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The Latin American exception: why is childhood asthma so prevalent in Brazil?

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Ten years ago most researchers in Western countries “knew” what caused asthma, and we knew how to prevent it.¹ Asthma was an atopic disease caused by allergen exposure. The fundamental etiological mechanism was that allergen exposure, particularly in infancy, produced atopic sensitization and continued exposure resulted in asthma through the development of eosinophilic airway inflammation, bronchial hyper-responsiveness and reversible airflow obstruction.

This Eurocentric view of asthma etiology was in fact never strongly evidence-based.^{2,3} Less than one half of asthma cases are attributable to atopy and/or eosinophilic airway inflammation² and (non-allergic/non-atopic) neutrophilic airway inflammation may account for the

other half.⁴ Furthermore, although there are some clear cases of allergen exposure causing asthma in adults in the occupational environment, overall there is little evidence that allergen exposure is a major primary cause of asthma³ and even some evidence that allergen exposure early in life may have a protective effect.¹ Certainly, allergen exposure does not appear to be the major primary cause of asthma that it has been assumed to be, nor to account for global patterns, or the striking increases in prevalence over time.⁵

As the “established” asthma risk factors are increasingly being called into question, epidemiological studies are playing a major role in the search for new theoretical paradigms which are more consistent with the epidemiological evidence and which have greater explanatory power. In particular, the “hygiene hypothesis” has been prompted by the results of several epidemiological studies showing that overcrowding and unhygienic conditions were associated with a lower prevalence of atopy, eczema and hay-fever although the evidence for asthma is less consistent.⁶ An increase in microbial exposure and infections has been proposed as an explanation for these findings.⁷

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The International Study of Asthma and Allergies in Childhood (ISAAC)⁸ has played a major role in these recent developments, and has revealed major international differences in asthma prevalence⁹ that do not appear to be explained by the “established” asthma risk factors. ISAAC has been a truly global study,¹⁰ and has been particularly successful in Latin America. The Phase I findings, involving more than 700,000 children showed a particularly high prevalence of reported asthma symptoms in English-speaking countries. However, the ISAAC survey also showed that centers in Latin America also had particularly high symptom prevalence. The high prevalences in Brazil have now been confirmed in the ISAAC Phase III study of Solé et al.,¹¹ published in the current issue of this journal.

There are several reasons why the findings, and particularly the conclusions, of Solé et al. should be regarded with caution. Firstly, although all of the centers included in the report by Solé et al apparently used the ISAAC Phase III protocol,¹² not all of them are official ISAAC centers. A few will not be included in the global ISAAC Phase III reports because their sample sizes or response rates were too low, or in some other way they did not meet the ISAAC criteria. Thus, their findings may not be comparable with those of other Brazilian centers which did meet the criteria for inclusion as official ISAAC centers.

Secondly, there is reason for skepticism about the findings relating to latitude. One does not need to be a Brazilian citizen to realize that many things probably vary by latitude in Brazil, not just climate. Furthermore, as the authors themselves acknowledge, the asthma prevalence differences were strongest for physician-diagnosed asthma, the ISAAC question which is likely to be most susceptible to regional differences in diagnostic practice. The same likely bias will apply to the findings for “severe asthma,” since this involved physician-diagnosed asthma as part of its definition. In contrast, regional differences in reported asthma symptom prevalence were more modest. Also, interestingly, some of the largest differences in asthma prevalence were found for two centers in the same city, i.e. West and South São Paulo. This was particularly the case for severe asthma in both age groups (6-7 year olds: 8.4% versus 4.8% respectively; 13-14 year olds: 5.6% versus 2.9% respectively) and active asthma in the 6-7 year olds (31.2% versus 24.4%). This is an interesting observation that suggests that other factors than geographical location and climate may be involved in the observed differences in asthma prevalence. Further follow-up to explain the relative difference of almost 50% in the prevalence of severe asthma between two populations in the same city could prove extremely useful in identifying specific risk and/or protective factors (see below).

The high prevalences in Brazil reported by Solé et al. are of major international importance. In ISAAC Phase I, the Spanish-speaking centers of Latin America showed

higher prevalences than Spain itself, and the Portuguese-speaking centers in Brazil showed higher prevalences than the Portuguese centers.¹³ The best indication of what is now happening globally will be provided by the forthcoming findings of Phase III of the ISAAC study.¹⁴ However, the Brazilian findings clearly indicate that asthma prevalence continues to be high in Brazil, and is increasing.

These high prevalences in Latin America received relatively little attention in discussions of the ISAAC Phase I findings, possibly because they were difficult to interpret. Now that they have been confirmed, at least in Brazil, by Solé et al.,¹¹ it is important that the causes of these high prevalences are investigated further, particularly because they appear to contradict the “hygiene hypothesis”.

In fact, there are many other anomalies with the hygiene hypothesis, and it does not appear, at least on its own, to explain the global asthma prevalence patterns and time trends.¹ One particular anomaly is the relatively high asthma prevalence in U.S. inner city populations living in poverty.¹⁵ Furthermore, although the hygiene hypothesis may explain an increase in atopy and *allergic* asthma, there is a large proportion of asthma that is not associated with atopy.² However, whatever mechanism is involved, it is becoming increasingly clear that the package of changes associated with Westernization may be contributing to the global increases in asthma prevalence, and that this process involves an increase in asthma susceptibility rather than an increase in exposure to “established” asthma risk factors.⁴

So what other aspects of Westernization may explain the global asthma prevalence increases? The striking increases in asthma prevalence globally cannot be primarily due to genetic factors, since they are occurring too rapidly, and therefore they must be occurring due to changes in environmental exposures. It seems that as a result of this package of changes in the intrauterine and infant environment, we are seeing an increased susceptibility to the development of asthma and/or allergy. There are a number of elements of this package, including changes in maternal diet, increased fetal growth, smaller family size, reduced infant infections and increased use of antibiotics and immunization, all of which have been (inconsistently) associated with an increased risk of childhood asthma, but none of which can alone explain the increases in prevalence.⁵

Thus, it is important that we consider the “forest” of changes that occur with Westernization, as well as doing studies of specific “trees.”¹ It is likely that the package is more than the sum of its parts, and that these social and environmental changes are all pushing infants’ immune systems in the same direction. To know what that direction is, and which components of the package are responsible, requires that better etiologic theories of asthma are developed to replace the allergen theory,

or to incorporate it as a special case. Studying the causes of the high asthma prevalence in all regions of Brazil would appear to be a good place to start, particularly since the high asthma prevalence in Brazil and South and Central America appears to contradict the hygiene hypothesis.¹

Studies to identify specific risk and protective factors that may further explain the regional differences in asthma and allergy prevalence would be useful. In particular, it would be of interest to assess why asthma prevalence is substantially higher in children living in West São Paulo compared to South São Paulo. Comparisons between rural and urban populations could also generate valuable information, particularly since in many Western countries it has been shown that growing up on a farm may confer protection against allergies and asthma.¹⁶ Brazil is well placed to pursue this research since it has: (i) a high asthma prevalence; (ii) an interesting distribution of urban and rural populations; and (iii) substantial differences in exposure to traditional lifestyle factors, degree of Westernization, ethnicity, indoor and outdoor air pollution, infection rates, etc. Future studies in Brazil focusing on the issues described above would not only be of major interest for Brazil, but would also be of great value internationally as they are likely to provide valuable insights into asthma etiology and the causes of the global asthma patterns and time trends.

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