Effects of Allergen Exposure and Environmental Risk Factors in Schools on Childhood Asthma

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Abstract

Purpose of Review—This review aims to assess the prevalence of common allergen exposures and environmental risk factors for asthma in schools, examine the underlying mechanisms of these environmental risk factors, and explore possible prevention strategies.

Recent Findings—Cockroach, mouse, dust mites, fungi, viral infections, ozone pollution, and cleaning products are common allergen exposures and environmental risk factors in schools which may affect asthma morbidity. Novel modifiable environmental risk factors in schools are also being investigated to identify potential associations with increased asthma morbidity.

Summary—While several studies have investigated the benefit of environmental remediation strategies in schools and their impact on asthma morbidity, future studies are warranted to further define the effects of modifiable risk factors in schools and determine whether school mitigation strategies may help improve asthma symptoms in students with asthma.

Keywords

Pediatric asthma; Schools; Environmental exposures; Obstructive lung disease

Introduction

Asthma is the most common chronic disease in children, affecting 4.4% of preschoolers and 6.4% of elementary school children [1]. A disease of the lower airways, asthma is defined by chronic airway inflammation that is induced by a variety of triggers as well as flow obstruction that can be reversed by a short-acting β-2 agonist (SABA), most commonly albuterol [2]. Symptoms of asthma include shortness of breath, chest tightness, wheezing, and periodic nocturnal cough [2]. It is an episodic disease characterized by periods of exacerbation and asymptomatic presentation.

Children with chronic asthma exacerbations face increased academic and social burdens. A population-based matched case-comparison cohort study looking at the effects of asthma on school performance found that young males hospitalized due to asthma had a greater risk of discontinued schooling and a reduced reading and numeracy skill set [3]. Psychologically, asthma has been identified as a major contributor to social, emotional, and economic issues. It can manifest with secondary consequences of poor sleep, anxiety, depression, and attention disorders [4].

Asthma triggers are multifactorial and can be due to biological (dust mites, mold, dander, mice, and cockroaches), environmental (smoking), or chemical (pollution and high ozone levels) causes [5]. In the school environment, asthma triggers include cockroach, mouse, dust, fragrances, viral respiratory illnesses, and cleaning agents [6]. Since students spend approximately 1000 h a year in a school setting, they are routinely exposed to potential asthma triggers [7]. This exposure is often exacerbated in poorly funded urban school settings with poor ventilation systems. While there has been increased interest and advocacy during and post the COVID-19 pandemic for ventilation reform in schools, recommended filtration systems were rarely used in lower-income school districts, with mid-poverty level and rural schools less likely to report implementing resource-intensive strategies [8]. Rural schools have been reported to be less likely to use portable HEPA filtration systems, and mid-poverty-level schools were less likely to have replaced or upgraded HVAC systems [8].

Previous review papers on childhood asthma classroom triggers have focused on the prevalence of common allergens in school settings, with less emphasis on immunological pathology. This review paper will address the prevalence of common allergen exposures and environmental risk factors for asthma in schools while focusing on the underlying immunobiology of these triggers as it pertains to the classroom setting, highlighting the role of mouse and cockroach allergens, viral infections, ozone pollution, dust mites, fungi, and cleaning products.

Mouse Allergen

Mouse allergen has been found in 99% of inner-city school dust samples [9•], with students exposed to these allergens in school also likely exposed to them at home. The SICAS study reported that students had greater levels of mouse allergen exposure in their classrooms compared to homes while adjusting for home exposure [10], and additionally, independent of allergic sensitization and home exposure, mouse allergen school exposure was associated with a dose–response relationship with reduced lung function and greater asthma symptoms [11]. Phipatanakul et al. found that 100% and 74% of kitchens across Baltimore and Cleveland, respectively, had detectable levels of mouse allergens [12•]. Studies have found that early exposure to mouse allergens is significantly associated with an increased risk of wheezing in the first 7 years of life [13] and that there is a dose–response relationship between exposure to mouse allergens and future sensitizations [14, 15]. Additionally, in classrooms with rodent allergen levels above 1.6 μg/g of dust, students have an elevated risk of developing rodent-specific IgE [16, 17]. Students exposed to mouse allergens have more severe asthma than their non-exposed peers. They require higher fluticasone dosages and have shown greater declines in FEV_1/FVC [18].

The major asthma-related allergen associated with mice is Mus m 1, a urinary protein (MUP) belonging to the lipocalin superfamily. It is encoded by the Mup genes which are found in most adult mice [19]. In asthma, MUP induces a cytokine response dominated by IL-4 [20] which exacerbates asthma by promoting Th2 differentiation and IgE synthesis and inhibiting eosinophil apoptosis. It supports inflammatory cell migration by enhancing vascular cell adhesion molecule-1 (VCAM-1) and directing T cells, monocytes, basophils, and eosinophils to inflammatory loci [21]. IL-4 is thus a therapeutic target of interest for children with asthma, with Dupilumab, a monoclonal antibody (mAb) that targets the interleukin-4 (IL-4) receptor alpha subunit, currently approved in ages 6 years and up for moderate to severe asthma with an eosinophilic phenotype or oral corticosteroid dependent asthma [22].

Cockroach Allergen

Mouse allergens are frequently looked at in conjunction with cockroach allergens. Studies evaluating high mouse allergen levels in Boston kitchens found that households with mice also had significant levels of cockroach allergens [23]. The two most common cockroach allergens are Bla g 1 and Bla g 2, which are present in cockroach saliva, secretions, debris, and fecal matter [24] and can be found in 67% of school dust [25]. Children sensitized to cockroach allergens, particularly Bla g 1, have been shown to have poor asthma control and worsened symptoms. They are more likely to have asthma defined by a wheezing phenotype and suffer from greater rates of asthma-induced hospitalizations [26, 27].

In addition to inducing an IgE-mediated response, cockroach allergens contain glycans which have been linked to immune pathway disturbances. PAR-2, toll-like receptors (TLRs), and C-type lectin receptors (CLRs) are pathways used by cockroach allergens to penetrate epithelial cells and induce inappropriate T cell responses [28]. In Bla g-sensitized asthma patients, exposure to cockroach allergens was correlated with 10 times larger than normal T cell response. The reaction was predominantly Th2-dominated [29].

Respiratory Syncytial Virus

Children are key transmitters of upper respiratory viruses due to increased immune susceptibility coupled with poor hygiene. Most schools either lack a standardized method of hygiene enforcement in place or are unable to enforce it among all students effectively [30]. Impaired communication between school systems and a lack of a reporting protocol often facilitate outbreaks to spread rapidly among communities and schools [31]. Often, these viral exposures can be quite hazardous to children with asthma.

The most common upper respiratory tract infection contracted in the school setting among young children is respiratory syncytial virus (RSV) [32]. RSV has been identified as both an asthma exacerbator and a causal agent. In infants and young children, a prominent RSV infection has been associated with altered Th1/Th2 responses and increased Th2 allergen sensitization. Additionally, severe RSV infection can broaden Th2 responses beyond common asthma triggers and apply to other allergens [33].

Around 80–85% of asthma exacerbations in young children have been associated with upper respiratory tract infections, of which RSV is the largest contributor. In children with asthma,

infection with an upper respiratory tract virus has been identified as the leading cause of reduced peak expiratory flow, wheezing, and cough [34]. It has been found that RSV induces a severe asthma phenotype through its neuroimmune interaction with the transient receptor potential vanilloid subtype 1 (TRPV1) [35]. This protein channel is moderated by nerve growth factor (NGF) and is present in bronchial epithelial cells. It is responsible for increased mucus production and cough stimulation in airway diseases. When RSV infects bronchial epithelial cells, it induces increased NGF expression, leading to elevated TRPV1 levels and airway sensitivity and inflammation [35].

There are several preventative measures that can be taken against RSV. High-risk infants and children enrolled in a childcare program can be advised to obtain an anti-RSV monoclonal antibody (palivizumab) as prophylaxis. Given that this monoclonal antibody has considerable side effects, it is often reserved for severe asthma cases [36]. Other preventive measures include schools implementing more tightly regulated hygiene protocols while paying closer attention to, and reporting, outbreaks.

Air Pollutants

The geographic location of schools plays a major role in childhood allergen exposure. Schools are made "walkable" at the expense of airway pollution. Schools that are easily accessible are often found near dense road networks with high exposure to traffic pollution [37]. Using spatial analysis to examine residential and school proximity to major roadways and pediatric asthma morbidity, Hauptman et al. found that major roadway proximity was independently associated with increased asthma symptom days [38].

Ozone is a major pollutant produced by gas-fueled vehicles. While vehicles do not release ozone directly, they produce nitrogen oxides and volatile organic compounds. A photochemical reaction between these two substances then creates ozone [39]. While the calculated median concentration of ozone in schools has been shown to be below the WHO guideline value of 100 μg/m as a marker for a maximum 8-h mean concentration, the average value was calculated from a wide range of data points. At some schools, the measured ozone concentrations were as high as 114 $\mu g/m^3$. The main source of this high value was outdoor ozone pollution entering the indoor classroom space. This was commonly found in urban schools exposed to high amounts of traffic pollution [40].

Ozone is particularly damaging to children with asthma due to its nature as a strong oxidizing gas. Ozone is easily soluble in water and, when inhaled, has the ability to deeply penetrate into the lungs [41]. Inhaled ozone reacts with airway lining fluid in order to create reactive oxygen species (ROS) and generate a local oxidative stress environment and epithelial damage. The release of ROS leads to an influx of eosinophils and neutrophils which are associated with severe asthma exacerbations. Ozone further increases neutrophilic inflammation by activating toll-like receptors (TLRs) 1, 2, and 4, leading to increased concentrations of macrophages and overexpression of IL-6 and KC/CXCL1, with under-expression of TNFα and MIP1α [42].

In addition to inducing a hyperinflammatory pulmonary state contributing to asthma exacerbations, ozone exposure promotes corticosteroid resistance. Described as the inability

to increase FEV_1 by 15% after a 7-day oral corticosteroid regimen, glucocorticoid resistance is especially prevalent in Th2-low asthma. Glucocorticoid resistance is linked to glucocorticoid receptor (GR) dysfunction in which the classic isoform (GRα) is transformed into GRβ which fails to bind corticosteroids. Ozone-related oxidative stress has been shown to induce overexpression of GRβ [42]. The neutrophil influx induced by ozone-related oxidative stress further contributes to corticosteroid resistance. Studies have shown a positive correlation between IL-6/IL-17a and STAT3. It has been reported that higher plasma IL-6 levels in children are associated with increased asthma severity, with risk for both asthma exacerbation and lower lung function based on longitudinal analyses, early signs of metabolic dysfunction evidenced by high CRP, and elevated BMI [43]. STAT3 has been reported to have increased expression in ozone-exposed experimental groups, which has also been associated with increased corticosteroid resistance [44]. IL-6 and IL-17 are produced by TH17, and the IL-6/STAT pathway has been implicated in increased corticosteroid resistance in children with asthma due to associated neutrophilic airway inflammation [44].

NO_2 and ozone are principal elements of smog, with NO_2 a pollutant generally produced by the combustion of fossil fuel, power plants, and automobile exhaust and heating as a source of indoor exposure. NO_2 has been reported to have a dose-dependent association with wheezing and asthma [45]. In a study of inner-city children, higher levels of indoor NO_2 have been described to be associated with increased asthma symptoms and lower peak flows [46]. In a study by Gaffin et al., the effect of indoor NO_2 exposure in schools was examined, and it was reported that indoor classroom NO_2 was significantly associated with greater airflow obstruction in children with asthma [47]. The effect of NO_2 exposure in inner-city schools on obese students with asthma has also been examined, where Permaul et al. found that students with obese BMI had increased susceptibility to classroom NO_2 exposure and asthma symptoms, where with each 10 ppb increase in NO_2, those with obese BMI had greater odds of having an asthma symptom day [48].

More recently, additional air pollutants are being investigated as novel modifiable risk factors for asthma. Radon is an air pollutant well known for its carcinogenic effects. However, little is known about its effects on asthma morbidity. Recent data suggest an association of radon exposure with chronic obstructive pulmonary disease (COPD) and non-cancer morbidity and mortality [49, 50]. In a school-based cohort of children screened for asthma morbidity and respiratory symptoms, short- and long-term radon exposure at schools was associated with increased odds of having an asthma diagnosis and school absences [51]. Additionally, recent work has demonstrated that radon is associated with increased asthma symptoms and elevated F_ENO in inner-city children with asthma, suggesting that radon exposure may be a novel and modifiable environmental risk factor for asthma morbidity in children [52].

Dust Mites

Dust mites, a major asthma trigger found in both the home and school environment, are arthropods that thrive in humid, indoor environments and are commonly found in school carpeting systems. Studies have shown that compared to hardwood flooring, carpeting results in elevated allergen exposure, especially from dust mites while removing carpeting

reduces dust mite allergen levels [53]. In children with asthma, exposure to dust mites manifests as reduced peak flow and increased bronchosensitivity and bronchospasms [54].

The most common dust mite species is *Dermatophagoides pteronyssinus*, contributing to sensitization in 50–80% of asthmatics. High levels of dust mites have been positively correlated with increased clinical visits for those with asthma [55]. The allergic reaction to dust mites is induced by their fecal matter which gathers in dust and is then inhaled. The fecal pellets have an average diameter of 20–30 mm but are commonly fragmented into small particles (2–6 μm) which penetrate small airways [56].

Dust mite fecal matter contains the cysteine peptidase protein Der p 1, which targets both the innate and adaptive immune systems [57]. Der p 1 causes epithelial damage by cleaving tight junction proteins between the epithelial cells lining the respiratory pathways. While α1-antitrypsin typically serves as an antiprotease protectant, Der p 1 inhibits anti-protease lung defenses and is resistant to degradation, causing further epithelial damage by breaking down pulmonary surfactant [55]. The epithelial injury results in elevated levels of pro-inflammatory TH-2 cytokines such as TSLP, CCL20, IL-25, and IL-33. Der p 1 has also been shown to target cytokine production, particularly IL-6 and TNF (both markers of inflammation), by activating TLR4 and protease-activated receptors (PAR-2) [58].

The identification and isolation of Der p 1 offer a potential target for allergen-specific immunotherapy. Recent studies have looked at the effects of proDerp1αS, an allergen-directed immunotoxin targeting IgE and FcεRI-positive implicated in mite allergies. ProDerp1αS binds to the cysteine domain of Der p 1 and targets its protease activity [59]. When applied to effector cells sensitized with dust mite allergens, proDerp1αS resulted in cell granulation and death [59].

Molds/Fungi

Fungal species are highly diverse and capable of colonizing a range of different environments. In the school environment, they can exacerbate and induce asthma symptoms. The most common fungi species found in schools are *Alternaria* spp., *Aspergillus* spp., *Cladosporium* spp., and *Penicillium* spp. Fungal spores thrive in moist environments and are easily spread by indoor ventilation systems. They have a long exposure period, and the fungal spore season is twice as long as the pollen one [60]. The association between fungi and asthma exacerbation has been well described, and in 2006, the term severe asthma with fungal sensitization (SAFS) was first coined [61]. Fungal spores are often found in higher concentrations in inner-city schools, with Baxi et al. reporting in a study evaluating 37 inner-city schools that children with asthma who are sensitized to Alternaria and exposed to this fungus in their classroom had significantly more days with asthma symptoms than those who were sensitized and not exposed [62]. In this study, the mean of total fungi was 316.9 spores/m^3, with collected values ranging from 15.0 to 59,345.7 spores/m^3 [62], and 100 spores/m^3 the suggested safety limit set for Alternaria [62].

One of the most common indoor fungal species, *Alternaria* spp. is the major cause of fungal allergies and atopic fungal sensitivities. Sensitization to *Alternaria* spp has been positively correlated with asthma, increased airway inflammation, and severe respiratory presentations

[60]. The response to *Alternaria* manifests as elevated Th2 cytokines, eosinophil infiltration, and increased IgE serum levels. An *Alternaria*-induced chronic rhinosinusitis mouse model showed increased IL-4 following *Alternaria* exposure, with IL-4 directing the differentiation of Th2 cells and its overexpression, suggesting an early Th2 inflammatory response [63].

In neonatal mouse models, exposure to *Alternaria* resulted in increased levels of IL-33 and IL-13 + ILC [64]. IL-33 has been shown to induce eosinophilia while simultaneously increasing eosinophil survival through the upregulation of adhesion molecules [65]. Elevated IL-33 levels in response to fungal spore exposure have also been linked to oral corticosteroid resistance [64].

Cleaning Products

Following the reopening of schools during the COVID-19 pandemic, healthcare protocols regarding classroom cleaning heightened and the use of disinfectants in the classroom increased [66]. Chronic exposure to irritants found in cleaning products, however, has been linked to an increased risk of asthma. These irritants induce chronic inflammation by damaging the respiratory epithelium and inducing an innate immune-mediated response [67].

Common cleaners have been found to include endocrine-disrupting compounds (EDCs), a class of chemicals that target hormone signaling and have hormonal, neuronal, and metabolic effects. Compounds such as propylene glycol and glycol ethers (PGEs) are regularly found in school cleaning products [68]. A longitudinal study reported that children exposed to increased concentrations of airborne PGEs had a 1.5-fold greater likelihood of developing asthma, a 2.8-fold greater likelihood of developing rhinitis, and a 1.6-fold greater likelihood of developing eczema [69].

One of the most common chemicals found in school cleaners is triclosan, with over 10 million pounds being produced annually in the USA. It is commonly used for its antimicrobial and antifungal properties. In schools, triclosan is found in anti-microbial soaps and detergents. While alone triclosan does not induce an allergic response when combined with common allergens, it increases allergen-specific IgE, IL-13, and lung eosinophil numbers, consequently exacerbating asthmatic responses [70]. As allergies in children have increased, particularly food allergy, triclosan's synergistic effects on asthma, in combination with allergies, are being further investigated [71].

The role of EDCs is currently being further explored regarding discrepancies in asthma rates among male and female children. Females are more likely to exhibit severe asthma that manifests in a wheezing phenotype compared to males [72]. The spectrum of EDC's effects, particularly phthalates which are found in most scented cleaning products [73], includes inhibition of testosterone and thyroid hormone and inducing an estrogenic state [68]. Sex hormones are linked to asthma and have important effects on immune development. Testosterone and its subsequent metabolites exert an immunosuppressive effect by promoting the development of regulatory T cells [74], while female sex hormones have the opposite effect. Estrogen has been linked to bronchial hyperreactivity through the nitric oxide (NO) pathway [75]. Given that EDCs have a hormone-modifying effect,

their role, as well as the role of common cleaning products in schools, warrant further exploration.

School Intervention

Work in the schools to identify the effectiveness of a classroom and school-based environmental intervention to reduce asthma morbidity was recently described by the School Inner-City Asthma Intervention Study (SICAS-2) [9•]. In the SICAS-2 study, a randomized clinical trial that assessed the effect of school-wide integrated pest management or classroom high-efficiency particulate air filter purifiers on asthma symptoms in students with active asthma, 236 children with asthma who lived in inner-city neighborhoods and from 41 schools were included. Validated classroom interventions to reduce allergen environment content were employed, with integrated pest management (IPM) applied every 3 months as needed, and HEPA filter purifiers used. Allergen content and exposure (dust and airborne) were collected and measured in classroom samples at baseline and post-intervention. Additionally, the evaluation of dust collections from participants' homes was similarly collected. The number of symptom days with asthma during a 2-week period was the primary outcome, with symptom days evaluated every 2 months during the 10 months following randomization. Although neither school-wide IPM nor classroom HEPA filters reached the trial's primary outcome in reducing asthma symptoms throughout the school year, in post hoc analysis, the study reported that school IPM reduced asthma symptoms by 63% during peak fall/winter asthma exacerbations. IPM also reduced school absences due to asthma (secondary outcome) [9•]. Post hoc analysis also evaluated the effect of classroom HEPA filtration in the subset of students with higher indoor classroom mold levels compared to home mold levels and found that classroom HEPA filters were effective in decreasing indoor mold levels, which was associated with improvements in students' $FEV_1\%$ [76]. Further analysis of the study findings taking into further consideration asthma symptoms at baseline, allergen levels, and particle exposures may be required, with additional strategies likely necessary in order to sustain benefits in a school community setting.

Conclusions

Asthma is a chronic condition impacted by multifactorial genetic and environmental risk factors, which include socioeconomic considerations contingent on a child's zip code and diverse exposures in the home and school setting. This review focuses on the effects of allergen exposures and environmental risk factors in schools on childhood asthma, summarizes the pathophysiology of environmental exposures, and discusses several preventative measures. While several studies have explored the benefit of environmental remediation in schools and its impact on asthma morbidity [9•], future studies are warranted to further define the effects of modifiable risk factors in schools and determine whether school mitigation strategies may improve asthma symptoms in students with asthma.

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