



Difficult-to-control asthma: epidemiology and its link with environmental factors

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Purpose of review

The aim of the present review was to discuss the epidemiology of inadequate asthma control with an examination of contributing environmental factors.

Recent findings

Despite advances in asthma therapies, a proportion of patients with asthma continue to have difficulty in gaining adequate asthma control. Asthma severity and control in childhood are of particular importance as they translate to asthma morbidity in adulthood. Children with comorbid severe allergic rhinitis were more likely to have uncontrolled asthma. Recent data suggest that mouse allergen, more so than cockroach allergen, may be the most relevant urban allergen exposure. Tobacco smoke exposure, even passive exposure, leads to increased asthma symptoms and decreased response to inhaled corticosteroids. Efforts to ban smoking in public places have resulted in promising asthma results for entire populations. Energy-saving efforts to tighten a home's air leaks can lead to increased indoor pollutant levels and, therefore, must be accompanied by efforts to reduce, filter, or exchange indoor pollutants. Obesity is independently associated with decreased asthma control. Furthermore, the detrimental effects of pollutant exposure are enhanced in an overweight individual with asthma.

Summary

Lack of asthma control can be because of a complex web of factors including adherence, intrinsic factors, and environmental exposures. Further research into intervention strategies is needed to achieve improved rates of asthma control.

Keywords

allergic rhinitis, asthma, mouse allergy, obesity, tobacco

INTRODUCTION

There have been great advances in the development of asthma controller therapies in the past two decades; however, inadequate asthma control is still a reality for a large proportion of patients. Uncontrolled asthma results in a reduced quality of life for the individual and a major economic burden for society. Poor adherence to standard controller medications and insufficient avoidance of known asthma triggers are common factors contributing to uncontrolled asthma. Furthermore, there are other factors intrinsic to the patient or present in their living environments that are associated with reduced asthma control. Intrinsic factors associated with asthma control include race, ethnicity, weight, and socioeconomic status. External factors include exposure to allergens and pollutants including tobacco smoke. All of these factors overlap in a single individual to enhance or diminish asthma control. In the present review, we summarize recent data regarding asthma control and the link to

environmental factors. A specific focus has been placed on intriguing recent findings that may lead future research. Additionally, an emphasis has been placed on vulnerable populations including children and inhabitants of urban areas.

OVERVIEW AND EPIDEMIOLOGY OF DIFFICULT-TO-CONTROL ASTHMA

The prevalence of asthma has increased in recent decades with now an estimated 25 million people, including more than 6 million children, with

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KEY POINTS

- Asthma severity and control in childhood are of particular importance as they have been shown to translate into asthma morbidity in adulthood.
- Recent data suggest that mouse allergen, more so than cockroach allergen, may be the most relevant urban allergen exposure.
- In Scotland, the passage of a public smoking ban was associated with a significant reduction in childhood asthma hospitalizations.
- Using simulation models, it was demonstrated that weatherization efforts targeted solely toward eliminating air leakage led to an increase in asthma morbidity, but this adverse effect was mitigated by efforts to increase air exchange (exhaust fans) and efforts to eliminate indoor pollutant sources (gas stoves, smoking).
- Future research into environmental intervention strategies may result in increased rates of asthma control for large proportions of children and adults with asthma.

asthma in the United States [1,2]. Severe asthma is the least common form of asthma accounting for only 5–10% of all cases; however, it accounts for nearly 50% of all asthma healthcare costs [2–4]. Severe asthma often presents early in life and is frequently associated with atopic conditions [2]. Difficult-to-treat asthma is defined as poor control because of incorrect diagnosis, comorbidities, or poor adherence. In contrast, treatment resistant asthma is defined as difficult-to-control asthma despite appropriate adherence and management of comorbidities.

Achieving and maintaining asthma control are the goal of asthma treatment. Despite advances in asthma therapies, a proportion of patients with asthma continue to have difficulty in gaining adequate asthma control. For example, a study [5] from 2004 demonstrated that asthma-limited normal physical activity in 36% of asthmatics in the United States with worldwide rates ranging from 17% in Japan to 68% in Central and Eastern Europe. Subsequent studies [6,7] found similar rates with 46% of children and 55% of adults having uncontrolled asthma. A recent study has shown some promise that asthma control in children has improved in the past decade. When compared with a similar cohort a decade before, a current cohort had better asthma control and less oral glucocorticoid use [8[¶]]. Asthma severity and control in childhood are of particular importance as they translate into asthma morbidity in adulthood. The

Melbourne Asthma [9[¶]] Study followed asthmatic patients from childhood to the age of 50 years and found that clinical outcomes and lung function in adult life are strongly determined by asthma severity in childhood. Several factors have been associated with inadequate control including socioeconomic status, allergic rhinitis, obesity, and passive smoke exposure [2,7,10–13]. Further information on these associated factors, including recent findings, is presented in this review.

ALLERGIC RHINITIS AND ENVIRONMENTAL ALLERGEN EXPOSURE

Children with severe and uncontrolled asthma are more likely to have allergic sensitization [7,11,14,15]. Sasaki *et al.* [15] recently reported that children with comorbid severe allergic rhinitis were almost four-fold more likely to have uncontrolled asthma. Additionally, the severity of the rhinitis symptoms was inversely correlated with the findings on the Childhood Asthma Control Test [15]. Most children with severe asthma are sensitized to multiple environmental allergens [14]. Allergen immunotherapy has been demonstrated to assist in asthma control [16].

Indoor allergen exposure in inner-city areas has been of particular interest given that children living in urban areas have increased asthma severity, decreased asthma control, and greater healthcare use [10]. In a landmark study, Rosenstreich *et al.* [17] found cockroach allergen to be highly detectable in inner-city homes. Furthermore, this study [17] demonstrated children with asthma who were sensitized and exposed to high levels of cockroach allergen had increased asthma morbidity. Portnoy *et al.* [18] recently developed a practice parameter for assessment of environmental cockroach exposure and methods for allergen reduction and avoidance. Mouse allergen has also been found to be prevalent in both urban homes and schools with home mouse allergen levels associated with cockroach infestation [19,20]. Home exposure to mouse allergen in the inner-city has been associated with increased asthma morbidity [21]. Recent data suggest that mouse allergen, more so than cockroach allergen, may be the most relevant urban allergen exposure [22]. Ahluwalia *et al.* [23] observed that in an inner-city community with high exposure to mouse and cockroach allergens, mouse allergen was more strongly and consistently associated with poor asthma outcomes. Based on this finding, it was suggested that community-based asthma intervention strategies should prioritize reducing mouse allergen exposure.

TOBACCO EXPOSURE

Studies [24,25] have demonstrated that more than 50% of urban children with asthma are exposed to environmental tobacco smoke. Among inner-city children with asthma, exposure to higher levels of environmental tobacco smoke was associated with increased frequency of nighttime asthma symptoms [26]. Furthermore, smoke exposure leads to asthmatic patients being refractory to standard controller therapies, namely inhaled corticosteroids [27]. Kobayashi *et al.* [28] demonstrated that passive smoke exposure impaired histone deacetylase-2 function, which could contribute to steroid resistance in children with asthma. In Scotland, the recent passage of a public smoking ban was associated with a significant reduction in childhood asthma hospitalizations [29]. Similar bans on public smoking are taking effect in countries around the world, whereas limiting second-hand smoke exposure in private residences is more difficult. The measurement of cotinine levels has become a useful tool for determining passive smoke exposure. Hassanzad *et al.* [30] found that higher cotinine levels in serum, urine, and saliva were associated with a higher risk for severe asthma. The monitoring of cotinine levels may be beneficial for the evaluation of uncontrolled asthma. Finally, there has been more recent attention placed on the potential hazards of third-hand smoke (THS) in children. THS is residual nicotine and other chemical pollutants remaining in the indoor environment and on household surfaces for weeks to months after active tobacco smoking has stopped. Young children may be more susceptible to the adverse effects of THS exposure because of their crawling and ingestion of nonfood items [31]. More research regarding the health effects of THS is expected in the future.

AIRBORNE POLLUTANTS AND THE EFFECT OF ENERGY EFFICIENT BUILDINGS

Intermittent increases in outdoor air pollutants have been linked to increased asthma morbidity and decreased asthma control in inner-city areas [32]. Furthermore, these pollutants are known to infiltrate indoors, and many pollutants are higher indoors as compared with outdoors [33]. Indoor levels of airborne pollutants are higher in urban homes as compared with rural homes [34] with exposure to indoor particulate matter in inner-city homes being independently associated with increased respiratory symptoms and rescue asthma medication usage [35]. A multifaceted approach to intervention including the use of high-efficiency particulate air purifiers has been shown to reduce levels of particulate matter in urban homes [36].

In an era of increasing importance being placed on energy efficiency, caution must be used to protect indoor air quality. Building construction and renovation methods have evolved to limit the leakage of air between the indoor and outdoor space of living environments. Although these approaches may have the beneficial effect of tightening a home and saving on energy costs, it may have the unintended consequence of increasing levels of indoor air pollution. Using simulation models, Fabian *et al.* [37^{***}] demonstrated that weatherization efforts targeted solely toward eliminating air leakage led to an increase in asthma morbidity. These increases in asthma events after weatherization were mitigated by efforts to increase air exchange (exhaust fans) and efforts to eliminate indoor pollutant sources (gas stoves, smoking) [37^{***}]. In addition to decreasing air exchange, construction efforts to reduce energy costs may use building materials that themselves add to the indoor pollutant burden [38].

OBESITY AND SUSCEPTIBILITY TO POLLUTANT EXPOSURES

Although obesity and asthma are highly prevalent, the interactions between these two conditions are complex. Obesity may directly lead to dyspnea and asthma symptoms because of deconditioning and reduced exercise tolerance. In turn, obesity may contribute to an inflammatory state resulting in worsening and difficult-to-control asthma. Alternatively, obesity may lead to a reduced efficacy of standard asthma therapies, thus contributing to inadequate asthma control. It has been demonstrated that asthmatic patients who are overweight or obese have blunted in-vitro and in-vivo responses to glucocorticoids [39,40]. Although the exact mechanism was not clear, Schatz *et al.* [41] found that an elevated body mass index increased the risk for asthma exacerbations in both children and adults with adults being particularly susceptible in the fall and winter months. Likewise, Forno *et al.* [12] discovered that markers of adiposity were associated with asthma severity and control with atopy significantly mediating the effect of adiposity on asthma outcomes.

To further complicate the picture, overweight and obese individuals may be more susceptible to the respiratory effects of exposure to airborne pollutants. This may be because of increased pulmonary deposition of airborne pollutants or an increased inflammatory effect of pollutant exposure in the lungs of obese patients. In inner-city children with asthma, Lu *et al.* [42] demonstrated that being overweight or obese increased the effect of exposure to

indoor pollutants (particulate matter of 2.5 μm or less in diameter and NO_2) on asthma symptoms. A similar interaction between obesity and pollutant exposures was seen in a large multicenter trial in China [43]. Based on these results, it would seem reasonable to consider interventions aimed at weight loss that may decrease the adverse effects of pollutant exposure on asthma control, despite the challenges encountered in all behavior management interventions.

INNER-CITY ASTHMA: LOCATION VERSUS GENETICS AND INCOME

For decades, there has been recognition of the high burden of asthma morbidity and difficulty with achieving asthma control for adults and children living in urban areas. It has been considered that a number of factors have contributed to the current state of inner-city asthma including poor housing conditions, close proximity to pollution sources, psychosocial and financial stressors, race/ethnicity, and access to appropriate healthcare. In recent years, there has been more of an in-depth analysis into the relative contribution of these different factors on asthma prevalence and asthma morbidity. Interestingly, Keet *et al.* [44] demonstrated that the high asthma burden in US inner-city areas was largely explained by demographic factors and not by purely living in an urbanized location. In fully adjusted models, black race, Puerto Rican ethnicity, and lower household income were strong independent risk factors for asthma exacerbations and emergency department visits for asthma. In contrast, simply residing in the urban area was not associated with asthma outcomes. Although the prevalence of asthma is high in these inner-city areas, the prevalence was equally high in some poor nonurban locations. To complicate the discussion further, Thakur *et al.* [45] found that socioeconomic status has an important role in asthma development, but has differing effects, both positive and negative, depending on race and ethnicity. It is reassuring that there may be improvements in racial disparities for asthma morbidity. Akinbami *et al.* [46^{***}] used an at-risk analysis, which accounts for differences in asthma prevalence, to assess racial disparities in asthma outcomes. In doing so, it was found that black/white disparities for asthma remained the same (mortality) or decreased (emergency department visits, hospitalizations). Further research to elucidate the relative responsible factors in inner-city asthma will be helpful to strategize effective interventions to control and possibly prevent asthma in these populations.

CONCLUSION

Recent research has shown some promise of improved asthma control across populations in the past decade; however, there are still a large proportion of patients who continue to have difficulty in gaining adequate asthma control. Achieving asthma control and reducing asthma severity in childhood are of particular importance given that recent findings demonstrated childhood asthma control translated into adult asthma morbidity. In addition to adherence to treatment regimens, the management of comorbid conditions is vital to maintaining asthma control. This includes the management of highly prevalent coexisting allergic rhinitis and the avoidance of environmental allergens. In urban environments, recent data suggest that mouse allergen, more so than cockroach allergen, may be the most relevant allergen exposure. Tobacco smoke exposure, even passive exposure, leads to increased asthma symptoms and decreased response to inhaled corticosteroids. Efforts to ban smoking in public places have resulted in promising asthma results for entire populations. It will be interesting to see how this develops as smoking bans continue to become more prevalent. More research is needed into the health effects of the newly described THS exposure, especially in young children who may be specifically more susceptible. Likewise, more research is needed into the respiratory effects, both beneficial and possibly harmful of recent changes in building construction directed toward energy saving. Finally, the complex interplay of asthma and obesity must continue to be evaluated with a focus on intervention efforts that will help provide optimal asthma control for this frequent condition in our society.

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Conflicts of interest

There are no conflicts of interest.

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- of outstanding interest

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