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ORIGINAL ARTICLE

Asthma Symptoms and Airway Narrowing in Children Growing up in an Urban versus Rural Environment

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The development of asthma and allergy appears to be the result of gene-environment interaction. Potential environmental risk factors such as outdoor and indoor air pollution, infections, allergen exposure, diet, and lifestyle patterns may trigger respiratory symptoms and compromise lung function in children. Specific features of urban and rural lifestyle may constitute distinct risk factors but may also coexist within certain socioeconomic levels. Children of rural environments are at lower risk for asthma and aeroallergen sensitization. The protective effect has been associated with close contact with large animals, but the genetic factor also plays a contributory role. Children with prolonged exposure to urban environment are at increased risk of reduced lung function and those that reside in polluted areas exhibit slower lung growth. It is possible that polluted urban environment *per se* facilitates subclinical small airway disease. Evidence to date supports a strong relation between residential area as a potential risk factor for childhood asthma symptoms and airway obstruction and a western type of socioeconomic development.

Keywords Air pollution, allergy, lung function, sensitization, rural, urban, wheezing

INTRODUCTION

The development of childhood asthma and allergy appears to be the result of gene-environment interaction; indeed, early-life exposures interact with the child's genotype and determine response to environmental factors and subsequent risk for disease (1, 2).

Although the clinical spectrum of asthma is variable, there is a common underlying final pathway that leads to airway narrowing (3). There are several factors that trigger this process (4). However, the level of the association of each factor and its potential causal role are not fully understood. It is possible that certain factors under different circumstances play different roles on airway pathology, resulting in distinct clinical manifestations (5).

Children living in rural environment seem to be at lower risk of asthma than their urban counterparts (6); moreover, children living in a farming environment are at decreased risk of developing asthma (6–8). In addition, children exposed to outdoor or indoor air pollutants experience aggravation of their symptoms (9–12). Lastly, the effect of long-term exposure of children to certain aeroallergens appears to depend on the type of allergen and the timing of exposure in the child's life (13, 14).

This review examines the role of residential area as a potential risk factor for asthma symptoms and airway obstruction in children.

URBAN AND RURAL ENVIRONMENTS

Characteristics that define urban *versus* rural environment include occupation with agriculture, population density, and socioeconomic aspects such as age, structure of employment, and population changes. Living environment is characterized as "urban" when it involves high population density, housing in apartment buildings, and high level functions, while a "rural" area traditionally involves low-density population and agricultural and/or farming occupation. Thresholds may vary greatly depending on particular characteristics within each country. During the last decades a worldwide increasing trend in urbanization—with migration from rural to urban environments—has resulted in substantial growth of urban populations, particularly in the developing countries (15, 16).

Certain characteristics of urban living such as sedentary lifestyle, excess food intake, car transportation, clustering within homes, and high level of exposure to air pollution have significant effects on children's health (17). Depending on their socioeconomic status (SES), people may adopt a "rural" lifestyle, even if they reside in the city, making the distinction between "rural" and "urban" living difficult; consequently, it is more meaningful to examine separately the major risk factors for childhood asthma and allergies within urban and rural environments.

Outdoor and Indoor Air Pollution

Primary air pollutants are emitted into the atmosphere from sources such as factory chimneys and exhaust pipes or may be carried by the wind in suspended contaminated dusts. Secondary air pollutants are formed *de novo* in the atmosphere. They arise from chemical reactions of primary pollutants, potentially involving the natural components of the atmosphere.

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such as oxygen and water. The most familiar secondary pollutant is ozone (O_3), which arises almost entirely from chemical reactions dependent on the altitude. Particulate primary and secondary air pollutants comprise particles of various sizes in solid or liquid phase that remain suspended in the atmosphere (18).

Some pollutants are encountered in appreciable concentrations only in proximity to their source of emission. Examples are the various chemicals emitted from specific industrial processes or from inadequately controlled household and community sources such as burning of biomass fuels, not uncommon in developing countries. Pollutants from urban sources, such as nitrogen oxides (N_xO_y) and carbon monoxide (CO) generated by road traffic, tend to be in higher concentrations throughout the city rather than in adjacent rural areas (19). Sulphate particles and ozone readily travel thousands of kilometers—known as long-range transport—crossing national boundaries. Fine aerosols of black carbon from burning of fossil fuels or biomass are also capable of “long-range transport.” Emissions from motor traffic contribute significantly to the concentrations of local pollutants worldwide. Populations who live, work, or attend school near high traffic areas are considered as high-risk groups regardless of their urban or rural residential area (18).

Children spend more time outdoors than adults, mostly in summer during late afternoon. Their exposure to outdoor air pollution is a matter of concern since their immune system and lungs are still developing. In addition, exposure of the pregnant mother to increased levels of air pollutants may harm the fetus. Recent epidemiological studies have shown that pollutant levels in the air, including ambient particles and gaseous pollutants such as ozone, nitrogen dioxide (NO_2), and CO are associated with long- and short term adverse health effects (20).

The indoor environment represents an important microenvironment for children, as they spend most of their time indoors, especially during the cold months of the year. Most indoor air pollutants originate from combustion of solid fuels, tobacco smoking, emissions from construction materials or furnishings, and improper maintenance of ventilation and air conditioning systems (21). The importance of each source in a particular area varies according to the level of socioeconomic development rather than the “urban” or “rural” assignment of the environment (18, 21, 22).

Improvements in energy efficiency have led to airtight homes with reduced ventilation and raised levels of indoor pollutants. Thus, even minor pollutants from gas cookers, new furnishings, dampness, household products or naturally occurring radon gas can lead to significant exposures and undesirable health effects (23).

Infections

Exposures to infectious agents are among environmental factors that may contribute to the increased trends in the prevalence of asthma and allergy.

Inner-city children appear to have more episodes of acute respiratory infection than children of rural areas due to overcrowding, poor nutrition or sanitation, and indoor air pollution. These factors may apply to both urban and rural areas, depending mostly on the family's socioeconomic status

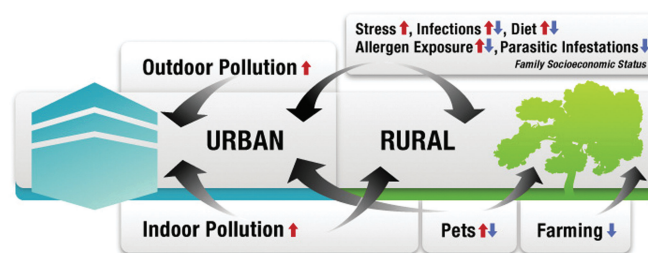


FIGURE 1.—Conceptual model showing the effect of various environmental factors on asthma and allergies in children residing in urban *versus* rural areas. Certain environmental influences are associated with increased risk or protection irrespective of urban or rural living; expression of asthma phenotype is influenced by family socioeconomic status. Abbreviations: ↑ increased risk; ↓ decreased risk (protection).

(SES). Poor socioeconomic and hygiene conditions have been associated with increased occurrence of hepatitis, bacterial, or parasitic infections (24–26). The “hygiene hypothesis” has proposed that the increase in the prevalence of allergic diseases can be attributed to improved living conditions, new vaccinations, and use of antibiotics that are responsible for the reduced number of infections in early life (27). The immunological mechanism that has been proposed to explain this hypothesis contends that exposure to viral and/or bacterial infections in early life facilitates type-1 (Th1) immunity and the release of corresponding cytokines (i.e. $IFN-\gamma$) and thus inhibits the type-2 (Th2) allergic immune response (28). The observation that individuals exposed to helminth infections with a prominent type-2 (Th2) response have a reduced prevalence of allergic disease has cast doubt on this biological model. A more current version of the hygiene hypothesis suggests that infections in early life trigger regulatory immune signals preventing the development of allergy (29, 30).

Allergen Exposure

Epidemiological studies suggest that children living in rural as compared to urban environments have a lower risk of sensitization to inhaled allergens. Several risk/protective factors that are by no means unique to rural environments have been identified or proposed, such as microbial exposures and close animal contact in rural areas, to explain the phenomenon. Nevertheless, it is not yet clear whether the reduced risk of sensitization in rural areas is due to the protecting effect of farming or to the increased risk of sensitization to aeroallergens in urban environments that is possibly enhanced by high-traffic pollution (31, 32).

Several reports have shown that living in a farming area with regular close contact with livestock and large animals is negatively associated with atopy (33). It has been proposed that increased exposure to airborne bacterial endotoxin in animal stables prevents the development of allergy through stimulation of Th-1 and suppression of Th-2 lymphocytes leading to down-regulation of IgE production (7). Furthermore, children of farmers in Europe with low prevalence of allergy and atopy carry a genetic variation of toll-like receptor-2 (TLR-2), i.e., a genetic variation related to susceptibility to asthma and allergy (34). Host response to environmental endotoxin depends, at least in part, on the

timing of exposure and the genetic variation of expression of endotoxin TLRs (35).

A population-based longitudinal cohort study showed low prevalence of atopy in children in rural environment, but no association between atopy and farming was revealed (32). In the rural areas of this study, inhabitants have little contact with large animals and thus constitute an entirely different rural milieu than the one reported by studies from central Europe (36, 37).

The lower risk of sensitization to pollen among children living in rural environment can be explained by the induction of tolerance to pollen that is achieved by repeated exposure to high doses of allergens during early life (5). However, this mechanism is not accepted by all investigators (38, 39).

Regarding sensitization to pets, it appears that more urban than rural children are sensitized to pets despite the fact that children raised in rural areas are more likely to be exposed to cat or dog. It is possible that early pet exposure in rural areas may prevent the development of atopic sensitisation (32, 40, 41); high-dose exposure to cat dander has been associated with clinical tolerance with a modified Th-2 immune response leading to the production of G4 instead of E antibodies (42, 43). However, these observations differ from those in Kuwait showing that pet ownership increased the risk of sensitization to pets and those in Cyprus where there was lack of association between pet sensitization and pet ownership in an urban setting (44, 45). It is likely that living in a cold urban environment or in houses with modern energy-saving systems may result in exposure to higher levels of pet allergens with subsequent risk of sensitization and allergic airway disease. Furthermore, in high-traffic urban environments, other factors such as outdoor air pollution, including diesel exhaust particles (46), NO₂ (47), sulphur dioxide (SO₂) (48), domestic air quality (10), may facilitate allergen sensitization in children. Thus, lower allergen sensitization in children in a rural environment may not be exclusively attributed to rural protection, but potentially to an urban living effect, or to both. Other factors, including increased construction activity or volatile organic compounds (VOCs), mechanical exhaust, and supply ventilation, may also play a role (10, 49).

Diet

Urban environment and lifestyle exert a strong influence on nutritional habits of infants and older children in developed countries, and in societies undergoing a developmental and/or environmental transition (50). The health consequences of urban lifestyle is not confined to residents of cities and large towns but are rather becoming manifest in rapidly changing, previously traditional societies in remote rural areas. In the era of globalization infant feeding practices, dietary habits, and lifestyle patterns of children are changing (50–52).

In such settings there are prominent trends towards increasing intake of snacks, fast food and sweetened beverages that gradually replace the consumption of home-made food (52). In addition, it has been noted that regular consumption of fish rich in omega-3 fatty acids and of fresh fruits and vegetables may exert a protective effect in the development of asthma (53), while consumption of unpasteurized farm

milk may protect from allergy, albeit at the risk of increasing exposure to unknown health hazards (54).

EFFECT ON RESPIRATORY SYMPTOMS

In recent years, a large number of studies evaluated the association between urban risk factors and asthma symptoms (17, 28).

Air Pollution and Asthma Symptoms

Although the impact of air pollution on asthma symptoms continues to be under debate, several studies document the short- and long-term effects of ambient air pollution on the respiratory tract of children (19, 20).

In an American prospective study of 990 children followed for a 22-month period, in eight cities, asthma exacerbation occurred 2 days after peak measurements of CO and NO₂ while the 3-day sum of SO₂ levels was marginally related to asthma symptoms (55). A survey in northern Marseille demonstrated that emergency room visits for asthma increased by 6%, when O₃ levels increased either the same day (10 µg/m³) or 2 to 3 days before these visits (56). Other reports have shown that the effects of air pollution on asthma in children differed according to the regional SES (57).

The impact of common indoor air pollutants from combustion—solid fuels, gas stoves, fireplaces, tobacco smoke, and particles from poorly maintained ventilation systems—on asthma symptoms have also been extensively studied (21–23). Passive smoking is directly related to respiratory morbidity, whereas the effect of chemical pollutants in the exacerbation of respiratory symptoms remains inconclusive (23, 58). In developing countries, children exposed to high levels of pollutants from biomass combustion experience respiratory symptoms regardless of urban or rural residence (59, 60).

Many VOCs such as formaldehyde, toluene, and chloroform are also found in modern buildings particularly in those within urban areas (61). Observational studies have suggested an association between VOC exposure and asthma (62, 63).

Sensitization and Asthma

Sensitization of children to inhaled allergens as a risk factor for asthma symptoms appears to be of varying importance worldwide as other environmental factors also influence the threshold for gene-environment interaction (6, 64, 65). A recent analysis of Phase II of the International Study of Asthma and Allergy in Childhood (ISAAC) data concluded that prevalence rates of asthma symptoms and atopic sensitization vary widely (65). High prevalence was mostly related to nonatopic wheezing, whereas the association between atopic sensitization and asthma symptoms increased with economic development.

Interestingly, high allergen exposure appears to increase the risk of sensitization in predisposed children but does not always correlate with clinical manifestations. In a cross-sectional survey in rural and urban Korea, children were evaluated by questionnaire and skin prick tests to common local aeroallergens including citrus red mite and Japanese cedar pollen (66). The sensitization rate among children residing

in rural environment was 14.2% for citrus red mite and 9.7% for Japanese cedar pollen, while among children of urban residence it was found to be 1.3% and 0.2%, respectively. The prevalence of current wheeze in the rural area was similar between sensitized and non-sensitized children to either citrus red mite or to Japanese cedar pollen. In a more recent study, children living in a rural environment had lower sensitization to pollen allergens such as *Parietaria officinalis* and olive trees than those living in urban area, and there was no association between urban or rural living and the risk of asthma or wheeze (32).

The Multicentre Allergy birth-cohort Study (MAS) (67) showed that exposure to cat allergen during infancy was associated with increased cat-specific immunoglobulin G (IgG) and IgE levels. Children with very high exposure to cats had decreased the likelihood of IgE but increased IgG specific sensitization that was associated with low risk of wheeze. However, increased cat-specific IgG levels did not protect children with cat-specific IgE from wheeze.

Lastly, in the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study (68), early exposure to house dust mite and cat allergen was associated with sensitization to both allergens, while only cat-sensitized subjects had persistent wheeze. In subgroups with a history of maternal atopy, early exposure to mite and dog allergen was associated with asthma and persistent wheeze, respectively. It appears that early-life exposures interact with the child's genotype to determine the response to environmental factors and subsequent risk of disease (1, 2).

Wheezing and Parasitic Infection

Allergic diseases appear to be rare in populations residing in the rural tropics that frequently experience infections with geohelminth parasites. Epidemiological studies investigating the relationship between asthma and geohelminth infections have provided conflicting findings (69–76).

Some studies propose that helminth infections may protect against asthma and allergies (69–71) through various mechanisms (72). Such protection seems paradoxical as helminth infections are characterized by a strong Th2-type immune response, with elevated IgE levels and eosinophil count. An important difference between Th2-type responses in allergy and parasitic infection is that in “allergy” the immunological response is inappropriate, whereas in infection, the host immune response serves the purpose of limiting the infection.

Three variables play a role in the relationship between asthma and geohelminth infections: the acute or chronic phase of helminth infection, the load of the parasite, and the species involved. Acute helminth infection probably increases allergic manifestations, whereas chronic infection appears to act protectively (73). In areas of high prevalence of geohelminth infections the risk of allergy is decreased, while the converse is probably true in areas of low prevalence (74). Lastly, not all helminth infections suppress the development of allergic reactions (75, 76).

Socioeconomic Status, Stress, and Asthma Symptoms

Asthma outcomes are clearly “socially patterned” with asthma ranking as a leading cause of health disparities among

lower-income urban communities (77, 78). Several studies have shown a link between low SES and immunological markers of asthma (79, 80). Low SES asthmatic adolescents exhibited higher levels of eosinophils and asthma associated cytokines (IL-5, IL-13), but marginally lower morning serum cortisol levels than asthmatics of high SES, a finding that can be ascribed to decreased activity of the hypothalamic-pituitary-adrenal axis.

An association between traffic-related air pollution (NO₂) and asthma solely among urban children exposed to violence has also been recently detected (81). These findings agree with evidence that chronic stress may shape biologic response in early life (82) and potentiate effects of air pollution through common physiologic systems.

EFFECT ON LUNG FUNCTION

Long-term exposure of healthy children and adolescents to urban environment has been associated with an increased risk of reduced lung function.

Lung Growth

Forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV₁) are the most common parameters used in epidemiological studies for the evaluation of lung growth. Longitudinal studies in healthy children, exposed to high levels of ambient air pollution, have shown lower FVC (83, 84) and a deficit in attained FEV₁ by the time children reach adulthood (85).

In the prospective Children's Health Study, lung function of children from schools in 12 southern California communities was measured annually for a period of 8 years. Deficits in FEV₁ growth and other spirometric measures were associated with exposure to NO₂, acid vapor, particulate matter of aerodynamic diameter less than 2.5 μ m (PM_{2.5}), and elemental carbon. Exposure to pollutants was associated with significant deficits in the FEV₁ at the end of the study (85). It is also of interest that subjects who moved to areas with lower PM₁₀ concentration showed increased growth of lung function, while the opposite was true for those who moved to higher PM₁₀ concentration areas. A stronger trend was found for subjects who had migrated at least 3 *versus* those who had migrated 1 to 2 years before the evaluation visit (86).

Similarly, a prospective cohort study in Poland of children living in two areas of Krakow with different ambient air pollution (87) showed an association between ambient pollutants and a poorer gain of lung volumes. More children with poor lung growth resided in the more polluted areas of the city. In a 4-month prospective study, examining the effect of air pollution on lung function of asthmatic *versus* non-asthmatic children, exposure to pollution had a greater effect on lung growth in the asthmatics' group (88).

In another population-based longitudinal cohort study in Greece (9), children residing in a rural area exhibited lower FVC values; however, catch-up growth of children of rural residence occurred over the next 4 years (85). The decrease in FVC growth in the urban environment was attributed to chronic exposure to high levels of air-borne pollutants previously documented.

Airway Narrowing

Maximal expiratory flow measurements are the most sensitive means to assess narrowing of the bronchi or bronchioles in epidemiological studies. Air flows at mid-FVC (FEF_{50}) have been considered better indices for small airway narrowing than FEV_1 and FVC, whereas the ratio FEV_1/FVC is less sensitive (89, 90).

In the southern California communities study, children's lung function was associated with new onset asthma and exposure to ambient air pollutants (91). Decreased airway flows were associated with new onset asthma. The hazard ratio of new onset asthma in children over the 10th to 90th percentile range of mean mid-expiratory flow was 0.50 (95% CI 0.35 to 0.71) in areas of low air pollution. This protective effect on lung function was reduced in children exposed to higher levels of particulate matter with an aerodynamic diameter less than $2.5 \mu m$. A similar pattern was observed for FEV_1 . However, little variation in hazard ratio was observed for ozone.

In the Greek study (9), there was an independent relationship between decreased FEF_{50} and urban living at 8 to 100 and at 12 to 14 years of age. Furthermore, there was an independent association between decreased FEF_{50} and family history of atopy that was similar in both areas. Lower FEF_{50} in the urban area can be interpreted in the context of the cumulative effect of long-term exposure to airborne pollutants. The concomitant absence of difference in wheezing between the urban and rural areas suggests that the polluted urban environment *per se* can be associated with sub-clinical small airway disease. Others have reported similar findings (91, 92).

The effect of allergic sensitization on airway pathology appears to vary according to the sensitizing allergen. The Greek data revealed positive correlations between sensitization to mites and diagnosed asthma, but not between sensitization and asthma symptoms. A negative association between sensitization to mites and spirometric indices of large (FEV_1) and small (FEF_{50}) airways in children 8 to 10 years of age was also detected (9).

A negative association between FEV_1 and sensitization to house dust mite—but not to seasonal outdoor allergens—has also been described in symptomatic asthmatic children (93–97). The proteolytic enzymatic activity of mite can damage the airway epithelium and cause asymptomatic airway narrowing, thus offering an additional distinct biologic role of these common perennial aeroallergens in the pathogenesis of asthma (98). Poor perception of symptoms, an alternative explanation of these findings, was not thought to explain the study results as it has previously been shown that subjects with asymptomatic airways hyperresponsiveness are not poor perceivers of airway narrowing (99). In a population-based longitudinal study, Ulrik and Backer showed that sensitization to house dust mite had a negative impact on FEV_1 in children and adolescents without respiratory symptoms and/or evidence of airway hyperresponsiveness (100). Similarly, Illi et al. recently showed that children sensitized to perennial allergens in the first 3 years of life had wheezing and decreased lung function at school age (97).

CONCLUSIONS

The increasing trend for urbanization, during the last decades, characterized by changes in housing, population density, and SES, accounts, at least partially, for the increased prevalence of childhood asthma. Several environmental risk factors associated with residential area, such as outdoor and indoor air pollution, infections, allergen exposure, diet, and lifestyle patterns, can trigger or aggravate respiratory symptoms and affect children's lung function. Risk factors of asthma symptoms and airway obstruction in urban or rural environment may have distinct roles but may also be influenced by the socioeconomic development of the area. As a consequence children raised in rural environments show a lower risk of asthma and aeroallergen sensitization that has been attributed to a "protective" farming effect due to close contact with large animals in combination to genetic predisposition. Conversely, children exposed for years to an urban environment are at increased risk of reduced lung function and slower lung growth. It is possible that the polluted urban environment *per se* facilitates subclinical small airway disease.

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