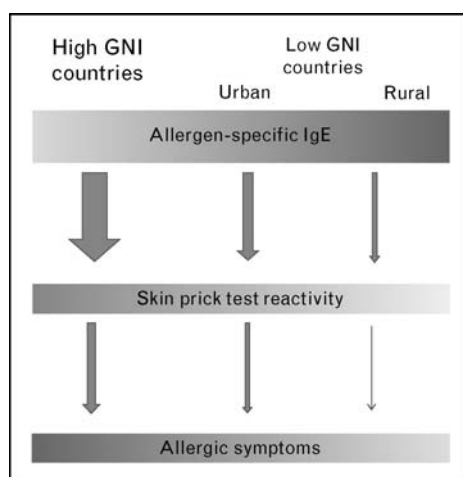
Figure 1 The geographic variation of wheeze, skin reactivity to allergens and exercise-induced bronchospasm in Africa, highlighting prevalence differences within and between countries



prevalence of allergic sensitization had doubled in the past 10 years, although was still lower than what is generally reported from affluent countries [5[•],8^{••}]. The prevalence of SPT changed along with affluence, as well as urban and rural gradient, with highest in urban rich (20.2%), followed by urban poor (10.3%) and lowest in rural (9.9%) populations. The doubling in allergic sensitization was also reflected in a similar increase in EIB in urban rich, urban poor and rural children [2^{••}]. The question of whether the use of local allergens in SPT would have resulted in higher prevalences of allergic sensitization remains to be answered, but it is clear that the relationship between SPT positivity and allergic disease symptoms are weak in countries with a low gross national income (GNI) [8^{••},10[•]], which would include many countries in Africa. Some interesting data have been published recently on the earlier steps of allergic disease development [8^{••}]. The relationship between IgE and SPT reactivity to the same allergen is reported to be much less strong in developing countries than in affluent ones. For example, in Gabon where 47% of children had specific IgE to house dust mite, only 11% were SPT positive to this allergen, indicating that having elevated specific IgE levels does not always mean atopic skin reactivity [11]. Again, the data collected from a wide geographical area during ISAAC II surveys show this point very elegantly as depicted in Fig. 2 [8^{••}].

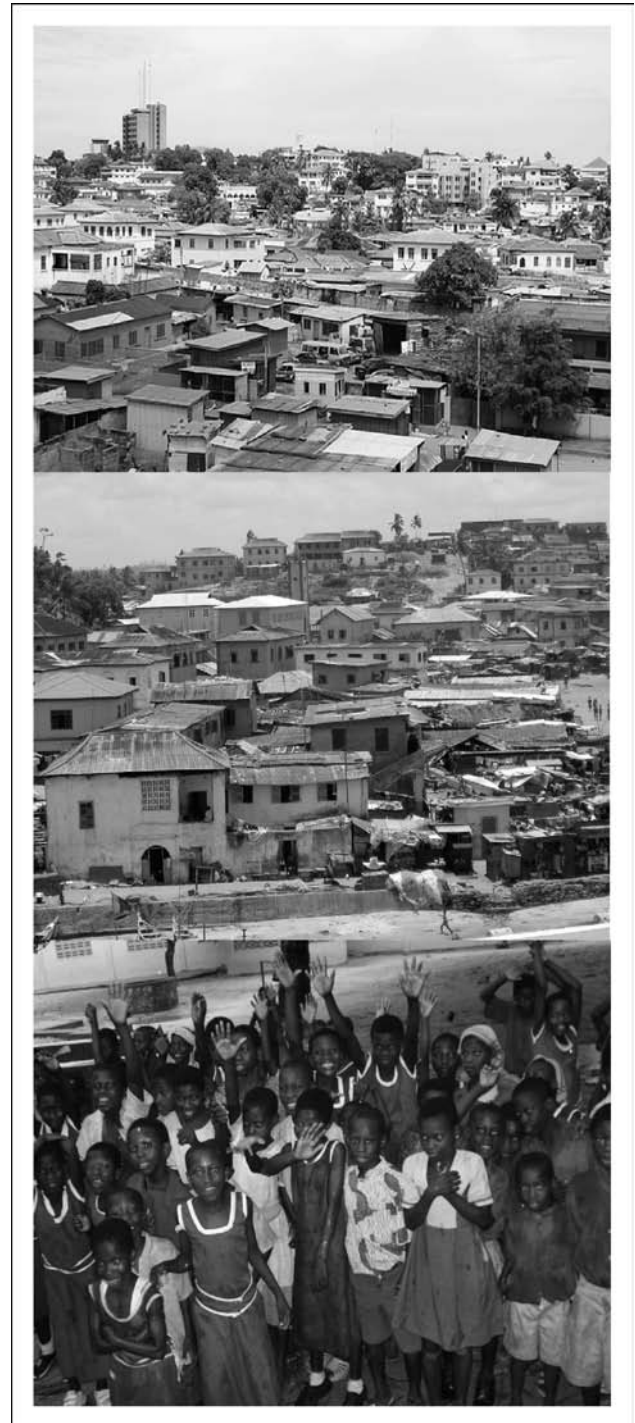
Although rapid urbanization in Africa has often been the factor to which increasing allergy is attributed to [2^{••},12], not all studies have reported the urban–rural downward

Figure 2 The relationship between allergen-specific IgE, skin reactivity to allergens and translation of this into allergic symptoms seem to vary depending on the geographic location characterized by GNI



In countries with a high GNI, there is a strong relationship between IgE, SPT and symptoms whereas in countries characterized by low GNI, these relationships become less strong, particularly as a function of urban and rural living. The thickness of arrows indicates the strength of the association from strong (thick) to weak (thin). GNI, Gross national income; SPT, skin prick test.

Figure 3 Photographs of urban and rural settlements in Ghana



From top to bottom; urban Accra, rural Ada and rural schoolchildren.

gradient in allergy prevalence. A few studies show a higher prevalence of allergic sensitization in rural compared with urban communes [13]. An important aspect of such studies is the definition of a 'rural' and an 'urban' area (Fig. 3). Obviously, it is important to understand the

basis of the trends seen in epidemiological studies to clearly identify the true cause of the rise in allergy prevalence in Africa. To pursue this, rural and urban areas must be properly defined and environmental triggers clearly differentiated in risk areas and in protective areas in African communities. Moreover, now that there are standardized data that indicate that sensitization to allergens show great geographical variation and that specific IgE does not always translate into SPT reactivity, nor does sensitization have similar predictive value for allergic disease outcome, it will be critical to identify modulating factors and mechanisms that account for the changing relationship between sensitization, skin reactivity and organ-specific allergic disease.

Environmental factors and allergy development

The environmental determinants of allergy seem to be inextricably tied with socioeconomic factors. The recently published ISAAC phase II data have shown GNI to make an important contribution to the development of allergic disorders [8[•],10[•]]. Now, the identification of exactly what is associated with GNI and important for the development of allergies forms a formidable task.

Allergens

Although it is understood that exposure to allergens is primarily important to sensitization and subsequent development of allergic disease, allergen avoidance does not seem to improve symptoms much [14]. Also, no direct association is always found between allergen levels and sensitization. It is not clear if there is a threshold of linear dose-dependent effect of allergen exposure and allergic sensitization. This notwithstanding, with temperatures generally more than 20 °C and 80% relative humidity, conditions in many parts of Africa generally favor mite growth and other important allergen sources such as mould. The geographical differences that exist between allergy prevalence need also to be considered within the context of differential allergen exposure. For example, though domestic house dust mites are quite ubiquitous, but preferentially abundant in upholstered urban indoor environments, the rural farming areas have much higher levels of storage mites, which are associated with agricultural areas and damp environs [15]. In a broader context, this underscores the importance of allergy research being tailored to suit the local situation.

Exposure to microorganisms and parasites

The hygiene hypothesis has triggered interest in the relationship between infections and allergic disorders and given the disproportionately high burden of infectious diseases on the African continent, it is not surprising that several studies have addressed this issue.

Inferences from the hygiene hypothesis have also led to investigations of the role of microbial components such as endotoxin and muramic acid in the development of allergic disorders [16–19]; however, with the exception of data from India [19], there are no data from developing countries in general and from Africa in particular, on the relationship between microbial components and allergic disorders.

Within the African context, helminth infections have been explored for their role in the development of allergy. Several epidemiological studies [6,20,21] have shown that having helminth infections may be associated with decreased risk for atopy or wheeze. A recent study [22] conducted in Uganda has shown that current infection with filarial parasite *Mansonella perstans* decreased the risk of SPT positivity by 87%. However, *Schistosoma mansoni* infection had no effect in the same study, which is in contrast to a previous report [23]. This might not be surprising as schistosome infection was recorded 1 year prior to performing SPT; therefore representing history of infection. Moreover, treatment was given within the year prior to SPT measurements.

Immunologically, research in Africa is complicated by the high prevalence of helminth infections, which do not only share the common trait of elevated IgE with allergic diseases but also the general T helper 2 (Th2) immune response. The elevated IgE to specific targets, either environmental allergens or parasite-derived molecules, often do not seem to be strong predictors of SPT positivity. This may in part explain the findings that the low GNI countries tend to show a weak relationship between IgE and skin reactivity to allergens. Whether these infections are also responsible for the low associations between SPT and allergic diseases, depicted in Fig. 1, has yet to be studied properly.

The negative association between an infectious agent that drives strong Th2 responses and allergic diseases that are associated with Th2 responses would seem surprising. Animal models have investigated the relationship between helminth infections and allergies, showing that chronic, but not acute infections, confer protection from allergy [24–29]. The mechanisms responsible for the protection, investigated in animal models, point towards a role for regulatory cells such as regulatory T cells and regulatory B cells, which suppress the allergic phenotype [30,31]. These results seem to support the findings that parasite-induced IL-10, an anti-inflammatory cytokine, may play a role in suppressing allergic responses [23]. However, a recent study from Ecuador [32], where geohelminth infections, at a moderate intensity, are prevalent, used a case–control design and utilized whole blood culture assays, and found no role for *Ascaris*-induced IL-10. The discrepancy between results of this study

from the one reporting a role for IL-10 [23], might be due to the use of whole blood versus purified peripheral blood mononuclear cell culture to study cytokine production in response to antigens. Of relevance to data on IL-10 and allergies might be the finding that in Gabonese school-children with *IL10* gene polymorphisms that promote high IL-10 production, there was a lower risk for atopy [33].

A recent molecular immunological study conducted in rural Ghana [6] reported substantial differences in the expression of genes that were associated with atopy, in helminth-infected individuals, suggesting that helminth infections suppress the expression of *TLR-2* and *SOC3-3* genes and might therefore protect against SPT positivity. However, the number of atopic individuals was too low to allow a definitive causal relationship to be established. Altogether, there is as yet no definitive immunological explanation for the inverse association between helminth infections and allergies, but further elucidation of specific regulatory pathways as well as detailed characterization of allergen-specific IgEs induced during a helminth infection are needed.

It has to be noted that the causal relationship between helminthes and allergy has generated debate following findings, which suggest that helminth infection could worsen allergic conditions. Recently, several groups have reported that high titres of *Ascaris*-specific IgE is associated with atopic disorders in rural Bangladeshi children [34], in South African [7] as well as in a Venezuelan study [35]. Also, Pinelli *et al.* [36] has shown in a murine allergic airway inflammation model that infection with *Toxocara canis* leads to an exacerbation of allergic symptoms. These apparently conflicting results indicate that the nature of these infections – intensity, chronicity and species – may be important to consider in the relationship between helminth infections and allergies [37].

An alternative hypotheses proposed on this subject is that being allergic protects against helminth infection and studies have indeed demonstrated that factors, which predispose to allergy also confer a protection from helminth infection in endemic regions. A recent study in China [38] looking at Th2 immune signaling showed that a genetic haplotype of signal transducer and activator of transcription 6 (STAT 6) protects against parasitic worm infections. The ongoing or planned trials [39,40] with human helminthes in allergic individuals might help us give an answer to the question whether allergic individuals are less susceptible to helminthes or not.

Nutrition or diet

There are complex inter-relationships between GNI, socioeconomic status, urban–rural gradient, exposure to infections and nutrition that are often difficult to

disentangle. It is known that helminth infections, for example, affect the nutritional status of a child and are often associated with poor living conditions [41]. Given the discrepancies in studies of the relationship between helminth infections and allergic disorders, recent studies of nutritional status as well as diet and their association with allergies in Africa, is of particular interest. A study in South Africa [42] observed that with increasing BMI, there was a greater association between allergen-specific IgE and SPT. More recently, an elegant study [43**] of diet used food frequency questionnaires in rural and urban areas of South Africa and applied principal component analysis to the data. This study identified a principal component that represented ‘urban’ diet that was associated with increased risk of SPT positivity irrespective of rural or urban residence. It was not possible to identify single nutrients that could account for this effect of diet. Future studies may need to take a similar approach and combine it with immunological studies to understand the mechanisms underlying the influence of this dietary component on the development of allergies.

Lessons from African–Americans

It is often reported that African–Americans have a greater prevalence of allergic diseases and asthma, particularly in poor urban settings, this observation has in part been attributed to higher exposure to cockroach and mouse allergens [44], but is also suspected to be due to genetic differences. As already discussed, in the African continent, the prevalence of allergies is thought to be lower than what is seen in countries such as the USA. However, Africans in the USA and Europe seem to suffer more from life threatening and emergency room asthma than the white Americans and Europeans [45–48]. This would indicate that Africans might have a genetic makeup that predisposes them to inflammatory diseases.

Regarding this, Le Souëf *et al.* [49] present the view that the genetic tendency towards strong Th2, which they presume has evolved for parasite expulsion early in the development of mankind, predisposes to asthma and allergy in modern societies of developed countries. This being of particular interest when one considers the very high prevalence of allergic disorders in African–Americans [50]. Polymorphisms in several candidate genes that encode for Th2-related molecules such as IL-4 and IL-13 show higher frequency of alleles that have a strong Th2-promoting activity in African–Americans [49], suggesting that these alleles have been conserved to combat parasitic infections in Africa but are now in the USA leading to problems in allergic disorders.

It is important to mention, however, that different parasites elicit very different immune responses. Although

malaria parasites can induce an inflammatory Th1 response and are associated with high mortality rate, helminth infections, for the most part, chronically infect the majority of their hosts, maintaining a Th2 environment and hardly kill their hosts. Thus, helminths on their own would not be expected to be a strong evolutionary driving force for Th2, and malaria would be predicted to select for Th1 genes.

The genetic studies of African-Americans are few in numbers and have been reviewed recently providing some genetic information on allergy and asthma among people of African ancestry. Scirica and Celedón [51] highlight the limited number of studies on asthma genetics in ethnic minority groups stressing that it is important that the candidate genes revealed by the few preliminary investigations are followed up in statistically powerful studies among African migrants, those on the home continent and in people of African descent. Barnes *et al.* [52] also give a comprehensive review of asthma genetics among African-Americans, which further highlights the need for more studies in this area.

In this context, it is argued that although a network of genetic factors may exist for determining a disease, the effects may be visible only when certain environmental triggers are present. Thus, a more integrated approach to genetic studies within well defined environmental context could make genetic findings more uniform across different studies.

Conclusion

At present, there are few studies in Africa regarding allergic disorders. With the view to the difficulties in defining allergic diseases in Africa and the complex role of the very varied environmental exposures on the continent, research in this area may seem a formidable task. Yet, if approached properly, the studies on this continent could give us important clues in the search for causes of the disease and molecular mechanisms underlying the development of these and other inflammatory diseases. The knowledge is needed not only to halt the allergic march in industrialized countries, but also to combat the increasing burden of allergic diseases that urban centers in Africa are facing.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 490).

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