

Review article

Asthma in Latin America: a public health challenge and research opportunity

Asthma has emerged as an important public health problem in many Latin American countries over the past decade. In Brazil and Costa Rica, the prevalence of asthma and associated morbidity is as great or greater as reported in traditional high prevalence countries such as the US, but remains neglected as a public health priority. Asthma in Latin America is associated particularly with underprivileged populations living in cities but remains relatively rare in many rural populations. The causes of asthma in Latin America are likely to be associated with urbanization, migration, and the adoption of a modern 'Westernized' lifestyle and environmental changes that follow these processes that include changes in diet, physical activity, hygiene, and exposures to allergens, irritants, and outdoor and indoor pollutants. Because of the enormous social, genetic, and environmental contrasts within and between Latin American countries, and the large differences in prevalence associated with these differences, the investigation of asthma in Latin America provides important research opportunities to identify the social and biological mechanisms that underlie asthma development. Asthma in Latin America poses enormous challenges for health policy makers, health services, and researchers to respond to and alleviate the growing burden of asthma disability, particularly among marginalized urban populations.

**P. J. Cooper^{1,2,3}, L. C. Rodrigues⁴,
A. A. Cruz⁵, M. L. Barreto⁶**

¹Centro de Investigaciones FEPIS, Quininde, Esmeraldas Province Ecuador; ²Instituto de Microbiología, Universidad San Francisco de Quito, Quito, Ecuador; ³Centre for Infection, St George's University of London; ⁴Infectious Diseases Epidemiology, London School of Hygiene and Tropical Medicine, London, UK; ⁵World Health Organization, Geneva, Switzerland; ⁶Instituto de Saúde Coletiva, Universidade Federal de Bahia, Brazil

Key words: asthma; allergy; Latin America; urbanization.

Philip J. Cooper
Casilla 17-14-39
Carcelen
Quito
Ecuador

Accepted for publication 21 August 2008

The prevalence of asthma has increased more than 10-fold in many affluent societies since the 1960s (1–3). This trend has affected children in particular and asthma is now the most common chronic disease of childhood in many countries (4). A recent international epidemiological study, ISAAC (the International Study of Asthma and Allergies in Childhood), has provided evidence that this trend may have reached a plateau in many industrialized countries (5). A striking observation from the early ISAAC studies was the high prevalence of asthma symptoms reported from some countries in Latin America that was as high as reported from known high prevalence countries such as the UK, Australia, and New Zealand (5, 6).

Asthma is a heterogeneous condition and is the final presentation of different aetiologies and pathways that are associated with diverse and complex genetic backgrounds (7). Asthma in Latin America is considered to be a disease of an urban environment in which there are extreme social inequalities with the majority of the population living in poverty and lacking access to basic infrastructure. The few studies conducted in rural areas of Latin America suggest that rural populations are for

unknown reasons protected against asthma, having a lower prevalence of allergy (8) and asthma (9, 10). Two important demographic processes are likely to drive the asthma epidemic in Latin America over the next 50 years, urbanization and rural–urban migration. Both continue to occur at a rapid rate and are fuelled by high fertility, widespread social and economic changes, and the 'urbanization' of the rural environment.

Asthma in countries such as Brazil is an important cause of morbidity and mortality and is a significant drain on health resources (11), but data to quantify the public health impact of asthma are scarce in many Latin American countries. Both the prevalence and morbid consequences of asthma are likely to be highly variable between Latin American countries. The study of asthma and allergy in Latin America offers important opportunities and challenges for research: the identification of risk and protective factors among populations with extremes of disease prevalence, and the investigation of gene–environment interactions for asthma in populations with a high degree of genetic admixture. Further, the large numbers of severe asthmatics present in urban

centres will provide new opportunities for aetiological and therapeutic research (12, 13).

Epidemiology of asthma in Latin America

Before ISAAC, available data on asthma prevalence and morbidity in Latin America was limited (14). Estimates of asthma prevalence were highly variable and ranged from 0.4% in Peru (15) to 19.1% in Brazil (16). ISAAC, by using standardized methodologies, has permitted reasonably reliable comparisons of the prevalence of asthma symptoms between and within countries. The ISAAC Phase I studies, that evaluated child-completed questionnaires of allergy symptoms among children aged 6–7 years and 13–14 years, included 17 centres from nine countries in Latin America (Table 1) (6). Phase I data must be interpreted with caution because of limited validation and important issues with respect to the reliability of child-completed questionnaires, although the results of video

questionnaires were broadly similar in the few Latin American centres where these were performed (6). Overall, the Phase I data from Latin America estimated the prevalence of recent wheeze, exercise-induced bronchospasm, and severe episodes of wheezing to be 16.9%, 19.3%, and 4.6%, respectively, for children aged 13–14 years (17). There were striking differences in asthma symptom prevalence between different countries (Table 1). For example, the prevalence of asthma ever and wheezing in the previous 12 months among adolescents aged 13–14 years ranged 6–28% and 7–27% and among children aged 6–7 years ranged 4–27% and 9–32%, respectively. The prevalence of asthma symptoms was high in Latin American countries in children of both age groups. Among 13–14 year olds, the prevalence of recent wheeze was greater than 15% (upper quartile of 56 participating countries worldwide) in Peru, Costa Rica, Brazil, Paraguay, Uruguay, and Panama. The prevalence of recent wheeze was lower (<10% or below median for countries) in Argentina, Chile, and Mexico.

Table 1. Prevalence of recent wheeze (within the previous 12 months) among school children participating in the ISAAC studies in Latin America

Country (centres)	ISAAC Phase I (13–14 year olds)		ISAAC Phase II (8–12 year olds)		ISAAC Phase III (13–14 year olds)	
	N	Wheeze (12 months) (%)	N	Wheeze (12 months) (%)	N	Wheeze (12 months) (%)
Argentina						
Buenos Aires	2996	9.9	–	–	–	–
Cordoba	–	–	–	–	3445	13.6 (+0.48)
Rosario	3008	11.8	–	–	–	–
Brazil						
Curitiba	3008	18.4	–	–	3628	18.9 (+0.09)
Porto Alegre	3198	24.7	–	–	3008	18.2 (–0.72)
Recife	3086	19.7	–	–	2865	19.1 (–0.07)
Salvador	3119	27.1	–	–	3022	24.6 (–0.33)
Sao Paulo	3008	23.3	–	–	3161	18.7 (–0.65)
Uruguiana	–	–	1971	25.6	–	–
Chile						
Central Santiago						
Punta Arenas	3482	6.8	–	–	3044	13.6 (+0.83)
South Santiago	3231	11.1	–	–	3026	17.0 (+0.98)
Valdivia	3231	11.5	–	–	3105	16.0 (+0.63)
Costa Rica						
Costa Rica	3200	23.7	–	–	2436	27.3 (+0.46)
Ecuador						
Pichincha	–	–	894	0.8	–	–
Mexico						
Cuernavaca	3102	6.6	–	–	1431	11.6 (+0.63)
Panama						
David	2885	17.6	–	–	3183	22.9 (+0.88)
Paraguay						
Asuncion	2996	19.4	–	–	3000	20.9 (+0.31)
Peru						
Lima	3158	26.0	–	–	3022	19.6 (–1.06)
Uruguay						
Montevideo	3072	19.0	–	–	3177	17.9 (–0.13)
Overall	52 549	16.9			44 550	18.8 (+0.32)

Phase III study shows change in prevalence per year between Phase I and III studies (brackets). Data is from references 5, 19, and 81.

The ISAAC Phase II study, using the same core allergy symptom questions, evaluated the prevalence of asthma symptoms among children aged 8–12 years by parental questionnaire in two centres in Latin America (Table 1): Brazil (Uruguaiana) and Ecuador (rural Pichincha Province), and suggested there may be large differences in asthma symptom prevalence between urban and rural areas – the prevalence of recent wheeze was 25.6% in Uruguaiana and 0.8% in rural Ecuador (18). Similarly, low rates of recent wheeze (3.3%) obtained by an ISAAC-based questionnaire were reported among children aged 4–6 years living in rural highland communities in Guatemala (10).

The ISAAC Phase III study repeated the child-completed questionnaires of Phase I in 66 centres in 37 countries worldwide after a period of 5–10 years to assess time trends in asthma prevalence (5). Overall, there was little average change in the prevalence of asthma symptoms in the participating centres (19). The prevalence of asthma symptoms did not appear to alter in countries that had a high prevalence of recent wheeze during the first survey (e.g. the UK), but rose in many centres of low or intermediate prevalence (5). Latin American countries provided data from seven centres in five countries for the 6–7 year age group and from 15 centres in nine countries for the 13–14 year group (Table 1). The time between surveys was 6–8 years. In the 6–7 year age group, the prevalence of recent wheeze rose in Costa Rica and Brazil; was unchanged in Mexico, Panama, and two of three centres in Chile; and fell in one centre in Chile. In the 13–14 year age group, the prevalence of recent wheeze rose in Mexico, Costa Rica, Panama, all three centres in Chile, and Argentina; was unchanged in three of five centres in Brazil, Paraguay, and Uruguay; and fell in Peru, and two of five centres in Brazil (Table 1). Overall, the only high prevalence centre at the first survey to have an increase in asthma symptom prevalence at the second survey was Costa Rica (increase from 32.1% to 37.6% in 6–7 year olds, 23.7% to 27.3% in 13–14 year olds). The decline in asthma symptom prevalence in high prevalence centres in Latin America may indicate that the prevalence of asthma has reached a plateau. The increases in low and intermediate prevalence centres raise the concern that asthma prevalence and morbidity will continue to increase in these areas.

The prevalence of asthma appears to be highly variable among Hispanic populations resident in the United States – Mexican Americans have the lowest and Puerto Ricans the highest rates (20). The prevalence of lifetime or current asthma (19.6% and 11.5%, respectively) among adults living in Puerto Rico was the highest reported of all US states or territories (21).

Asthma morbidity and mortality

Asthma in Latin America is associated with significant morbidity. The high asthma prevalence rates in the

ISAAC Phase I studies indicate significant morbidity in children and teenagers in Latin America (6, 22). The Asthma insights and Reality in Latin America (AIRLA) survey assessed asthma treatment and control among a large sample of asthma patients in seven Latin American countries (23). The survey provided evidence for a high level of patient morbidity and a high reliance on the use of emergency health services. Overall, only 2.4% of patients met all GINA (the Global Initiative for Asthma) criteria for optimal asthma control, and the reasons for this were a poor recognition of uncontrolled asthma, under-use of appropriate medications, inadequate patient education and lung function monitoring, and low patient expectations. More than 56% of patients in the survey reported daytime symptoms at least once per week, 45% were awakened by symptoms at night at least once per week, and more than half had been hospitalized or had used emergency care in the previous 12 months. A population survey conducted in six cities in Colombia indicated high rates of emergency department visits or hospitalization among asthmatics (24).

In parallel with the high prevalence of asthma, there is evidence for rising trends in asthma mortality in some Latin American countries. In Brazil, mortality rates rose in the 5–19 year age group over the period 1970 to 1992 and this age group had the highest asthma mortality (14), although later studies indicate that mortality rates in Southern Brazil peaked in the mid nineties and have declined since (25). Official health statistics in Brazil estimated a mortality rate from asthma of 1.5 deaths per 1000 inhabitants during the 1990s (14) that is between two and 10 times greater than that reported in the developed world (26).

Risk factors for asthma

Urbanization and modernization

The processes of urbanization and modernization are having profound effects throughout Latin America. Both processes occur hand in hand and reflect the processes of social and economic development, and the adoption of a modern lifestyle. Urban populations are growing rapidly in Latin America, and already 64% of the population of Latin America is estimated to live in urban areas, a proportion similar to that of Europe (73%) and North America (75%) (27). Urbanization has a profound effect on people's living conditions and health status and rapid urbanization has strained the capacity of local and national governments to provide basic services (e.g. sewage, water, electricity, etc.). The process of urbanization affects also the rural environment ('urban sprawl') in which there have been rapid changes to the natural environment (soil being replaced by concrete and asphalt), to housing and social networks, as well as on work and employment patterns. Urbanization feeds also rural–urban migration that may be a consequence of

searching for a better life, of social conflict, or of environmental degradation that limits the population that agricultural land can support.

Urbanization has been linked to asthma risk (28). The specific factors that contribute to this risk are not clear but may include changes in diet and physical activity, infectious disease and microbial exposures, increased exposure to antibiotics and vaccines, allergen exposures (both type and intensity), exposure to indoor irritants (e.g. formaldehyde derivatives in plastics), the effects of industrial and motor vehicle pollution, and psychosocial stressors including violence (29). It is possible also that urban populations are becoming more susceptible to the development of asthma (30). Large differences in asthma prevalence have been reported from urban and rural areas in Africa (31, 32) and Asia (33) with a much higher prevalence of asthma reported in urban compared to rural populations in some studies. Some recent studies suggest that the gradient in asthma prevalence between urban and rural populations in Africa is becoming less marked (31), and may be a consequence of the processes of urbanization and modernization extending into many rural environments. There is little or no data from Latin America on the effects of urbanization on asthma risk.

Migration

Several studies have examined the effects on asthma of migration from low to high asthma prevalence countries and indicate that birth in a low asthma prevalence country provides some protection after migration to a high prevalence country, but that the protection may decline with time of residence in the new environment (34). Hispanics living in the United States are considered to be at high risk of asthma and asthma-related morbidity. Data collected through national surveys in the US of Mexican Americans (MA) showed that Mexican-born MA children had lower rates of asthma compared to American born MA children (35, 36), and that the prevalence of asthma in Mexican-born adults with fewer than 10 years of residence in US was half the asthma prevalence of Mexican-born adults living in the US for 10 or more years (36). A study conducted in Sweden among native Swedes and immigrants showed that immigrants living in Sweden for less than 10.5 years had low levels of IgE and less specific allergy than natives but after more than 10.5 years of residence the IgE levels and specific allergy were similar to that of natives (37). These data support the importance of both place of birth and also length of residence in determining asthma risk among migrants.

A few studies in Europe (38, 39) and Asia (40) have examined migration within a country, and have provided evidence that birth and residence in a rural environment is protective against atopic disease, but that this protection may be lost or decreases after migration to a town in adulthood. These observations indicate that the protec-

tion afforded in environments of low asthma risk may not strictly limited to a time window in early life but rather may persist through adolescence and adulthood, and be dependent on the continuous presence of protective exposures.

Migration of populations from rural to urban areas within a country is likely to be associated with changes in many lifestyle and environmental exposures. In developing countries in Latin America such as Ecuador, migrant populations can be distinguished by the period of residence in an urban environment. Recent rural migrants tend to settle at the periphery of a city and bring with them social behaviours and lifestyle choices from their rural environment. Recent migrants may 'ruralize' their urban environment and live a lifestyle that, apart from restrictions of space, may change relatively little – for example, they may live in wood/bamboo houses (Fig. 1), have the same diet, raise animals, and maintain intimate contact with the soil. More established migrants (migrants and offspring of migrant parents) adopt a more urban lifestyle, eat a more urban diet, live in concrete houses, and reside in asphalt and concrete neighbourhoods (Fig. 1). The urban lifestyle may include changes in exposures to pets, infectious diseases and hygiene behaviours, activity levels, and smoking. The risks of asthma may differ between recent and established migrant populations depending on the important risk exposures that are prevalent, and is an area of active research (41).

Atopy

Atopy is considered to be an important risk factor for asthma in developed societies (42–46), although a number of studies indicate that a quarter to half of asthma may actually be attributable to allergic sensitization in population-based studies (47–49). The ISAAC Phase II study examined the association between allergen skin test reactivity (a proxy for allergic sensitization) and symptoms of recent wheeze in 32 study centres in 22 countries worldwide and showed that the fraction of current wheeze attributable to atopic sensitization varied enormously from 0% in Turkey (Ankara) to 94% in China (Guangzhou) (18). Very little wheeze from the two Latin American centres was attributable to allergen skin test reactivity (11% in both Ecuador and Brazil). Stratification of study centres into affluent and nonaffluent countries showed that a higher fraction of recent wheeze was attributable to atopy in affluent (41%) compared to nonaffluent countries (20%). Therefore, by far the majority of asthma observed in Latin America is likely to be nonatopic, although there is some evidence that more severe disease is more likely to be associated with atopy (23, 50).

It is not clear if atopy is causally related to the deterioration of lung function and increased bronchial hyper-reactivity in asthma (51). Atopic sensitization is



Figure 1. Rural–urban migration in Ecuador. The photographs illustrate changes in the living conditions and environment of Afro-Ecuadorians who have migrated to urban areas from rural communities in Ecuador. The original Afro-Ecuadorian population lives in traditional communities in a rain forest area of Esmeraldas Province (photographs A and B) and large numbers have migrated to Guayaquil over the past 20 years. Recent migrants tend to settle at the periphery of the city and live a ruralized lifestyle (photograph C). More established (photograph D) migrants acquire a more urban lifestyle and living conditions.

likely to contribute to airways inflammation and asthma symptoms (3, 52–54) but so can many other perennial inflammatory exposures such as environmental pollutants, and respiratory viral infections, that may be intense in the overcrowded slums of urban Latin America (50, 55, 56). The disassociation between asthma symptoms and atopy (9, 50, 55, 57), and the large variations in atopy prevalence between different populations (18), makes it unlikely that temporal increases in allergic sensitization are responsible for the high prevalence of asthma in Latin America.

A striking observation from epidemiological studies of school-age children in Latin America has been the high proportion of bronchial hyper-reactivity among non-asthmatics – 53% in Chile (55) and 40% in Costa Rica (58) – and may suggest that asymptomatic bronchial hyper-reactivity is widespread in the ‘aggressive’ (55) pro-inflammatory environment that characterizes the urban slums of Latin America.

Poverty and socioeconomic inequalities

Rural residence has been consistently identified as the strongest protective factor against asthma in epidemiological studies conducted in Europe (59, 60), Africa (31, 32, 61), and Asia (33) and rural residence appears to be protective against asthma in Latin America (9, 10). Rural residence is associated with a large number of environ-

mental factors including lifestyle, diet, and poor hygiene (e.g. microbial and helminth exposures). Many of the putative protective factors are associated with poverty (e.g. microbial exposures and exposure to farm animals). There is evidence that some factors associated with rural poverty such as household crowding, lack of access to a latrine, helminth infections, and socioeconomic level are protective against atopy in rural Ecuador (62) and Brazil (63), but currently no evidence that rural ‘poverty’ is protective against asthma. Because of the low prevalence of asthma symptoms in rural populations, very large epidemiological studies will be required to address this question adequately.

Paradoxically, poverty appears to be an important risk factor for asthma in urban centres in Latin America (20, 50, 53, 64–66). This is perhaps not unexpected – epidemiological studies conducted in developed countries have shown similar associations (47, 67, 68). Interestingly, although asthma is an important health problem of children living in inner cities in the US (69), the risk of asthma in inner city populations may be independent of ethnicity and income (70). Poverty is a complex social and economic condition and it is not easy to disentangle the effects of the many associated environmental and lifestyle factors that mediate the effect on asthma (66). Poverty at the individual level is associated with a number of known risk factors for asthma – smoking, high indoor and outdoor pollution, low birth weight and preterm

delivery, diet, and ethnicity. At the neighbourhood level, poverty may contribute to asthma risk through lack of good quality potable water, sewer systems, and waste collection and disposal. Poverty is also associated with poor access to and the under-use of health resources and with under-treatment that may contribute to the high prevalence of asthma and high levels of asthma morbidity reported from some urban centres of Latin America (13).

There is evidence from Europe that the relationship between poverty and asthma has changed over time. For example, a study in Sweden showed that conscripts of low socioeconomic status (SES) had a lower prevalence of asthma in an earlier cohort, but in a later cohort the low SES group had the highest prevalence, showing a reversal of the association with successive generations (71). A study in Germany showed that although the prevalence of asthma was higher among parents of high SES children, the same association of SES and asthma in children was not observed (72). Such observations indicate SES *per se* may not be causal for asthma, but that the effect is mediated by a complex set of factors that differ across different SES levels, and these factors have changed over time.

The 'poverty' factors associated with increased asthma risk in Latin America may include ethnicity and low maternal educational level (14). An ecologic analysis of socioeconomic factors associated with the prevalence of asthma using data from 20 cities in Brazil, showed positive associations with poor sanitation, infant mortality, GINI index (a measure of inequality), and all cause mortality (65). Surprisingly, the same study showed higher illiteracy rates were associated with less asthma, although this could reflect a reduced asthma risk among more recent rural migrants.

The indoor and outdoor environment

Latin America includes countries with very different climates, living conditions, and levels of industrialization and pollution. Pollution, both industrial and motor vehicle, is an important problem in many cities in Latin America where there are limited or no restrictions on emissions. Currently, there is limited data on the effects of pollution on asthma risk from Latin America (20), and data of the effects of outdoor air pollution in asthma causality from developed countries are controversial (73), although it has been associated with acute reductions in lung function in asthmatics (74). Regression modelling of the effects of air pollution on respiratory morbidity indicated important effects on hospitalizations due to asthma in Sao Paulo, Brazil (75). Further, an analysis of the health impact of air pollution estimated that the control of air pollution in Mexico City (Mexico), Santiago (Chile), and Sao Paulo could prevent over 150 000 deaths and four million asthma attacks over a period of 20 years (76). In the highly polluted environment of Mexico City, exposure to ozone was associated with

impaired lung function and respiratory symptoms (77). Asthma prevalence was lower in some of the ISAAC Phase I centres in Latin America with high levels of air pollution compared to those with much lower levels of air pollution (17, 78), and is consistent with the observation of a lower prevalence of asthma in a polluted area of East Germany compared to a cleaner area in West Germany (79). Current evidence, therefore, does not provide strong support for a causal association between atmospheric pollution and asthma, although some pollutants may trigger asthma exacerbations (80).

An impoverished urban environment provides conditions that concentrate different types of indoor allergens and irritants through household crowding, the use of carpets, sleeping on foam mattresses, the use of synthetic pillows and blankets, smoking, and the use of insecticides and household cleaning products. Asthma may be more prevalent in urban areas because of increased exposure to old foes that have been present always (such as indoor allergens from house dust mites and cockroaches) and new inhalable irritants (e.g. volatile compounds from plastics, paint, and other household products) that are characteristic of modern urban life.

The ISAAC studies showed the highest rates of asthma prevalence in hot humid equatorial coastal cities in Latin America (17, 81) that provide ideal breeding conditions for house dust mites and cockroaches, and exposure to high levels of indoor allergens may sensitize susceptible individuals, and cause or exacerbate the airways inflammation associated with asthma – a high proportion of asthmatics living in cities in Latin America are sensitized to house dust mites (82). The high prevalence of asthma in Costa Rica has been attributed to changes in bedding such as the use of foam mattresses and pillows that are associated with very high levels of mite and cockroach allergens (83).

Exposure to second-hand cigarette smoke is likely to be causally associated with acute lower respiratory tract infections and childhood asthma (80, 84). Studies conducted in Latin America have provided evidence that maternal smoking during pregnancy (85) and exposure to second-hand tobacco smoke (SHS) in infancy (86) is associated with increased asthma risk. SHS exposure is currently the only avoidable exposure for which there is strong evidence of an aetiological link with asthma, but epidemiological data on the size of this problem in Latin America is currently limited (87).

Hygiene

The hygiene hypothesis has tried to explain the temporal trends in asthma prevalence in terms of reduced infectious or microbial exposures in early life (60, 88). A large number of epidemiological studies have investigated the hypothesis and some have provided evidence in support (60). For example, the protective effect of farming observed in a number of studies conducted in Europe has been associated with endotoxin exposure in stables

Table 2. Risk factors for asthma in Latin America

Urbanization/modernization
Concrete vs soil environment
Migration of rural populations to urban areas
Changes in lifestyle, diet, and physical activity
Industrial and motor vehicle pollution
Exposure to indoor irritants and allergens
Access to health care (asthma diagnosis, vaccines, and antibiotics)
Psychosocial stress
Atopy, but a significant proportion of asthma is nonatopic
Poverty
Rural poverty protects but urban poverty is a risk factor
Factors associated with urban poverty are important such as
Smoking
Indoor and outdoor pollution
Low birth weight
Diet
Ethnicity
Educational level
Access to health care
Indoor and outdoor pollution
Outdoor
Industrial
Motor vehicle
Waste disposal
Indoor
Smoking
Allergens (house dust mite, cockroach, moulds, etc.)
Household cleaning products
Volatile compounds from plastics, paints, etc.
Hygiene
Endotoxin and microbial exposures
Exposures to vaccines and antibiotics
Sanitation and access to clean water
Helminth infections
Diet
Increased consumption of 'junk' food
Decreased consumption of fruit and vegetables
Genes

and barns (89), and similar types of microbial exposure could explain the low prevalence of asthma in rural Latin America. However, the high prevalence of asthma in many cities of Latin America, and also inner city areas of the US, has been taken as strong evidence against the hygiene hypothesis, because such areas are likely to be dirty, overcrowded, and unhygienic (3). There is mounting evidence from urban areas of Latin America that early respiratory viral infections, that are frequent in hot and humid coastal cities, may be important in the development of persistent childhood asthma (50, 55).

Helminth infections have been implicated as important protective infectious exposures (90). Several studies from areas highly endemic for helminth infections in Latin America have provided evidence for an inverse association between helminth infections and allergen skin test reactivity (8, 91, 92).

The association between helminth infections and asthma is less clear. Cross-sectional studies do not suggest an association between intestinal helminth infections and

recent wheeze (9), although there is some evidence for the development of a more attenuated form of asthma in individuals infected with *Schistosoma mansoni* (93). However, there is also evidence from other studies that exposure to intestinal helminth infections may enhance bronchial hyper-reactivity and asthma severity (50, 54, 94–98) and that anthelmintic treatment of subjects with asthma may reduce both the number of exacerbations and the need for medication (94). It is possible that the effects of helminths on asthma may vary according to prevalence – temporary infections acquired in areas of low prevalence may be associated with enhanced bronchial hyper-reactivity and asthma symptoms.

The dog helminth parasite, *Toxocara canis*, is not a natural infection of humans but may infect humans wherever dogs defaecate and is widespread in populations living in both temperate and tropical climates (99). *Toxocara canis* infection has been implicated as an important risk factor for wheeze in preschool children in a population living in the Amazon region of Brazil (100).

Diet, obesity, and physical activity

Urbanization and the urban lifestyle are likely to be associated with major changes in diet and physical activity. The most obvious effect of these changes is the increase in obesity. Obesity is a major problem in urbanizing populations in Latin America among both children and adults (101), and in transitional populations in Ecuador, for example, may be a probable consequence of a high volume carbohydrate diet in the absence of physical exercise. Such a diet may be appropriate for agricultural labourers but not for a newly sedentary population living in towns and cities.

Dietary changes may have a role in asthma development. It has been hypothesized for example, that decreasing antioxidant (e.g. fruit and vegetables), increased n-6 polyunsaturated fatty acid (PUFA) (e.g. margarine and vegetable oil), and decreased n-3 PUFA (e.g. oily fish) intakes have contributed to recent increases in asthma prevalence (102). In Latin America there is evidence of major dietary changes at the population level in favour of diets thought to be associated with asthma risk (103), although the potential impact of these changes on asthma prevalence has not been investigated.

There have been several reports of positive associations between body mass index and asthma (104, 105). Studies from Latin America have provided evidence for an association between elevated BMI and asthma risk in women (106, 107) and in both genders (108). The mechanism is not clear but it has been suggested that changes in physical activity that are associated with obesity could increase recurrent bronchial obstruction, which is the hallmark of the syndrome of asthma (109).

Children in urban Latin America spend increasing periods of time indoors because of changes in leisure habits (e.g. television and video games), and because of the

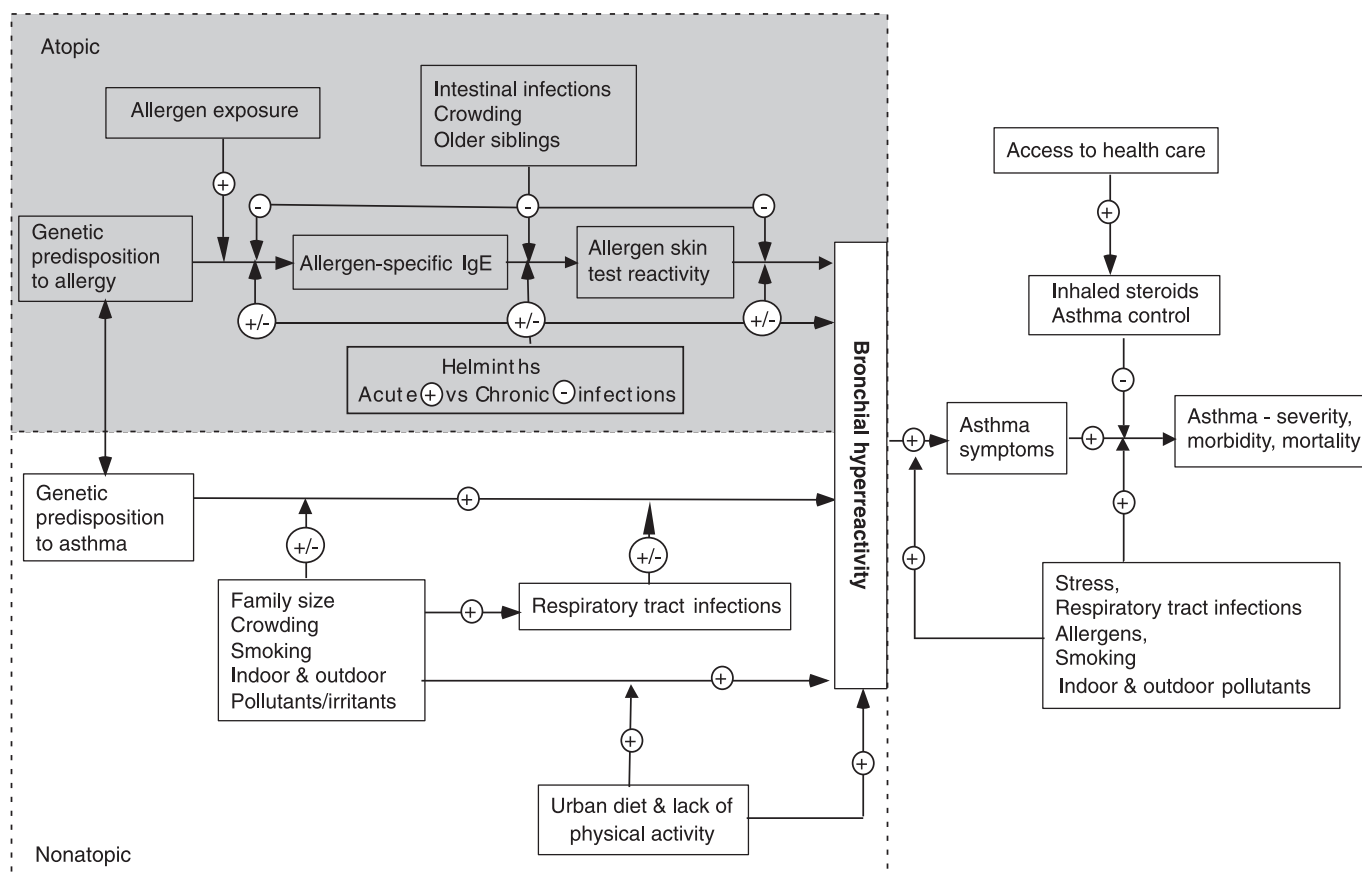


Figure 2. Conceptual framework for environmental and host factors affecting the development of atopic and nonatopic asthma in Latin America. The figure illustrates how different environmental exposures and genetic susceptibilities may lead to the development of bronchial hyper-reactivity and asthma symptoms that are associated with or not associated with atopy. The effects of intestinal infections (such as helminths), crowding, and older siblings may modify the development of asthma through effects on the development of allergic inflammation, while other distinct (environmental irritants and respiratory tract infections) or similar (crowding) exposures may effect the development of asthma through distinct biological mechanisms and genetic factors. Many social and environmental factors may be involved in determining asthma severity. Risk (+) and protective (−) effects are shown. Arrows pointing at arrows represent interactions. Urban residence would be expected to increase both atopic and nonatopic asthma through effects on important environmental exposures (e.g. decreasing helminth infection prevalence, increasing exposure to pollutants, urban diet and physical inactivity, increased allergen exposure, etc.).

risk of physical violence outdoors, particularly in lawless urban slums. Such new leisure habits are likely to be associated with increase exposure to indoor allergens and irritants, reduced physical activity, and increased obesity.

Gene–environment interactions

Latin American populations are derived from combinations of African, European, and Amerindian ancestors and the contribution of each racial group varies greatly across Latin America. Complex genetic traits are likely to be strongly linked with asthma phenotypes (7), and the high degree of genetic admixture of Latin American populations in combination with the large variations in environmental exposures may be an important determinant of the large variations in asthma prevalence. The high degree of genetic admixture makes genetic analyses

of asthma among Hispanic populations more complex because of genetic confounding (110, 111). Recent developments arising from the study of Hispanic (or Latino) populations living in the United States include the use of ancestry informative markers that estimate and control for genetic ancestry admixture mapping (110, 112), and statistical developments that allow for adjustment for population stratification resulting from genetic admixture (110, 111).

There is a growing literature on genetic markers for asthma among Hispanic populations living in the United States resulting from multicentre, multinational studies such as GALA (Genetics of Asthma in Latino Americans) that is investigating clinical, genetic and environmental risk factors among different Hispanic ethnic groups (113). However, to date few studies have provided convincing evidence of associations between asthma

Table 3. Important research questions, methodological issues, and appropriate study designs for the investigation of the causes of asthma in Latin America

Research question/risk factors	Methodological issues and challenges	Best study designs	Specificities of Latin America
Urbanization and modernization	Data must be collected in areas at different levels of urbanization and modernization to allow for investigation of which individual and area level factors are associated with asthma prevalence using hierarchical and multilevel analyses within conceptual frameworks	Ecologic Cross-sectional in more than one area Case-control in more than one area	Diversity of stages of urbanization and modernization
Atopic/nonatopic asthma	All studies must classify asthma phenotypes by allergen skin test reactivity, or preferably, presence of specific IgE	All	Apparent high proportion of nonatopic asthma
Influence of in utero and early life risk factors (e.g. infectious and microbial exposures)	Studies with collection of data from pregnancy and outcomes in later life. Expensive and require long periods of follow-up	Birth cohort	Diversity of exposures; good routine data available in some countries; research groups with experience in conducting large epidemiological studies; many infections highly prevalent
Poverty	Requires comprehensive and detailed data collection to explore which aspects of poverty are causally related to asthma risk. Conceptual frameworks and hierarchical analyses necessary because factors are likely to be strongly correlated	Cross-sectional Case-control Cohort	High degree of social inequality
Psychosocial factors	Necessary to establish temporal sequence to exclude the possibility of reverse causality (e.g. what is cause and which is effect in the association between maternal depression and asthma?)	Cohort	High level of violence in many urban centres.
Genetics and gene–environment interactions	Candidate gene and genome wide approaches to identify genetic determinants and gene–environment interactions. Requires well-defined clinical phenotypes, large sample sizes, and detailed environmental data	Family association Cross-sectional Case-control Cohort	Diverse ancestry (Amerindian, African, and European) and diversity of exposures
Indoor and outdoor pollution	Limited data on outdoor pollution available for many urban areas. Expensive and difficult to measure many indoor exposures (e.g. formaldehyde)	All	Diversity of exposures

phenotypes and gene polymorphisms (20). There is limited data also on gene–gene and gene–environment interactions in Hispanic populations, and the few studies that have been conducted have suffered from small sample sizes and other methodological limitations (20).

Research opportunities

Asthma in Latin America offers important opportunities for multidisciplinary clinical, epidemiological, and laboratory research. In several countries such as Brazil, Argentina, and Mexico there is excellent scientific infrastructure, training, and expertise available, and regional collaborations can capitalize on these resources. An example of such a collaboration is SCAALA (Social Changes, Asthma, and Allergies in Latin America), that is investigating the causes of asthma development in an urban cohort in Salvador, Brazil (114) and changes in risk factors for asthma associated with rural–urban migration in Ecuador (41). Asthma is emerging as an important

public health problem in the region, and both basic and clinical research is required now to investigate the causes and to identify potential preventive strategies.

The investigation of the risk factors associated with living in an urban environment and protective factors associated with rural residence may provide important clues to the causes of the epidemic (Table 2). Important research opportunities exist also in the investigation of the influence of urbanization and modernization in the region because many Latin American countries, and regions within countries, are at different stages in this modernization process.

The majority of asthma in Latin America is not associated with atopy (measured generally by allergen skin test reactivity) and important differences may underlie the pathoaetiology of atopic and nonatopic asthma. Epidemiological research into the causes of atopic and nonatopic asthma may provide important insights into the mechanisms underlying different asthma phenotypes. A conceptual model for the development of atopic and nonatopic asthma is provided in Fig. 2.

Research is required also on the impact of *in utero* and early life exposures on allergy and asthma development in low-risk rural and high-risk urban environments. Such studies should be prospective from birth, collect exposure information from pregnancy, and follow-up should continue to school age when the presence of asthma can be more reliably determined. The high risk of asthma in poor urban populations in Latin America is taken as evidence against the hygiene hypothesis, but poverty is complex and future studies should try to distinguish the effects of different factors associated with poverty and hygiene (66). Studies conducted in Latin American cities such as SCAALA-Salvador (114), that combine clinical, epidemiological, immunological, and social science research, offer an important opportunity to identify factors that mediate the biological and social mechanisms that underlie the development of asthma in Latin America. A discussion of possible study designs and methodology for addressing the important research questions into the causes of asthma in Latin America is provided in Table 3.

Genetic analyses must be integrated within these studies and the investigation of gene–gene and gene–environment interactions that mediate asthma in the highly genetically admixed populations of Latin America poses a considerable challenge. Such studies will provide important research opportunities because populations in Latin America provide enormous diversity in social, environmental, and genetic factors that are likely to mediate the large differences in prevalence observed, and the study of such populations is likely to provide important insights into the causes of asthma.

Conclusion

Asthma is highly prevalent and an important cause of morbidity in many Latin American countries, and is emerging as a public health problem in others. The ISAAC studies have provided evidence that the prevalence of asthma in Latin America is as high as observed in traditional high prevalence ‘English-speaking’ countries,

but that the prevalence is highly variable between and within countries. Asthma in Latin America is a disease that affects particularly the urban poor and may be relatively rare in rural populations. Unknown biological and social mechanisms are likely to underlie the epidemic of asthma in Latin America. The risk factors for asthma in Latin America include the processes of urbanization, and rural–urban migration, and the changes in lifestyle and environmental exposures that accompany these processes. Understanding how such exposures may increase or decrease asthma risk will be an important step towards identifying potentially useful public health interventions. A high proportion of asthma in Latin America is not associated with allergen skin test reactivity, however it is likely that exposure to indoor allergens as well as other indoor and external irritants contribute to airway inflammation and asthma symptoms. Because of the high prevalence of asthma in poor urban populations, it has been suggested that hygiene factors are unlikely to be important, but further research in this area is required. An important research opportunity in Latin America is the investigation of the causes of asthma in high- and low-risk populations to identify potential protective factors and avoidable risk factors that could be used to design new interventions.

Acknowledgments

PJC is supported by Wellcome Trust, Grant No. 074679/Z/04/Z. MLB, PJC, AAC, and LCR are involved in the SCAALA-Social Change Allergy and Asthma in Latin America – programme that is funded by The Wellcome Trust Latin American Centres of Excellence Programme, Grant No. 072405/Z/03/Z.

Disclaimer

Alvaro A. Cruz is a staff member of the World Health Organization. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions, policy or views of the World Health Organization.

References

1. Burney PG, Chinn S, Rona RJ. Has the prevalence of asthma increased in children? Evidence from the national study of health and growth 1973–86. *BMJ* 1990;**300**:1306–1310.
2. Beasley R, Crane J, Lai CK, Pearce N. Prevalence and etiology of asthma. *J Allergy Clin Immunol* 2000;**105**: S466–S472.
3. Platts-Mills TAE, Erwin E, Heymann P, Woodfolk J. Is the hygiene hypothesis still a viable explanation for the increased prevalence of asthma? *Allergy* 2005;**60**:S25–S31.
4. WHO. Global Alliance against Chronic Respiratory Diseases. General Meeting Report. Seoul, Republic of Korea, 1–2 June 2007. Geneva: World Health Organization, 2007 (http://www.who.int/gard/publications/MtgReport_GMSeoul_Final.pdf).
5. ISAAC. Worldwide variations in the prevalence of asthma symptoms: the International Study of Asthma and Allergies in Childhood (ISAAC). *Eur Respir J* 1998;**12**:315–335.
6. ISAAC. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. *Lancet* 1998;**351**:1225–1232.

7. Moffatt MF, Kabesch M, Liang L, Dixon AL, Strachan D, Heath S et al. Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. *Nature* 2007; **448**:470–474.
8. Cooper PJ, Chico ME, Rodrigues LC, Ordóñez M, Strachan D, Griffin GE et al. Reduced risk of atopy among school age children infected with geohelminth parasites in a rural area of the tropics. *J Allergy Clin Immunol* 2003; **111**:995–1000.
9. Cooper PJ, Chico ME, Griffin GE, Nutman TB. Allergy symptoms, atopy, and geohelminth infections in a rural area of Ecuador. *Am J Resp Crit Care Med* 2003; **168**:313–317.
10. Schei MA, Hessen JO, Smith KR, Bruce N, McCracken J, Lopez V. Childhood asthma and indoor woodsmoke from cooking in Guatemala. *J Exp Anal Environ Epidemiol* 2004; **14**:S110–S117.
11. Franco R, Santos AC, do Nascimento HF, Souza-Machado C, Ponte E, Souza-Machado A et al. Cost-effectiveness analysis of a state funded programme for control of severe asthma. *BMC Public Health* 2007; **7**:82.
12. WHO. Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach. Geneva: World Health Organization, 2007 (<http://www.who.int/gard/publications/GARD%20Book%202007.pdf>).
13. Ponte E, Franco RA, Souza-Machado A, Souza-Machado C, Cruz AA. Impact that a program to control severe asthma has on the use of Unified Health System resources in Brazil. *J Bras Pneumol* 2007; **33**:15–19.
14. Fischer GB, Camargos PAM, Mocelin HT. The burden of asthma in children: a Latin American perspective. *Pediatr Respir Rev* 2005; **6**:8–13.
15. Carrasco E. Epidemiologic aspects of asthma in Latin America. *Chest* 1987; **91**:S93–S97.
16. Hijjar MA, Pinheiro Feitosa JV, Gerhardt Filho G. A asma na favela do escondidinho – Município do Rio de Janeiro. *Boletim da Campanha Nacional contra a Tuberculose* 1988; **2**:53–58.
17. Mallol J, Solé D, Asher I, Clayton T, Stein R, Soto-Quiroz M. Prevalence of asthma symptoms in Latin America: the International Study of asthma and allergies in childhood (ISAAC). *Pediatr Pulmonol* 2000; **30**:439–444.
18. Weinmayr G, Weiland SK, Björkstén B, Brunekreef B, Büchele G, Cookson WO et al. Atopic sensitization and the international variation in asthma symptom prevalence in children. *Am J Respir Crit Care Med* 2007; **176**:565–574.
19. Pearce N, Ait-Khaled N, Beasley R, Mallol J, Keil U, Mitchell EA et al. Worldwide trends in the prevalence of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax* 2007; **62**:758–766.
20. Hunninghake GM, Weiss ST, Celedón JC. Asthma in Hispanics. *Am J Respir Crit Care Med* 2006; **173**:143–163.
21. Centers for Disease Control and Prevention. Asthma prevalence and control characteristics by race/ethnicity: United States, 2002. *MMWR* 2004; **53**:145–148.
22. Sole D, Wandalsen GF, Camelo-Nunes IC, Nasipz C, ISAAC-Brazilian group. Prevalence of symptoms of asthma, rhinitis, and atopic eczema among Brazilian children and adolescents identified by the International Study of Asthma and Allergies in Childhood (ISAAC) – Phase 3. *J Pediatr* 2006; **82**:341–346.
23. Neffen H, Fritscher C, Schacht FC, Levy G, Chiarella P, Soriano JB et al. Asthma control in Latin America: the Asthma Insights and Reality in Latin America (AIRLA) survey. *Rev Panam Salud Publica* 2005; **17**:191–197.
24. Dennis R, Caraballo L, García E, Caballero A, Aristizabal G, Córdoba H et al. Asthma and other allergic conditions in Colombia: a study in 6 cities. *Ann Allergy Asthma Immunol* 2004; **93**:568–574.
25. Chatkin G, Chatkin JM, Fritscher CC, Cavalet-Blanco D, Bittencourt HR, Sears MR. Asthma mortality in southern Brazil: is there a changing trend? *J Asthma* 2007; **44**:133–136.
26. Beasley C, Pearce N, Crane J. Worldwide trends in asthma mortality during the twentieth century. In: Sheffer A, editor. *Fatal asthma*. New York: Marcel Dekker, 1998:13–29.
27. United Nations Fund for Population Activities. Population issues – migration and urbanization. <http://www.unfpa.org/6billion/populationissues/migration.htm>.
28. Weinberg EG. Urbanization and childhood asthma: an African perspective. *J Allergy Clin Immunol* 2000; **105**:224–231.
29. Wright RJ. Exploring biopsychosocial influences on asthma expression in both the family and community context. *Am J Respir Crit Care Med* 2008; **177**:129–130.
30. Douwes J, Gibson P, Pekkanen J, Pearce N. Non-eosinophilic asthma: importance and possible mechanisms. *Thorax* 2002; **57**:643–648.
31. Nicolaou N, Siddique N, Custovic A. Allergic disease in urban and rural populations: increasing prevalence with increasing urbanization. *Allergy* 2005; **60**:1357–1360.
32. Addo-Yobo EO, Woodcock A, Allotey A, Baffoe-Bonnie B, Strachan D, Custovic A. Exercise-induced bronchospasm and atopy in Ghana: two surveys ten years apart. *PLoS Med* 2007; **4**:e70.
33. Viinainen A, Munhbayarlakh S, Zevgee T, Narantsetseg L, Naidansuren TS, Koskenvuo M et al. Prevalence of asthma, allergic rhinoconjunctivitis and allergic sensitization in Mongolia. *Allergy* 2005; **60**:1370–1377.
34. Gold DR, Acevedo-Garcia D. Immigration to the United States and acculturation as risk factors for asthma and allergy. *J Allergy Clin Immunol* 2005; **116**:38–41.
35. Eldeirawi K, McConnell R, Freels S, Persky VW. Associations of place of birth with asthma and wheezing in Mexican American children. *J Allergy Clin Immunol* 2005; **116**:42–48.
36. Holguin F, Mannino DM, Anto J, Mott J, Ford ES, Teague WG et al. Country as birth as a risk factor for asthma among Mexican Americans. *Am J Respir Crit Care Med* 2005; **171**:103–108.
37. Kalyoncu AF. Symptoms of asthma, bronchial responsiveness and atopy in immigrants and emigrants in Europe. *Eur Respir J* 2002; **19**:980–981.
38. Aberg N, Engstrom I, Lindberg U. Allergic diseases in Swedish school children. *Acta Paediatr Scand* 1989; **78**:246–252.
39. Nilsson L, Castor O, Lofman O, Magnusson A, Kjellman NIM. Allergic diseases in teenagers in relation to urban or rural residence at various stages of childhood. *Allergy* 1999; **54**:716–721.
40. Viinainen A, Munhbayarlakh S, Zevgee T, Narantsetseg L, Naidansuren TS, Koskenvuo M et al. The protective effect of rural living against atopy in Mongolia. *Allergy* 2007; **62**:272–280.
41. Cooper PJ, Chico ME, Vaca MG, Rodriguez A, Alcantara-Neves N, Genser B et al. Risk factors for asthma and allergy associated with urban migration: background and methodology of a cross-sectional study in Afro-Ecuadorian school children in Northeastern Ecuador (Esmeraldas-SCAALA Study). *BMC Pulm Med* 2006; **6**:24.
42. Sears MR, Burrows B, Flannery EM, Herbison GP, Hewitt CJ, Holdaway MD. Relation between airway responsiveness and serum IgE in children with asthma and in apparently normal children. *NEJM* 1991; **325**:1067–1071.

43. Clifford RD, Pugsley A, Radford M, Holgate ST. Symptoms, atopy, and bronchial response to methacholine in parents with asthma and their children. *Arch Dis Child* 1987;**62**:66–73.
44. Clifford RD, Howell JB, Radford M, Holgate ST. Associations between respiratory symptoms, bronchial response to methacholine, and atopy in two age groups of schoolchildren. *Arch Dis Child* 1989;**64**:1133–1139.
45. Witt C, Stuckey MS, Woolcock AJ, Dawkins RL. Positive allergy prick tests associated with bronchial histamine responsiveness in an unselected population. *J Allergy Clin Immunol* 1986;**77**:698–702.
46. Backer V, Ulrik CS, Hansen KK, Laursen EM, Dirksen A, Bach-Mortensen N. Atopy and bronchial responsiveness in random population sample of 527 children and adolescents. *Ann Allergy* 1992;**69**:116–122.
47. Court CS, Cook DG, Strachan DP. Comparative epidemiology of atopic and non-atopic wheeze and diagnosed asthma in a national sample of English adults. *Thorax* 2002;**57**:951–957.
48. Pearce N, Pekkanen J, Beasley R. How much asthma is really attributable to atopy? *Thorax* 1999;**54**:268–272.
49. Kurukulaaratchy RJ, Matthews S, Arshad SH. Defining childhood atopic phenotypes to investigate the association of atopic sensitization with allergic disease. *Allergy* 2005;**60**:1280–1286.
50. Pereira MU, Sly PD, Pitrez PM, Jones MH, Escouto D, Dias ACO et al. Nonatopic asthma is associated with helminth infections and bronchiolitis in poor children. *Eur Respir J* 2007;**29**:1154–1160.
51. Salvi SS, Babu KS, Holgate ST. Is asthma really due to a polarized T cell response toward a helper T cell type 2 phenotype? *Am J Respir Crit Care Med* 2001;**164**:1343–1346.
52. Sporik R, Holgate ST, Platts-Mills TA, Cogswell JJ. Exposure to house-dust mite allergen (Der p I) and the development of asthma in childhood. A prospective study. *NEJM* 1990;**323**:502–507.
53. Benício MH, Ferreira MU, Cardoso MR, Konno SC, Monteiro CA. Wheezing conditions in early childhood: prevalence and risk factors in the city of São Paulo, Brazil. *Bull World Health Organ* 2004;**82**:516–522.
54. Silva JM, Camara AA, Tobias KR, Macedo IS, Cardoso MR, Arruda E et al. A prospective study of wheezing in young children: the independent effects of cockroach exposure, breast-feeding and allergic sensitization. *Pediatr Allergy Immunol* 2005;**16**:393–401.
55. Mallol J, Castro-Rodriguez JA, Cortez E, Aguirre V, Aguilar P, Barrueto L. Heightened bronchial hyperresponsiveness in the absence of heightened atopy in children with current wheezing and low income status. *Thorax* 2008;**64**:167–171.
56. Mallol J, Andrade R, Auger F, Rodriguez J, Alvarado R, Figueroa L. Wheezing during the first year of life in infants from low-income population: a descriptive study. *Allergol et Immunopathol* 2005;**33**:257–263.
57. Penny ME, Murad S, Madrid SS, Herrera TS, Piñeiro A, Caceres DE et al. Respiratory symptoms, asthma, exercise test spirometry, and atopy in schoolchildren from a Lima shanty town. *Thorax* 2001;**56**:607–612.
58. Soto-Quiros ME, Silverman EK, Hanson LA, Weiss ST, Celedón JC. Maternal history, sensitization to allergens, and current wheezing, rhinitis, and eczema among children in Costa Rica. *Pediatr Pulmonol* 2002;**33**:237–243.
59. Riedler J, Eder W, Oberfeld G, Schreuer M. Austrian children living on a farm have less hay fever, asthma and allergic sensitization. *Clin Exp Allergy* 2000;**30**:194–200.
60. Eder W, Ege MJ, von Mutius E. The asthma epidemic. *NEJM* 2006;**355**:2226–2235.
61. Yemaneberhan H, Bekele Z, Venn A, Lewis S, Parry E, Britton J. Prevalence of wheeze and asthma and relation to atopy in urban and rural Ethiopia. *Lancet* 1997;**350**:85–90.
62. Cooper PJ, Chico ME, Rodrigues L, Strachan D, Anderson HR, Rodriguez EA et al. Risk factors for atopy among school-age children in a rural region of the Tropics. *Clin Exp Allergy* 2004;**34**:845–852.
63. Araujo MI, Lopes AA, Medeiros M, Cruz AA, Sousa-Atta L, Solé D et al. Inverse association between skin response to aeroallergens and *Schistosoma mansoni* infection. *Int Arch Allergy Immunol* 2000;**123**:145–148.
64. Mallol J. Asthma in the World. Asthma among children in Latin America. *Allergol Immunopathol (Madr)* 2004;**32**:100–103.
65. Cunha SS, Pujades MR, Barreto ML, Genser B, Rodrigues LC. Ecological study of socio-economic indicators and prevalence of asthma in schoolchildren in urban Brazil. *BMC Public Health* 2007;**7**:205.
66. Cunha SS, Barreto ML, Rodrigues LC. The importance of research on the association between socioeconomic conditions and asthma. *Rev Panam Salud Publica* 2007;**22**:438–440.
67. Rona RJ, Hughes JM, Chinn S. Association between asthma and family size between 1977 and 1994. *J Epidemiol Community Health* 1999;**53**:15–19.
68. Almqvist C, Pershagen G, Wickman M. Low socioeconomic status as a risk factor for asthma, rhinitis and sensitization at 4 years in a birth cohort. *Clin Exp Allergy* 2005;**35**:612–618.
69. Litonjua AA, Weiss ST. Is vitamin D deficiency to blame for the asthma epidemic? *J Allergy Clin Immunol* 2007;**120**:1031–1035.
70. Aligne CA, Auinger P, Byrd RS, Weitzman M. Risk factors for pediatric asthma. Contributions of poverty, race, and urban residence. *Am J Respir Crit Care Med* 2000;**162**:873–877.
71. Braback L, Hjert A, Rasmussen F. Social class in asthma and allergic rhinitis: a national cohort over three decades. *Eur Respir J* 2005;**26**:1–5.
72. Bergmann RL, Edenharter G, Bergmann KE, Lau S, Wahn U. Socio-economic status is a risk factor for allergy in parents but not in their children. *Clin Exp Allergy* 2000;**30**:1740–1745.
73. Strachan DP. The role of environmental factors in asthma. *Br Med Bull* 2000;**56**:865–882.
74. McCreanor J, Cullinan P, Nieuwenhuijsen MJ, Stewart-Evans J, Malliarou E, Jarup L et al. Respiratory effects of exposure to diesel traffic in persons with asthma. *NEJM* 2007;**357**:2348–2358.
75. Farhat SC, Paulo RL, Shimoda TM, Conceição GM, Lin CA, Braga AL et al. Effect of air pollution on pediatric respiratory emergency room visits and hospital admissions. *Braz J Med Biol Res* 2005;**38**:227–235.
76. Bell ML, Davis DL, Gouveia N, Borja-Aburto VH, Cifuentes LA. The avoidable health effects of air pollution in three Latin American cities: Santiago, São Paulo, and Mexico City. *Environ Res* 2006;**100**:431–440.
77. Castillejos M, Gold DR, Dockery C, Tosteson T, Baum T, Speizer FE. Effects of ambient ozone on respiratory function and symptoms in Mexico City schoolchildren. *Am Rev Respir Dis* 1992;**145**:276–282.
78. Neffen HE. Asthma prevalence and risk factors in Latin America. *Curr Allergy Clin Immunol* 2007;**20**:8–10.
79. von Mutius E, Martinez FD, Fritzsche C, Nicolai T, Roell G, Thiemann HH. Prevalence of asthma and atopy in two areas of West and East Germany. *Am J Respir Crit Care Med* 1994;**149**:358–364.

80. Gilmour MI, Jaakkola MS, London SJ, Nel AE, Rogers CA. How exposure to environmental tobacco smoke, outdoor air pollutants, and increased pollen burdens influences the incidence of asthma. *Environ Health Perspect* 2006;**114**:627–633.
81. Sole D, Melo KC, Camelo-Nunes IC, Freitas LS, Britto M, Rosario NA et al. Changes in the prevalence of asthma and allergic diseases among Brazilian schoolchildren (13–14 years old): comparison between ISAAC phases one and three. *J Trop Pediatr* 2006;**53**:13–21.
82. Fernández-Caldas E, Baena-Cagnani CE, López M, Patiño C, Neffen HE, Sánchez-Medina M et al. Cutaneous sensitivity to six mite species in asthmatic patients from five Latin American countries. *J Investig Allergol Clin Immunol* 1993;**3**:245–249.
83. Soto-Quiros M, Bustamante M, Gutierrez I, Hanson LA, Strannegård IL, Karlberg J. The prevalence of childhood asthma in Costa Rica. *Clin Exp Allergy* 1994;**24**:1130–1136.
84. Strachan DP, Cook DG. Health effects of passive smoking. 6. Parental smoking and childhood asthma: longitudinal and case-control studies. *Thorax* 1998;**53**:214–212.
85. Celedon JC, Soto-Quiros ME, Silverman EK, Hanson L, Weiss ST. Risk factors for childhood asthma in Costa Rica. *Chest* 2001;**120**:785–790.
86. Barraza Villareal A, Sanin Aguirre LH, Tellez Rojo MM, Lacasana Navarro M, Romieu I. Risk factors for asthma in school children from Ciudad Juarez, Chihuahua. *J Asthma* 2003;**40**:413–423.
87. Centers for Disease Control and Prevention. Exposure to secondhand smoke among students aged 13–17 years: worldwide, 2004–2007. *MMWR* 2007;**56**:497–500.
88. Strachan DP. Hay fever, hygiene, and household size. *BMJ* 1989;**299**:1259–1260.
89. Braun-Fahrlander C, Lauener R. Farming and protective agents against allergy and asthma. *Clin Exp Allergy* 2003;**33**:409–411.
90. Cooper PJ, Barreto M, Rodrigues LC. Human allergy and intestinal helminth infections: a review of the literature and discussion of a conceptual model to investigate the possible causal association. *Br Med Bull* 2006;**80**:203–218.
91. Hagel I, Lynch NR, Pérez M, Di Prisco MC, López R, Rojas E. Modulation of the allergic reactivity of slum children by helminthic infection. *Parasite Immunol* 1993;**15**:311–315.
92. Rodrigues LC, Newland P, Cunha SS, Genser B, Alcantara-Neves N, Cruz AA et al. Early infections with intestinal helminths reduce the risk of atopy later in childhood. *Clin Exp Allergy* 2008;**38**:1769–1777.
93. Medeiros M Jr, Figueiredo JP, Almeida MC, Matos MA, Araújo MI, Cruz AA et al. *Schistosoma mansoni* infection is associated with a reduced course of asthma. *J Allergy Clin Immunol* 2003;**111**:947–951.
94. Lynch NR, Palenque M, Hagel I, DiPrisco MC. Clinical improvement of asthma after anthelmintic treatment in a tropical situation. *Am J Respir Crit Care Med* 1997;**156**:50–54.
95. Palmer LJ, Celedón JC, Weiss ST, Wang B, Fang Z, Xu X. *Ascaris lumbricoides* infection is associated with increased risk of childhood asthma and atopy in rural China. *Am J Respir Crit Care Med* 2002;**165**:1489–1493.
96. Hunninghake GM, Soto-Quiros ME, Avila L, Ly NP, Liang C, Sylvia JS et al. Sensitization to *Ascaris lumbricoides* and severity of childhood asthma in Costa Rica. *J Allergy Clin Immunol* 2007;**119**:654–661.
97. Takeuchi H, Zaman K, Takahashi J, Yunus M, Chowdhury HR, Arifeen SE et al. High titre of anti-*Ascaris* immunoglobulin E associated with bronchial asthma symptoms in 5-year-old rural Bangladeshi children. *Clin Exp Allergy* 2008;**38**:276–282.
98. Hagel I, Cabrera M, Hurtado MA, Sanchez P, Puccio F, Di Prisco MC et al. Infection by *Ascaris lumbricoides* and bronchial hyper reactivity: an outstanding association in Venezuelan school children from endemic areas. *Acta Trop* 2007;**103**:231–241.
99. Cooper PJ. *Toxocara canis* infection: an important and neglected risk factor for asthma? *Clin Exp Allergy* 2008;**38**:551–553.
100. Ferreira MU, Rubinsky-Elefant G, Gontijo de Castro T, Hoffmann EHE, da Silva-Nunes M, Cardoso MG et al. Bottle feeding and exposure to *Toxocara* as risk factors for wheezing illness among under-five Amazonian children: a population-based cross-sectional study. *J Trop Pediatr* 2007;**53**:119–124.
101. Filozov C, Gonzalez C, Sereday M, Mazza C, Braguinsky J. Obesity prevalence and trends in Latin-American countries. *Obes Rev* 2001;**2**:99–106.
102. Devereux G, Seaton A. Diet as a risk factor for atopy and asthma. *J Allergy Clin Immunol* 2005;**115**:1109–1117.
103. Bermudez OI, Tucker KL. Trends in dietary patterns of Latin American populations. *Cad Saude Publica* 2003;**19**:S87–S99.
104. Schaub B, von Mutius E. Obesity and asthma, what are the links? *Curr Opin Allergy Clin Immunol* 2005;**5**:185–193.
105. Chinn S, Rona RJ. Can the increase in body mass index explain the rising trend in asthma in children? *Thorax* 2001;**56**:845–850.
106. Bustos P, Amigo H, Oyarzun M, Rona RJ. Is there a causal relation between obesity and asthma? Evidence from Chile. *Int J Obes Relat Metab Disord* 2005;**29**:804–809.
107. Del-Rio-Navarro BE, Fanghanel G, Berber A, Sanchez-Reyes L, Estrada-Reyes E, Sienna-Mongre JJ. The relationship between asthma symptoms and anthropometric markers of overweight in a Hispanic population. *J Investig Allergol Clin Immunol* 2003;**13**:118–123.
108. Santillan AA, Camargo CA. Body mass index and asthma among Mexican adults: the effect of using self-reported vs measured weight and height. *Int J Obes Relat Metab Disord* 2003;**27**:1430–1433.
109. Platts-Mills TAE, Sporik RB, Chapman MD, Heymann PW. The role of domestic allergens. In: Chadwick D, Cardew G, editors. *The rising trends in asthma*. West Sussex, UK: John Wiley and Sons Ltd, 1997:173–185.
110. Choudhry S, Seibold MA, Borrell LN, Tang H, Serebrisky D, Chapela R et al. Dissecting complex diseases in complex populations: asthma in Latino Americans. *Proc Am Thorac Soc* 2007;**4**:226–233.
111. Salari K, Burchard EG. Latino populations: a unique opportunity for epidemiological research of asthma. *Paediatr Perinatal Epidemiol* 2007;**21**:S15–S22.
112. Salari K, Choudhry S, Tang H, Naqvi M, Lind D, Avila PC et al. Genetic admixture and asthma-related phenotypes in Mexican American and Puerto Rican asthmatics. *Genet Epidemiol* 2005;**29**:76–86.
113. Choudhry S, Coyle NE, Tang H, Salari K, Lind D, Clark SL et al. Population stratification confounds genetic association studies among Latinos. *Hum Genet* 2006;**118**:652–664.
114. Barreto ML, Cunha SS, Alcântara-Neves N, Carvalho LP, Cruz AA, Stein RT et al. Risk factors and immunological pathways for asthma and other allergic diseases in children: background and methodology of a longitudinal study in a large urban center in North-eastern Brazil (Salvador-SCAALA study). *BMC Pulm Med* 2006;**6**:15.