



## Asthma, Air Pollution and Environmental Exposure

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### Asthma and Depression

A large number of asthmatic patients, particularly females, present inadequate disease control. Depressive symptoms are reportedly common in asthma and have been related to poor disease control, but the mechanism of this association is still unclear. Poor quality sleep, frequently observed in asthmatics, is also a manifestation of depression and has been related to uncontrolled asthma [1]. This study by Campos aimed to investigate the relationship between depressive symptoms, sleep quality, and asthma control. This was a cross-sectional study of 123 women with previous diagnosis of asthma from a reference center in Fortaleza, Brazil. Depressive symptoms were assessed by the Beck Depression Inventory; quality of sleep was evaluated by the Pittsburgh Sleep Quality Index (PSQI), daytime sleepiness by the Epworth Sleepiness Scale, and asthma control by the Asthma Control Test. Asthma control in women is independently associated with depressive symptoms and quality of sleep, suggesting that these patients might benefit from simple measures to promote healthy sleep behavior and sleep hygiene and also that routine screening for depression can be relevant, particularly, in poorly controlled cases [1].

The occurrence of depression with asthma is very common, especially in women, and can influence behavioral factors, such as treatment compliance, self-assessment, and management of environmental triggers, that can collectively result in stress, poor asthma management and control [2].

Asthma is very heterogeneous and new theories and treatments are emerging. It can be associated with rhi-

nosinuitis and it is a growing epidemic among children and adults in the US and caused by many factors. Genetic variation, innate immune genes, those involved in tissue remodeling and inflammatory mediators might contribute to its pathogenesis [3].

### Asthma and Rhinosinuitis

This recent review article discussed chronic rhinosinuitis, epidemiology, pathogenesis, innate adaptive immunology, nuclear factor-kappa B related to inflammation, sepsis, complement, reactive oxygen species, asthma, sinusitis, elderly pathogenesis, oxidative stress, depression, seasonal variation, and other topics related to trauma and stress [4].

A literature search was conducted from several articles, prospective studies, recent reviews and earlier reports [4]. A synergistic relationship develops between activation of the innate immune system and the loss of organ barrier functions. Asthma and sepsis, a common condition encountered in hospital environments remains an important cause of death at intensive care units.

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## Asthma Pathogenesis

This earlier article reviewed current concepts of airway inflammation with a special emphasis on the epithelium, and airway remodeling [5]. Future therapeutic strategies may involve these targets and a synergistic approach in preventing remodeling in selected asthmatic patients [5].

## Pediatric Asthma Issues

The management of pediatric asthma exacerbations is based on trials in children of all ages. Recent studies from 2009 raised the possibility that preschoolers (younger than 6 years) with viral-induced wheezing and children exposed to tobacco smoke might be at an increased risk of treatment failure [6].

## Asthma, Obesity and Sleep Apnea

With the increase in the global prevalence of obesity, there is a parallel rise in the proportion of obese patients admitted to the ICU's, referred for major surgery or requiring long-term non-invasive ventilation (NIV) at home for chronic respiratory failure. These authors addressed other aspects of care of obese patients, including antibiotic dosing and catheter-related infections [7]. Obstructive sleep apnea is associated with rhinitis and asthma and is highly prevalent in the general population worldwide, especially in its mild form [8]. Clinical manifestations correlate poorly with disease severity measured by the apnea-hypopnea index (AHI), which complicates diagnosis. Full polysomnography might be more appropriate to assess suspected mild cases because limited ambulatory diagnostic systems are least accurate in mild disease. Treatment options in mild obstructive sleep apnea includes continuous positive airway pressure (CPAP) and oral appliance therapy, in addition to positional therapy and weight reduction. Although a small number of asthmatics have severe disease, accounting for the majority of morbidity related to the illness. Severe asthma comprises a heterogeneous group of phenotypes.

## Treatment Options for Asthma

Targeted treatments for these phenotypes represent a major advancement in the management of severe asthma [9]. Omalizumab improves asthma control in patients with a predominant allergic phenotype. Monoclonal antibodies targeted to interleukin 4 $\alpha$  and interleukin 5 have shown substantial benefit in patients with the eosinophilic asthma phenotype; so too have monoclonal antibodies targeted to interleukin 13 in patients with a type 2 allergic phenotype [9]. Bronchial thermoplasty, a new technique to decrease airway smooth muscle mass, improves symptoms and reduces exacerbations in patients with severe uncontrolled asthma and also in chronic air-flow obstruction phenotype.

Reslizumab is a humanized anti-interleukin 5 monoclonal antibody that disrupts eosinophil maturation and promotes programmed cell death. Castro assessed the efficacy and safety of reslizumab in patients with inadequately controlled, moderate-to-severe asthma [10]. Common adverse events on reslizumab were similar to placebo. The most common adverse events were worsening asthma symptoms 52% for placebo and 40% for reslizumab in one study [10].

## Role of Eosinophils

Eosinophilic airway inflammation is associated with increased corticosteroid responsiveness in asthma, but direct airway sampling methods are invasive or laborious. Minimally invasive markers for airway eosinophilia could present an alternative method, but estimates of their accuracy vary [11].

## Role of Biomarkers

Korevaar conducted a systematic review and assessed the diagnostic accuracy of markers against a reference standard of induced sputum, bronchoalveolar lavage, or endobronchial biopsy in patients with asthma or suspected asthma [11].

## Childhood Asthma

Early life influences are crucial for the development of distinct childhood asthma phenotypes. Besides genetics, epigenetics and environmental factors have an effect on innate and adaptive immune regulatory networks. Crucial determining factors for complex immune regulation and barrier function include family history of atopy, respiratory infections, microbiome, and nutrition [12].

## Neuroendocrine Immunology

Frieri reviewed concepts of neuro-endocrine immunology, dysregulation, stress, and treatment of allergic and autoimmune diseases. Neuro-endocrine hormones triggered during stress may lead to immune dysregulation resulting in atopic, autoimmune diseases or decreased host defense. The stress response and induction of a dysregulation of cytokine balance can trigger the hypothalamic-pituitary-adrenal axis and sympathetic nervous system that contains chiefly adrenergic fibers and tends to depress secretion, decrease the tone and contractility of smooth muscle, and increase heart rate [13].

These authors reviewed substance P at the neuro-immune crosstalk in the modulation of inflammation, asthma and antimicrobial host defense [14]. It modulates a variety of inflammatory processes, including asthma, trauma, systemic inflammatory response syndrome or sepsis [14].

Neuro-endocrine hormones triggered during stress may lead to immune dysregulation or altered or ampli-

fied cytokine production, resulting in atopic, autoimmune diseases or decreased host defense [15]. The stress response and induction of a dysregulation of cytokine balance can trigger the hypothalamic-pituitary-adrenal axis and sympathetic nervous system [15]. The multiple roles of Th2 cells in maintaining allergic inflammation and altering the balance between Th1 and Th2 responses are important mechanisms for allergic inflammation, and can also relate to stress [15]. Mast cells are important in allergic diseases and asthma, but they also have a role in trauma and neuro-inflammation and contribute to end-organ damage after trauma related to complement activation [15].

### Asthma Oxidative Stress

Oxidative stress occurs in asthma as a result of inflammation but also from environmental exposure to air pollution which can occur in children [15]. The specific localization of antioxidants in the lungs suggests the important role of oxidative stress, and therapeutic interventions that decrease exposure to the environment [15].

### Air Pollution

Khreis reviewed children's exposure to traffic-related air pollution (TRAP) that can contribute to their development of asthma. They conducted a systematic review and performed meta-analyses to analyze the association between TRAP and asthma development in childhood [16]. The overall risk estimates from the meta-analyses showed statistically significant associations for BC, NO<sub>2</sub>, PM<sub>2.5</sub>, PM<sub>10</sub> exposures and risk of asthma development. Their findings support the hypothesis that childhood exposure to TRAP contributes to their development of asthma. Future meta-analyses would benefit from greater standardization of study methods including exposure assessment harmonization, outcome harmonization, confounders' harmonization and the inclusion of all important confounders in individual studies [16].

### Air Pollution and Asthma

Bowatte summarized the evidence from recently published original studies investigating how glutathione S-transferase (GST) gene polymorphisms modify the impact of air pollution on asthma, allergic diseases, and lung function [17]. Current studies in epidemiological and controlled human experiments found evidence to suggest that GSTs modify the impact of air pollution exposure on respiratory diseases and allergies. Of the nine articles included in this review, all except one identified at least one significant interaction with at least one of glutathione S-transferase pi 1 (GSTP1), glutathione S-transferase mu 1 (GSTM1), or glutathione S-transferase theta 1 (GSTT1) genes and air pollution exposure [17]. The findings of these studies, however, are markedly different. This difference can be par-

tially explained by regional variation in the exposure levels and oxidative potential of different pollutants and by other interactions involving a number of unaccounted environment exposures and multiple genes [17].

Although there is evidence of an interaction between GST genes and air pollution exposure for the risk of respiratory disease and allergies, results are not concordant. Further investigations are needed to explore the reasons behind the discordancy [17].

### Traffic Related Air Pollution

Bowatte sought to determine whether exposure to TRAP in middle age is associated with allergic sensitization, current asthma, and reduced lung function in adults, and whether these associations are modified by variants in Glutathione S-Transferase genes [18]. Traffic-related air pollution (TRAP) exposure is associated with allergic airway diseases and reduced lung function in children, but evidence concerning adults, especially in low-pollution settings, is scarce and inconsistent. The study sample comprised the proband 2002 laboratory study of the Tasmanian Longitudinal Health Study. Mean annual residential nitrogen dioxide (NO<sub>2</sub>) exposure was estimated for current residential addresses using a validated land-use regression model. Associations between TRAP exposure and allergic sensitization, lung function, current wheeze, and asthma (n = 1405) were investigated using regression models [18]. Increased mean annual NO<sub>2</sub> exposure was associated with increased risk of atopy, increase in NO<sub>2</sub> [2.2 ppb] and current wheeze. Similarly, living less than 200 m from a major road was associated with current wheeze and atopy and was also associated with having significantly lower pre bronchodilator and post bronchodilator FEV<sub>1</sub> and prebronchodilator forced expiratory flow at 25% to 75% of forced vital capacity. They found evidence of interactions between living less than 200 m from a major road and GSTT1 polymorphism for atopy, asthma, and atopic asthma. Overall, carriers of the GSTT1 null genotype had an increased risk of asthma and allergic outcomes if exposed to TRAP. Even relatively low TRAP exposures confer an increased risk of adverse respiratory and allergic outcomes in genetically susceptible individuals [18].

Fuertes examined whether TRAP and genetic polymorphisms related to inflammation and oxidative stress predict allergic rhinitis and sensitization.

### Role of Allergic Rhinitis

Allergic rhinitis was defined with a doctor diagnosis or reported symptoms at age 7 or 8 years. Associations between nitrogen dioxide, particulate matter 2.5 (PM2.5) mass, PM2.5 absorbance, and ozone, estimated for each child at the year of birth, and single nucleotide polymor-

phisms within the GSTP1, TNF, TLR2, or TLR4 genes with allergic rhinitis and aeroallergen sensitization were examined with logistic regression [19]. Models were stratified by genotype and interaction terms tested for gene-environment associations. Point estimates for associations between nitrogen dioxide, PM<sub>2.5</sub> mass, and PM<sub>2.5</sub> absorbance with allergic rhinitis were elevated, but only that for PM<sub>2.5</sub> mass was statistically significant (1.37 [1.01, 1.86] per 5 µg/m<sup>3</sup>). This result was not robust to single-cohort exclusions [19]. Carriers of at least 1 minor rs1800629 (TNF) or rs1927911 (TLR4) allele were consistently at an increased risk of developing allergic rhinitis regardless of TRAP exposure. No evidence of gene-environment interactions was observed. The generally null effect of TRAP on allergic rhinitis and aeroallergen sensitization was not modified by the studied variants in the GSTP1, TNF, TLR2, or TLR4 genes. Children carrying a minor rs1800629 (TNF) or rs1927911 (TLR4) allele may be at a higher risk of allergic rhinitis [19].

## Environmental and Pollen Exposures Related to Asthma

Home aeroallergen exposure is associated with increased asthma morbidity in children, however little is known about the contribution of school aeroallergen exposures to such morbidity.

Sheehan evaluated the effect of school-specific aeroallergen exposures on asthma morbidity among students, adjusting for home exposures in 284 students aged 4 to 13 years with asthma who were enrolled from 37 inner-city elementary schools in the northeastern United States between March 1, 2008, and August 31, 2013 [20]. Indoor aeroallergens, included rat, mouse, cockroach, cat, dog, and dust mites, measured in dust samples collected from inner-city schools.

Associations between school aeroallergen exposure and asthma outcomes during the school year were assessed, adjusting for home exposures. In this study of inner-city students with asthma, exposure to mouse allergen in schools was associated with increased asthma symptoms and decreased lung function [20]. These findings demonstrated that the school environment is an important contributor to childhood asthma morbidity. Future school-based environmental interventions may be beneficial for this important public health problem [20].

Home-based interventions to improve indoor air quality have demonstrated benefits for asthma morbidity, however little is known about the effect of environmental interventions in the school setting. Jhun piloted the feasibility and effectiveness of a classroom-based air cleaner intervention to reduce particulate pollutants in classrooms of children with asthma [21].

In this pilot study, a classroom-based air cleaner intervention led to significant reductions in (particulate matter with diameter of < 2.5 µm [PM<sub>2.5</sub>]) and black carbon. Future large-scale studies should comprehensively evaluate the effect of school-based environmental interventions on pediatric asthma morbidity [21].

A disparate burden of childhood asthma is seen among socioeconomically disadvantaged youth, often concentrated in urban areas with high poverty rates. Host factors that predispose a child to asthma include atopy, male gender, parental history of asthma, and also race, ethnicity, and genetic and epigenetic susceptibilities according to Milligan [22]. Environmental factors, such as improved hygiene, ambient air pollution, and early life exposures to microbes and aeroallergens, also influence the development of asthma. With greater than 90% of time spent indoors, home exposures (such as cockroach, rodent, and indoor air pollution) are highly relevant for urban asthma. Morbidity reduction may require focused public health initiatives for environmental intervention in high priority risk groups and the addition of immune modulatory agents in children with poorly controlled disease [22].

Gleason JA evaluated the associations between ozone, PM<sub>2.5</sub>, and four pollen types on emergency department pediatric asthma events during the warm season in New Jersey [23]. The ambient air pollutant ozone was associated with increases in pediatric emergency department asthma visits during the warm weather season. The different pollen types showed different associations with the outcome. High levels of tree pollen appear to be an important risk factor in asthma exacerbations [23].

The driving environmental factors behind the development of the asthma phenotype remain incompletely studied and understood. Sokol presented an overview of inhaled allergic/atopic and mainly nonallergic/nonatopic or toxicant shapers of the asthma phenotype, which are present in both the indoor and outdoor environment [24]. The inhaled allergic/atopic factors include fungus, mold, animal dander, cockroach, dust mites, and pollen; these allergic triggers and shapers of the asthma phenotype are considered in the context of their ability to drive the immunologic IgE response and potentially induce interactions between the innate and adaptive immune responses, with special emphasis on reactive oxygen species associated mechanism of pollen associated allergy induction [24]. The inhaled nonallergic/nonatopic, toxicant factors include gaseous and volatile agents, such as sulfur dioxide, ozone, acrolein, and butadiene, as well as particulate agents, such as rubber tire breakdown particles, and diesel exhaust particles. These toxicants are reviewed in terms of their relevant chemical

characteristics and hazard potential, ability to induce airway dysfunction, and potential for driving the asthma phenotype. Special emphasis is placed on their interactive nature with other triggers and drivers, with regard to driving the asthma phenotype. Overall, both allergic and nonallergic environmental factors can interact to acutely exacerbate the asthma phenotype; some may also promote its development over prolonged periods of untreated exposure, or possibly indirectly through effects on the genome. Further therapeutic considerations should be given to these environmental factors when determining the best course of personalized medicine for individuals with asthma [24].

Few studies have focused on pollen exposure and asthma in children. None have examined associations between persistent exposure to pollen in infancy and aeroallergen sensitization and asthma in childhood. Erbas examined the association between higher ambient levels of pollen in the first 3-6 months of life and risk of eczema, sensitization to food and aeroallergens at 2 years and asthma or hayfever at age 6-7 years combined [25]. Using a birth cohort of 620 infants with a family history of allergic disease born between 1990 and 1994, the authors examined risk of eczema or allergic sensitization (SPT > 3 mm to at least one of cow's milk, egg white, peanut, house dust-mite, rye grass, and cat dander) by age 2 and asthma or hay fever at age 6-7 [25]. Daily ambient levels of pollen were measured during this period. Cumulative exposure to pollen concentrations up to 6 months was associated with aeroallergen sensitization with the highest risk occurring at 3 months. Cumulative exposure to pollen up to 3 months was also associated with hay fever and between 4 and 6 months exposure with asthma only.

Persistent pollen exposure in infancy appears to increase the risk of asthma and hay fever in children. These results support the hypothesis that there is a critical window of opportunity in early development which may be important for modification of allergic outcomes [25]. The degree to which aeroallergens are contributing to the global increase in pediatric allergic disease is incompletely understood. Sheffield reviewed the evidence that links climate change to changes in aeroallergens such as pollen and outdoor mold concentrations and, subsequently, aeroallergen association with pediatric allergic disease and specifically explored the evidence on both the exacerbation and the development of allergic disease in children related to outdoor pollen and mold concentrations [26]. Pediatric allergic diseases include atopic dermatitis or eczema, allergic rhinitis or hay fever, and some types of asthma in children, typically defined as < 18 years of age. The authors discussed how the timing of aeroallergen exposure both in utero and in childhood could be as-

sociated with allergies and concluded that the magnitude and type of health impacts due to climate change will depend on improved understanding of the relationship between climatic variables, multiple allergen factors, and allergic disease. Improved public-health strategies such as adequate humidity control, optimum air filtration and ventilation, and improved anticipatory public-health messaging will be critical to adaptation [26].

The environment is a major contributor to allergic disease, and great effort is being expended to identify the chemical pollutants and allergens that make a significant impact. Exposure to high levels of ozone, sulfur dioxide, nitrogen dioxide, and diesel exhaust particles is known to reduce lung function [27]. Studies continue to delineate the role of these particles as adjuvants and carriers of allergens into the respiratory system. Current studies also show the exacerbation of allergic disease through fungal spore inhalation and continue to document the role of pollen in allergic rhinitis. Pollen also was recently associated with asthma epidemics, especially after thunderstorms. Forecasting models currently are being developed that predict the trajectories of pollen dispersal and may allow increased avoidance of dangerous outdoor conditions [27].

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