



Fogarty, A.W. (2014) What have studies of non-industrialized countries told us about the cause of allergic disease? *Clinical & Experimental Allergy*, 45 (1). pp. 87-93. ISSN 1365-2222

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**What have studies of non-industrialised countries told us
about the cause of allergic disease?**

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Key words: allergy, asthma, economic development, industrialisation

Abstract

The increase in allergic diseases that was observed in countries that had experienced rapid economic growth since the mid-20th century initiated a search for environmental exposures that may explain these phenomena that continues to the present day.

Societies that are in the earlier stages of the process of industrialisation provide an opportunity to compare the initial stages of economic development and the lifestyle changes that may accompany this, with other communities whose way of life may not have changed appreciably for centuries. These studies have consistently demonstrated higher levels of allergic disease in the relatively affluent populations compared to those who maintain a more traditional lifestyle. Environmental changes that have emerged from these studies that may modify the risk of allergic disease include microbial exposures including parasite infection, pollution, diet and obesity. In addition, food and drug allergies represent a neglected area of research in these countries that may be causing a relatively high burden of disease.

The increase in the prevalence of allergic diseases that was observed in developed countries in the second half of the 20th century resulted in a search for risk factors that were responsible. As higher levels of allergic disease were observed in countries that had experienced the rapid economic growth and the societal change that characterised this period, environmental exposures that had also changed were of particular interest, including diet, microbial exposures and pollution. Societies that are in the earlier stages of the process of industrialisation provide an opportunity to compare more affluent, often urban populations with other communities that may have had less opportunity to adopt an affluent lifestyle and hence live in a more traditional cultural setting. These studies of the causes of allergic diseases in non-industrial countries are potentially important as they may allow the identification of risk factors for allergic disease with less confounding by the many other factors that are also associated with the more affluent lifestyle that often accompanies economic development. This review will present some of the epidemiological studies of the aetiology of allergic disease in countries where economic development is less advanced compared to the more affluent parts of the world, selecting those that have increased our awareness of the more important exposures. Inevitably, consideration of the global literature for risk factors for allergic disease in non-industrialised settings will result in a very heterogeneous collection of studies where consideration of potential confounding factors and generalizability across populations will vary, and publication bias cannot be excluded. Nonetheless, if a risk factor is consistent across such a diversity of study populations then this can be considered relatively strong evidence that may advance our understanding of the impact of the environment on allergic disease. For asthma in particular, many of the studies have been in resource-limited settings and hence have used pragmatic definitions of asthma based on self-reported symptoms or disease, preventing detailed phenotyping of disease [1].

Ecological studies

The hypothesis that non-industrialised countries may have lower rates of allergic disease was supported by ecological studies comparing the different prevalences of allergic diseases in individual countries as their economies developed and industrialised in the 20th century. The International Study of Asthma and Allergies in Childhood (ISAAC) studies has provided standardised data that have allowed global comparisons of disease prevalence of wheeze, eczema, rhinitis and allergic conjunctivitis. The first ISAAC study collected data in 1996 on these allergic diseases from 463 801 children aged 13-14 years in 155 collaborating centres in 56 countries using a questionnaire, supported by a video asthma questionnaire in 42 countries [2]. This permitted standardised comparison of the prevalence of allergic disease between countries and the differences were large, with 12-fold variation in the 10th and 90th percentiles for the different disorders. For asthma symptoms

the highest prevalences were from the UK, Australia, New Zealand and the Republic of Ireland, while the lowest prevalences were from countries that included nations from Eastern Europe, China, India, Indonesia and Ethiopia [3]. For allergic rhinoconjunctivitis, those countries with the lowest prevalences were similar to those for asthma symptoms while the higher prevalence countries were more varied. The highest levels of atopic eczema were reported from urban Nigeria with over 17% prevalence, with lower prevalence countries similar to those with a lower asthma prevalence [4].

Phase Three of the ISAAC study resampled comparable populations in 2002 to 2003, with 193 404 children aged 6-7 years providing data from 37 countries, and 304 679 children aged 13-14 years providing data from 56 countries. The general picture was of an increase in prevalence of allergic disease by at least one standard error for at least one disorder, with increases more common in the younger age group [5]. The increases in the prevalence of asthma in Africa, Latin America and parts of Asia demonstrated that the global differences in disease burden between more and less affluent parts of the world were decreasing [6], with similar convergence starting to be seen for eczema in the same dataset [7]. The implications of these landmark studies is that wide variations still remained between all countries that were not explained by general affluence.

Early prevalence studies

The earliest data on the prevalence of allergic disease that was obtained by random population-based sampling is informative and invaluable as it provides an insight into the historical burden of disease before the standardised methodology of the ISAAC study protocols allowed comparison of the symptoms of allergic disease across countries. Hence, data from Papua New Guinea published in 1978 reported a history of wheeze of less than 1% in children living in the subsistence communities in the highlands compared to 15% for those living in the more developed coastal regions [8]. Similarly, a study of 1284 adult residents of the highlands of Papua New Guinea published reported a prevalence of current asthma of 0.25% [9], suggesting that in this non-industrialised society asthma was rare.

Urban-rural studies

Over the past four decades there have been a number of comparisons of the difference in allergic disease between urban and rural environments in non-industrialised countries. These have consistently demonstrated that urban inhabitants have a higher level of allergic disease than those with a rural lifestyle [10,11,12,13,14,15,16,17,18], and are summarised in Table 1. The general interpretation of these data is that urbanisation is associated with an increased risk of allergic disease, although the actual exposures that drive this remain unidentified. The study from Jimma,

Ethiopia is notable as it is a relatively large, population-based study where wheeze was much less common in the rural population compared to the urban population with an odds ratio of 0.31, and that although atopy was a strong risk factor for asthma in the urban areas, paradoxically it may have a possible protective effect in the rural areas [12].

However, the inevitable differences in economic development, culture, setting and the genetic constitution of the populations make comparisons between these studies or attribution of causal relationships challenging, and they have generally been hypothesis generating. Potential explanations for these gradients in allergic disease have included differential microbial exposure including parasites, diet, exercise and pollution among the many possibilities.

Longitudinal studies

There are no national longitudinal datasets of similar individuals demonstrating trends in allergic disease over time from developing countries. Longitudinal data are available from Ghana from a comparison of two cross-sectional studies sampled twice from a geographically defined population over a ten-year interval. These demonstrated that the risk of both exercise induced bronchoconstriction and skin sensitisation has almost doubled between 1993 and 2003, with consistently higher prevalences in urban rich children compared to urban poor and rural children [19].

Environmental exposures

Microbial exposures

Of the many possible hypotheses that have been considered to explain urban-rural differences of allergic disease in less economically developed countries, differential exposures to microbes have generated the most interest. There are many published studies in this category of studies from non-industrialised countries, and some of those that have particularly informed our understanding of this field will be considered.

There have been a number of different studies of the impact of exposure to parasites on allergic disease, and these have been summarised in a meta-analysis of the literature up to 2006. This concluded that while parasite infections in general do not protect against asthma, infection with hookworm is associated with a strong reduction in asthma risk (odds ratio 0.50) in nine studies and infection with *Ascaris lumbricoides* is associated with an increased risk of asthma (odds ratio 1.34) using data from 20 studies [20]. A subsequent meta-analysis on the related subject of atopy and current intestinal parasite infection in 2010, reviewed 21 studies and concluded that current parasite

infection associated with a reduced risk of skin sensitisation (odds ratio 0.69), with a protective association observed for *Ascaris lumbricoides*, *Tricuris trichuria*, hookworm and Schistosomiasis [21]. Obviously, each parasite species will generate its own immune response in the host individuals, and this is likely to be modified by the age of first infection, the burden and the chronicity of exposure to infection, all of which are factors that will vary between studies. Data from a cross-sectional prevalence survey in children living in South Africa has demonstrated that infection with *Ascaris lumbricoides* was associated with a decreased risk of skin sensitisation (odds ratio 0.63) but an increased risk of exercise induced bronchoconstriction (odds ratio 1.62), and the authors speculate that this may be a consequence of a pro-inflammatory influence of *Ascaris* on the lungs, [22]. Data from Gabon demonstrated that in schoolchildren aged 5 to 14 years old, those individuals with *Schistosoma haematobium* infection had a lower prevalence of skin sensitivity to house dust mite in those with no parasite infection with an odds ratio of 0.32 that was not explained by house dust mite sensitisation as measured by specific IgE. The parasite-induced anti-inflammatory cytokine interleukin-10 was inversely associated with skin-test positivity to house dust mite, and the authors speculate that this cytokine may play a central role in suppressing the atopic phenotype [23].

If true, the hypothesis that parasites may protect against allergic disease has implications for public health programmes that aim to improve population health by periodic administration of antihelminthic treatments. A cluster-randomised controlled trial in schoolchildren from 68 rural schools in Ecuador in 2002 to 2004 administered seven treatments of albendazole over 12 months to the intervention schools. A large reduction in geohelminth prevalence (odds ratio 0.13) was observed in those who received the intervention, demonstrating the efficacy of the albendazole intervention, with no associated increase in atopy or wheeze [24]. However, a comparison of communities also in Ecuador that had received regular ivermectin treatment for onchocerciasis control for at least 15 years with those that had received no regular anti-helminthic treatment, reported a higher prevalence of skin-prick test reactivity in those who had received anti-helminth medication compared to those who had not (16.7% v 8.7%), and noted that ivermectin treatment was associated with an increased prevalence of recent eczema symptoms (odds ratio 2.24) that was not explained by a reduction in geohelminth infection [25]. One interpretation of these studies is that the duration of exposure to anti-helminthic treatments may be an important variable that modifies the accumulative exposure to parasites, and hence any impact on the immune system, particularly in early life.

There have been a number of studies of the association between exposure to other infections and allergic disease. A study from Brasil investigated the impact of *Toxocara canis* infection, as this can

cause both asthma symptoms and eosinophilia. 47% of the 1148 children sampled were seropositive for toxocara IgG, and these individuals were less likely to have positive skin prick test sensitisation than those who were seronegative [26]. Data from the same population studied the association between the burden of infection on atopy and wheeze in children, reporting that children who were seronegative for *Toxoplasma gondii* exposure has higher specific immunoglobulin E (IgE) to aeroallergens, while an absence of serological evidence of exposure to *Ascaris lumbricoides*, *T gondii*, Herpes simplex virus and Epstein Barr virus were associated with higher prevalence of skin prick test sensitisation [27]. The investigators then measured serum cytokines in addition to allergic symptoms and measures of burden of infection, and used latent class analysis to define immune phenotypes as underresponsive, intermediate or responsive, the responsive phenotype being associated with increased atopy but not asthma [28]. This approach of combining clinical, microbiological and laboratory data of the immune response in epidemiological studies is powerful and innovative, and combined with longitudinal data from populations with a high burden of infectious disease is likely to provide further insights into the aetiology of allergic disease over the next few years.

Diet and obesity

Obesity is positively associated with wheeze and the risk of developing asthma [29], although the mechanisms that explain this observation are not fully understood. Cross-sectional data from rural China are consistent with the hypothesis that higher body mass index is associated with asthma, with those who had body mass indices (BMI) of 30kg/m² having higher risks of symptomatic airway hyperresponsiveness (odds ratios 2.3) compared to those whose BMI was 21kg/m² [30]. A recent report from an asthma clinic in Nigeria has documented obesity rates of 54% in attending patients, with the more obese asthmatics having lower lung function than their non-obese counterparts [31]. This has important potential implications for the burden of asthma in low-income and middle-income countries where population obesity has been increasing for the past three decades [32].

An interesting study of 3322 children living in urban and rural South Africa reported that body mass index was a risk factor for exercise-induced bronchoconstriction, with those in the highest tertile having an odds ratio of 2.17 compared to those in the lowest tertile [15]. Of particular interest was the higher prevalence of skin sensitisation for house dust mite in the presence of specific IgE in heavier children (odds ratio 34.6) compared to lighter participants (odds ratio 8.0), suggesting that in this population obesity may mediate expression of the allergic phenotype.

One of the earliest randomised controlled trials of the potential therapeutic benefits of antioxidants on asthma control was from Nigeria in 1979 [33]. This demonstrated substantially better asthma control in the group who received high dose ascorbic acid during the rainy season, although unfortunately these data could not be replicated in a similar study based in Nottingham, UK [34].

Air pollution

An important form of air pollution is the indoor air pollution that occurs as a by-product of burning a number of substances indoors with inadequate ventilation, often for cooking and heating. This is a health hazard that negatively impacts on the health of millions of individuals living in developing countries, causing acute respiratory infections and chronic obstructive pulmonary disease [35]. However, another likely consequence of exposure to solid fuel is the development and exacerbation of asthma. A case-control study from Kuala Lumpur in 1995 of cases of 158 children hospitalized for the first time with asthma identified exposure to mosquito coil smoke (odds ratio 1.73) as risk factors for an asthma admission [36], and visible air pollution within the home was also a risk factor for the presence of asthma in a case-control study from Kenya in 1995 [37]. Data from the second Indian Family Health Survey similarly reported that elderly individuals living in households using biomass fuels had a higher prevalence of asthma (odds ratio 1.59) than those who lived in households that burnt cleaner fuel [38]. A recent study observed Warao Amerindian children living in Venezuela in 2012 and demonstrated that those children who lived in an environment where the cooking was on an open wood fire had a higher risk (odds ratio 2.12) of having asthma symptoms than those children were exposed to cooking with gas [39].

One interesting study that may provide an insight into the processes involved in the development of allergic disease is from the previously mentioned population-based study in Jimma, Ethiopia. The use of kerosene, a non-biomass fuel, was associated with an increased risk of allergic sensitisation (odds ratio 1.78), wheeze (odds ratio 1.56) and eczema (odds ratio 2.82) compared to those who used biomass fuel only [40]. These data are notable as Jimma was comparatively undeveloped when these data were collected, the study sample of 2372 individuals is relatively large and the association observed with a combination of subjective and objective allergic outcomes consistent, although the possibility of residual confounding by an unmeasured risk factor that is associated with kerosene usage is an alternative explanation that cannot be excluded.

Another common avoidable cause of air pollution is the exposure either directly or indirectly to cigarette smoke, and as tobacco companies are now expanding into the markets of developing

countries [41], this will adversely impact on the populations of these countries. As this is amenable to control by public health legislation and demand management by taxation, studies of the negative impact of cigarette smoking on allergic disease such as asthma from developing countries are an important part of the process of improving population health by preventing smoking uptake and promoting smoking cessation. The role of exposure to environmental tobacco smoke in the development of asthma is well recognised, and has been reported in a variety of studies of children from a number of countries including Malaysia [36] and Cuba [42].

Outdoor pollution is also recognised as a potential risk factor for asthma [43,44], and the source of the pollution will vary widely from country to country depending on the location and stage of economic development. In an analysis of data from Jimma, Ethiopia, there was a dose-response in the association between the distance from the road and risk of wheeze for those who lived within 150m of a road, but not for those who lived further away [45]. A cross-sectional survey from the Niger Delta region of Nigeria reported that those who experienced traffic disturbance at home in the form of traffic noise or fumes within the house experienced a higher risk of wheeze (odds ratio 2.16), night cough (1.37) and rhinitis (odds ratio 1.40) compared to those who did not experience traffic disturbance [46]. Using data from a shantytown in Lima Peru, researchers analysed the association between the distance from a heavily transited avenue and asthma and atopy [47]. They observed that living close to the main road increased the risk of both wheeze and atopy as defined by skin allergy testing suggesting that in this population, the pollution associated with busy roads is a potential cause of allergic disease.

Paracetamol

The role of paracetamol in the aetiology of asthma and allergic has generated much interest and controversy over the past decade [48]. Two studies from Butajira, Ethiopia have studied this topic within a rural, developing country setting. 7649 adults and children were surveyed [49] and allergic symptoms were increased in those who consumed more than three paracetamol tablets in the past month for wheeze (odds ratio 1.89), rhinitis (odds ratio 2.52), eczema (odds ratio 1.90) and cockroach sensitisation (odds ratio 1.40) compared to those who had no paracetamol exposure. In a birth cohort from the same setting, administration of four tablets of paracetamol in a month at age one year was associated with higher risk of incident wheeze (odds ratio 7.25) in children aged three years old compared to those who had no paracetamol exposure [50]. These data demonstrate that the association of paracetamol with allergic disease is observed in developing countries, corroborating the observations from the earlier studies from more affluent societies [51]. However, the study design

prevents the demonstration of a causal relationship due to the difficulty of completely adjusting for residual confounding by factors such as viral infections, and randomised controlled trials will be required to determine if this association is causal or not.

Food allergy

The study of food allergies is challenging and requires standardised population-specific questionnaires, often followed by double-blind placebo-controlled food challenges [52]. A recent review has considered the literature on food allergy in Africa and concluded that “food allergy is definitely an emerging disease in Africa” [53]. Recent data from Mozambique of 447 university students reported a life-time prevalence of any self-reported food allergy of 19% while drug allergy was reported by 25% of respondents [54]. A similar questionnaire-based study of 400 randomly selected households in Dar Es Salaam, Tanzania reported food allergies in 17% of adults and 8% of medicines [55]. These data suggest that food allergies are common in these countries. This is a potentially large and clinically important burden of disease as food allergies can result in substantial morbidity and even mortality [56], while drug allergies may also cause serious adverse events or lead to the avoidance of affordable medications. Hence, comparable data on the scale of these problems in developing countries are required to understand aetiology of food allergies and the burden of disease that they represent.

Conclusion

The study of allergic disease in non-industrialised countries is a fertile area of research that has helped contribute to our understanding of disease aetiology, in particular by permitting the study and identification of risk factors as allergic disease prevalence starts to increase. In the future, this has the potential to contribute more to our understanding in the form of longitudinal studies nested in countries that are experiencing industrialisation. The impact of microbial exposure, air pollution especially indoor air pollution, drugs and diet on allergic disease is complicated, but data from developing countries will continue to provide insights into universal pathogenic processes. More data are particularly required to increase our knowledge of drug allergies, particularly antibiotics, in developing countries, as many of these healthcare systems are resource limited and alternative options may be scarce in certain settings. All of these developments will have the potential to positively contribute to the health services research infrastructure of these countries, hopefully benefitting both study participants and the wider global community with the knowledge gained on how to prevent or treat allergic disease.

Acknowledgements

Thanks for John Britton for comments on the manuscript.

Table 1. Cross-sectional studies of urban-rural differences in allergic disease

Country (area)	Year	Allergic disease outcome	Urban v Rural prevalences (%)	Possible risk factors for allergic disease
South Africa [10]	1979	Exercise induced bronchoconstriction	3.2 v 0.1	-
Zimbabwe [11]	1988	Exercise induced bronchoconstriction	3.1-5.8 v 0.1	Urban living Affluence
Ethiopia [12]	1996	Asthma	3.6 v 1.3	Brick house Exposure to cigarette smoke Tigrean ethnic group
Ghana [13]	1996	Exercise-induced bronchoconstriction Skin atopy	2.2-4.7 v 1.4 2.9-6.5 v 1.5	Affluence Housing
Kenya [14]	1998	Exercise induced bronchoconstriction	22.9 v 13.2	Short breastfeeding Parental education Biomass fuel and kerosene for cooking Motor vehicle fumes
Mongolia [17]	1999-2000	Asthma Allergic rhinoconjunctivitis Allergic sensitisation	2.1 v 1.1 18.4 v 9.3 31.0 v 13.6	-
Nigeria [18]	2004	Wheeze	5.7 v 4.1	
South Africa [15]	2004	Exercise induced bronchoconstriction	14.9 v 8.9	Atopy Obesity Affluence
Rwanda [16]	2009	Asthma diagnosis HDM skin sensitivity	9.3 v 8.3 13.2 v 7.6	Less education

HDM – house dust mite

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