



Influence of poverty and infection on asthma in Latin America

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Purpose of review

Asthma in Latin America is a growing public health problem and seems to be most prevalent and cause most morbidity among poor urban populations. This article will review the findings of recent human studies of the associations of asthma prevalence in Latin America with factors associated with poverty and inequality including childhood infections, stress, environment, nutrition and diet.

Recent findings

Most asthma in childhood in Latin America is nonatopic and has been associated with exposures related to environmental dirt, diet and psychosocial distress. These factors are strongly linked to poverty and inequality. Interestingly, infections with bacterial, viral and parasitic pathogens in childhood appear to attenuate atopy in childhood but have no effect on asthma symptoms. There are biologically plausible mechanisms by which dirt exposures (e.g. endotoxin and other microbial products and nonmicrobial irritants), diet and obesity and psychosocial stress may cause airways inflammation.

Summary

Most childhood asthma in Latin America is nonatopic for which important risk factors are those of poverty including poor hygiene (i.e. dirt), poor diet and obesity and psychosocial stress. There is evidence that exposures to infections in early childhood reduce atopy but not asthma. Research is needed to identify causes of nonatopic asthma that may be suitable for primary prevention or other public health intervention strategies for asthma in Latin America.

Keywords

asthma, atopy, childhood infections, diet, Latin America, obesity, poverty, psychosocial stress

INTRODUCTION

Approximately 300 million people have asthma worldwide of which 40 million are estimated to be in Latin America [1]. Asthma is a heterogeneous disorder with disease representing the outcome of distinct pathoetiological processes caused by interactions between diverse genetic backgrounds and environmental exposures. A large international study of asthma, phase I of the International Study of Asthma and Allergies in Childhood (ISAAC) [2], showed that the prevalence of asthma symptoms was as high in some Latin American cities as observed in countries known to have high prevalence such as the UK, although there were marked differences reported between countries within Latin America. The ISAAC phase III study [3] monitored changes in asthma prevalence in children over periods of 6–8 years in cities in Latin America and showed that asthma prevalence may have reached a plateau in high-prevalence countries but continues to increase in countries that had a lower reported prevalence in phase I. In parallel with the high prevalence, there is

also a large burden of morbidity [1,4,5] and high rates of mortality in many Latin American countries [6].

In industrialized countries, the prevalence of asthma has increased in recent decades [7] and the limited data available suggest that the prevalence of asthma is on the increase also in many low-income and middle-income countries [3]. The causes of the temporal trends of increased asthma prevalence over recent decades are not well understood but are likely to be associated with

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KEY POINTS

- Asthma has become an important public health problem in many Latin American countries.
- Population-based studies have shown that childhood asthma is primarily nonatopic.
- Nonatopic asthma in Latin American children has been associated with greater exposures to 'dirt', poor diet, obesity and psychosocial distress.
- Exposure to a high burden of chronic infections is associated with a lower prevalence of atopy but does not seem to affect asthma prevalence.

environmental and social changes associated with what has been termed a 'modern' lifestyle. Such changes are likely to include changes in diet [8] and nutrition, exposure to environmental irritants (e.g. allergens, indoor and outdoor pollutants, tobacco smoke) [9], alterations in exposures to microbial products [10,11] and increased stress [12].

POVERTY AND ASTHMA

Asthma is most prevalent among poor and marginalized populations in Europe [13,14] and the USA [12,15]. Similarly, asthma in Latin America has emerged as a disease that most affects the poor [16–18,19[■]].

Latin America not only has high levels of poverty but is also the continent with the highest level of social inequality [20]. Poverty in Latin American populations may contribute to asthma prevalence in a wide variety of ways. The urban poor, who suffer the highest prevalence of asthma, live in poor-quality and overcrowded housing and in neighborhoods often with limited or no access to basic services including clean water, sanitation and healthcare resources [21[■]]. Living in such an environment, the poor are likely to be exposed to a wide variety of pathogens from an early age including viral respiratory infections and to high levels of environmental irritants. Many of these factors are likely to contribute to the development of asthma and disease exacerbations and have a major influence on the asthma phenotype that develops. Most childhood asthma in both poor urban and rural populations in Latin America does not appear to be associated with atopy [16,22[■],23[■]].

Urbanization

The acquisition of a modern lifestyle is linked intimately with the process of urbanization, and

urbanization in Latin America has led to a growing number of people living in poverty and stressful and unsanitary environments. Many countries in Latin America have undergone an urban transformation in recent decades characterized by modest economic but high population growth, rural–urban migration and extreme inequality. Over sixty percent of the population in Latin America is now living in towns and cities, and this trend is set to increase. A high proportion of those who live in the growing cities do so in informal settlements and slums with limited infrastructure and access to basic services. Furthermore, the social, environmental and economic effects of urbanization have spread into even the most rural regions of Latin America, where they may be linked to asthma prevalence [24[■]].

Numerous studies have documented a greater prevalence of asthma in urban compared with rural populations in Africa [25,26], Asia [27] and Latin America [28[■]]. Urban–rural differences in asthma prevalence have been attributed to effects of wealth, lifestyle, housing and environment [29], among other factors. Rural exposures such as those associated with farming and exposures to livestock appeared to be protective against atopy and allergic symptoms in Europe [7,30]. An ecologic analysis of rural communities in Ecuador showed that increases in socioeconomic level and changes toward a more urban lifestyle were associated with the community prevalence of asthma in children [24[■]]. Ecologic studies of cities in Brazil [17] or across countries in Latin America (G. Fattore, M.L. Barreto, unpublished data) have found an increased prevalence of asthma to be associated with poverty, inequality (measured by the GINI index) and rates of mortality from external causes (an indicator of contextual stress).

Exposure to environmental irritants

Relevant environmental irritants include outdoor exposures to industrial and motor vehicle pollutants [31] and indoor exposures to domestic irritants, aeroallergens and environmental tobacco smoke (ETS) [32[■]]. Exposures to such irritants may contribute directly to the development of airways inflammation through activation of innate and/or adaptive immune responses. The urban poor tend to live in poor-quality housing adjacent to highly polluted industrial areas where traffic is dense and there are few controls on toxic emissions and rubbish is left to accumulate. Under such conditions of intense exposures to environmental irritants compounded by household crowding and the necessity for working women to leave their children in crowded day-care facilities where transmission of viral respiratory

tract infections is likely to be intense, it is hardly surprising that a high proportion of infants and young children living in Latin American cities have recurrent wheezing in early life [33[■]] and bronchial hyperreactivity [16,34]. Although ETS during pregnancy and postnatal life has been causally linked with acute lower respiratory tract infections and childhood asthma [32[■],35] in populations living in developed countries, there are few data from Latin America on the relative importance of ETS over other environmental irritants in the development of asthma.

Infections

Since the hygiene hypothesis was first proposed [36] as an explanation for the apparent protective effect of having older siblings against allergic rhinitis, a large body of evidence has shown that infections and probable surrogates of an increased frequency of infection such as daycare attendance [37], family size [38] and burden of infection [39] are protective against atopy. Evidence for a role of infections protecting against asthma is less clear and is complicated by the fact that respiratory tract infections, particularly those caused by RSV and rhinovirus, are strongly linked to asthma [40].

Studies linking infection and atopy and asthma in Latin America have focused on the role of individual pathogens such as intestinal helminths. Such studies have consistently shown that intestinal helminths are inversely associated with allergen skin prick test (SPT) reactivity [23[■],41,42[■]], an observation supported by a meta-analysis of international studies [43[■]]. Further, a prospective analysis in Brazil showed that having *Trichuris trichiura* infection in early life was protective against SPT in later childhood [44] independent of later helminth infections. Showing that treatment of such infections affects allergy prevalence would provide stronger evidence for a causal association. An observational study [45] looking at the effects of 15 years of anthelmintic treatment with ivermectin on the prevalence of allergy in school-age children showed that the prevalence of SPT was greater in children living in treated communities than in those living in non-treated communities. However, a previous cluster-randomized study in [46] which schools received either albendazole every 2 months or no treatment showed no effect on SPT reactivity after 12 months of treatment. Neither of the two studies [45,46], conducted in areas of high geohelminth prevalence, showed an effect on asthma prevalence. However, evidence from areas where the prevalence of *Ascaris lumbricoides* is low, which shows that the presence of *A. lumbricoides* infection in stool samples is a risk

factor for asthma symptoms [16], that treatment may reduce symptoms [47] and that having anti-*Ascaris* IgE is strongly linked to asthma symptoms [41,48]. Similarly, seropositivity for *Toxocara canis*, not a natural infection of humans, has been associated with an increased risk of asthma symptoms [49]. Prospective cohort studies followed up from birth may be required to disentangle the complex interactions between parasites and the development of atopy and allergic disease symptoms [50].

A recent cross-sectional analysis from the city of Salvador in Brazil examined the associations between eight different bacterial (*Helicobacter pylori*), viral (Epstein–Barr, herpes simplex, hepatitis A and herpes zoster) protozoal (*Toxoplasma gondii*) and helminth (*A. lumbricoides* and *Trichuris trichiura*) infections with atopy and asthma symptoms in children living in poor neighborhoods [42[■]]. This study showed that individual pathogens appeared to reduce positivity for the presence of aeroallergen-specific IgE and SPT but had no effects on asthma symptoms, whether atopic or nonatopic. Further, a heavy burden of infection had a greater effect on atopy than light infections but no effect on asthma. The findings of this study emphasize the weakness of studies that examine pathogens in isolation – many infections are transmitted in circumstances of overcrowding and poor sanitation and living conditions. Further, it is difficult to disentangle independent effects of specific pathogens because they are strongly correlated. Given the suggestion that the hygiene hypothesis is unlikely to be relevant in Latin America because of the high asthma prevalence among populations living in conditions of poor hygiene, this study [42[■]] does provide compelling support for a role of infections in reducing atopy but not asthma.

A possible mechanism by which infections and ‘dirt’ exposures may reduce atopy is through the increased production of interleukin 10 (IL-10), an immune regulatory cytokine with potent anti-inflammatory effects and which previously has been associated with a reduced prevalence of atopy in helminth-infected children [51]. Previous analyses using data from the same study in Salvador, Brazil, have shown that ‘dirt’ exposures associated with living in an unhygienic environment (i.e. lack of garbage disposal, no household sewage connection and lack of street paving) were associated with a reduced production of mitogen-induced Th1 and Th2 cytokines by peripheral blood leukocytes, and this effect was most evident among children who produced IL-10 [52[■]]. Similarly, data from the same study showed that the baseline or homeostatic production (i.e. in the absence of immunologic stimulation) of IL-10 was elevated among children who

had no access to clean water and sanitation as infants [53], indicating that dirt exposures in early life may have a role in the regulation of inflammatory responses. Important dirt exposures that are associated with elevated homeostatic IL-10 include chronic helminth infections [54,55], but a role for other microbial and infectious exposures with which helminth infections are strongly correlated cannot be excluded.

From these recent findings, we could hypothesize that the high prevalence of nonatopic symptoms of diseases previously assumed to be supposedly 'allergic' in poor populations in Latin America [16,19[■],22[■],23[■]] indicates that airway inflammation may be mediated through nonallergic pathways and the low prevalence of atopy is a direct consequence of living in an environment in which a high burden of infectious diseases leads to an attenuation of Th2-mediated inflammation. It is not just that infections attenuate atopy; there is evidence also that exposures to dirt may actually increase the risk of asthma symptoms.

The potential relevance of dirt exposures as risk factors for nonatopic asthma

Nonatopic asthma in children at a population level in Latin America accounts for more than 80% of asthma cases [19[■],23[■],56]. Further, risk factors for atopic and nonatopic asthma appear to be distinct [19[■],23[■]], and induced sputum from children with nonatopic asthma has a 'neutrophilic' phenotype [57], suggesting that the different phenotypes are real and may have distinct pathoetiologies. Thus, at least in the Latin American context, alternative nonallergic mechanisms of airways inflammation must be sought to explain the high prevalence of asthma.

Studies [16,34,58] in urban environments in Latin America have reported a high prevalence of nonatopic wheezing among children living in poor neighborhoods. Identified risk factors for nonatopic asthma point to different aspects of poverty, infection and dirt as being relevant: parental educational level, dampness and mould in the household, attendance at dirty schools, household pets, infections with intestinal helminths [16] and level of endotoxin in dust samples [59,60[■],61]. Respiratory infections [62] and dirt exposures [63] are more frequent among the poorest, and increased exposure to smoking in poor households may explain a proportion of nonatopic asthma [60[■]]. Data from Brazil show that strong risk factors for nonatopic asthma in children are those that could be considered to be associated with greater exposures to dirt in the indoor environment such as household rodent

infestations and frequency of household cleaning [19[■]].

Dirt contains highly potent microbial activators of the innate immune system such as endotoxin, a constituent of the cell walls of Gram-negative bacteria. Although endotoxin exposure has been associated with a lower prevalence of atopic asthma in rural areas in Europe, it was associated with an increase in the risk of nonatopic wheeze [61]. Others have reported high household levels of endotoxin to be associated with nonatopic wheeze [64], recurrent wheeze [65,66] and asthma severity [67]. Significant exposures to endotoxin cause nonatopic asthma in occupational settings [68].

Endotoxin is a potent activator of the innate immune system causing the release of pro-inflammatory cytokines and IL-12 by innate immune cells, and the production of interferon- γ by natural killer cells and T cells. Exposure to components of dirt such as endotoxin may therefore activate the innate immunity causing inflammation in the airways, bronchial hyperreactivity and asthma symptoms. Inhalation of endotoxin induces a pulmonary neutrophilia [67], an inflammatory phenotype that has been observed in induced sputum from Brazilian children with nonatopic asthma [57]. Other components of dirt that could have a role in the initiation of nonatopic reactions in the lungs include beta(1-3)glucans, a cell wall constituent of most fungi that also has pro-inflammatory effects via activation of innate immunity and has been associated with increased respiratory morbidity in occupational settings and with airflow variability in children [69]. House dust mite allergens such as Der p2 can activate innate immune responses directly via Toll-like receptor 4 (TLR4) [70] or beta(1,3)glucans-dependent pathways [71]. Further, genetic analyses across diverse populations show that among the genes that have been associated with asthma are those involved in innate immune responses by epithelium such as IL1-R1 [72]. Interactions between innate immune genes and the 'dirt' and infection-rich environment of urban Latin America in which Th2 responses appear to be attenuated could lead to inflammatory responses that favor the development of an inflammation in the lungs that is not typically allergic.

Diet and obesity

The occurrence of asthma has been associated with a reduced consumption of foods containing antioxidants (vitamin A, carotenoids, vitamin E, zinc, selenium and copper) [73-75] and with a greater consumption of saturated fats but a reduction in omega-3 polyunsaturated fatty acids (*n*-3-PUFAs).

Effects of lipid and antioxidant composition of the diet on innate and adaptive immune responses have been proposed as an explanation for the role of diet in asthma occurrence [76]. A 'Mediterranean'-style diet of fish, fruits, vegetables and whole cereals that is rich in antioxidants and n-3-PUFAs has been associated with a reduced prevalence of asthma [77–79]. A diet rich in fish is associated with elevated levels of selenium and zinc [80] and in many Latin American populations, wherein fish is frequently cooked in palm oil, with high levels of vitamin A. Selenium, zinc and vitamin A have antioxidant effects and have been associated with protection against asthma [75]. In Latin America, data from Mexico showed that children adherent to a 'Mediterranean' diet have less asthma [79,81]. Data from urban Brazil showed a one-third reduction in the prevalence of nonatopic asthma associated with fish consumption (S. D'Innocenzo, M.L. Barreto, unpublished data). A high dietary consumption of lipids and antioxidants obtained, for example, from fish cooked in palm oil could have anti-inflammatory effects that protect against asthma: omega 3 fatty acids obtained from fish reduce the innate response by inactivation of TLR4 [82] and suppression of the transcription factor NF- κ B [83], whereas selenium and zinc act as antioxidants [75,84,85]. The consumption of a diet low in antioxidants has been associated with increased neutrophilic inflammation in the lungs and worsening of asthma symptoms [86].

Obesity is growing fast and its associated morbidity is a major health problem in Latin America [87]. The prevalence of asthma, particularly nonatopic asthma, is directly associated with obesity [88]. In Brazil, the prevalence of nonatopic asthma was double in overweight and obese children compared with normal children [89[■]]. The endocrine activity of adipose tissue has been associated with wheezing and asthma [90,91]. Adipose tissue is metabolically active and releases pro-inflammatory mediators such as IL-6, TNF- α , C-reactive protein and leptin [92]. Leptin concentrations are increased in obesity and leptin stimulates a Th1 pattern of cytokine production [93]. Leptin concentrations have been associated with asthma in overweight children [90], although it remains unclear whether leptin is on the causal pathway between obesity and asthma [90]. Obesity has important physiological effects on lung function [88] and this combined with the pro-inflammatory state of obesity may contribute to asthma pathogenesis.

Exposure to stress/violence

Maternal stress [94] in early childhood, physical and sexual abuse [95] and emotional behavioral problems

and depressive symptoms [95] in childhood have been associated with asthma. The development of psychological distress in children has been associated with different aspects of asthma that is more difficult to manage, requiring higher doses of steroids and more frequent and prolonged admissions to hospital [96–98]. In Brazil, the prevalence of asthma was higher among children whose mothers had common mental disorders [99], among children with behavioral problems [100[■]], among those with insufficient social support (L. Marques dos Santos, unpublished data) and among children reporting family violence and severe corporal punishment (C. Bomfim, unpublished data). Asthma prevalence in children was associated also with the level of violence in the child's community [101[■]]. In general, these associations were stronger and more consistent for nonatopic than atopic asthma. The mechanisms by which psychological distress may contribute to the prevalence of nonatopic asthma are unclear. Particularly, there has been considerable confusion as to whether such stress may have a role in the development of asthma or solely act as an asthma trigger. There is evidence that nonatopic asthmatic patients are more vulnerable to asthma attacks if exposed to acute stress and abrupt emotional changes [102]. Stress is associated with the release of catecholamines, which can activate immune cells to release pro-inflammatory cytokines such as TNF- α , IL-1 and IL-8 [103]. In addition, chronic stress could interfere with the hypothalamic–pituitary axis to suppress the release of cortisol, a relative deficiency of which could promote pro-inflammatory effects [96,104]. The causal direction between psychological distress and asthma symptoms is not clear. Thus, whereas psychological distress could trigger pro-inflammatory processes that lead to asthma [105–107], asthma symptoms could lead to behavioral and emotional changes in the child and family members. However, prospective studies have indicated that behavioral disturbance antecede the development of wheeze and are not a secondary psychological reaction to disease ([106,107]; C. Feitosa, unpublished data).

CONCLUSION

Asthma has emerged over recent years as a major public health problem in several Latin American countries such as Brazil and is emerging as a health problem in others. The greatest burden of asthma in Latin America is in the urban poor who now constitute an increasingly large proportion of the population in all Latin American countries. The prevalence of asthma is highly variable between Latin American countries and present data suggest asthma in childhood is primarily nonatopic. The risk factors

associated with atopic and nonatopic asthma in children appear to be distinct and may have different causal pathways. Data from urban Brazil suggest that, in conditions of intense exposure to infectious diseases, burden of infection is associated with a reduced prevalence of atopy, but has little or no effect on asthma prevalence. Poverty and inequality are strongly linked to important risk factors for non-atopic asthma. The prevalence of nonatopic asthma is associated with environmental 'dirt' exposures and there are biologically plausible mechanisms by which high 'dirt' exposures (e.g. microbial products and infections) could explain the high prevalence of non-atopic asthma in Latin American children. Recent studies from Brazil indicate that the 'Bahian' diet that is rich in sea foods cooked in palm oil and coconut milk may be protective against nonatopic asthma. Similarly, many urban populations in Latin America live in an environment that is highly unequal, stressful and violent and accompanied by high levels of maternal mental illness and psychosocial stress in childhood. There is growing evidence that psychosocial stress may be an important risk factor for the development of nonatopic asthma in childhood. Such diverse causes (dirt, diet and stress) for non-atopic asthma may be associated with distinct biological pathways for inflammation. All are strongly associated with poverty and observational and even intervention studies will be required in the future to disentangle individual effects with the goal of identifying suitable preventive public health strategies.

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Conflicts of interest

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