Epidemiology and risk factors for asthma

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- The diagnosis of asthma has increased exponentially in **recent decades** parallel with urbanization and industrialization, and is now considered **a global public health issue**.

- According to the Global Burden of Disease report for 2015, asthma was the **most common** chronic respiratory disorder, with an estimated prevalence of **358 million** cases.

- In fact, the World Health Organization, through extra-polation from existing data, predicts a **further increase** in the number of asthmatics by an **additional 100 million in 2025**.

International prevalence

- The prevalence of asthma varies significantly in **different regions** of the world.
- The **highest rates** were found in the English-speaking countries and the lowest in Italy and Greece.
- **Overall robust increase** in asthma prevalence in most countries during the **second half of the 20th** century through the 1990s
- While asthma is **more prevalent** in higher income countries, the relationship between gross national product (GNP) and asthma frequency **is non-linear**.

- The importance of geographic location in the development of asthma has been highlighted **by migration** studies.
- International trends in **mortality rates** from asthma provide a barometer of **asthma burden** and the influences of **changing management guideline**.
- For instance between 1985 and 2005, the surge in use of **inhaled corticosteroids (ICS)** for asthma management led to a **progressive decline** in estimated **asthma mortality**.
- However, the reductions in years lived with disability (**YLDs**) have been **much smaller**.
- Also, **global asthma mortal**ity rates in the **past decade** appear to have **plateaued** without further decline since 2006, indicating the need for **novel strategies** to achieve further reduction.

Financial impact

- Despite **stable prevalence** in recent years, **asthma expenditures** have continued to **progressively increase**.
- Patients with **severe asthma** are thought to represent between **5 and 10%** of all subjects.
- Throughout the **three-year study**, the average cost for every uncontrolled asthma patient was $14,212 as compared with $6452 for controlled asthmatics.
- Asthma is also the leading cause of **school absenteeism** in the US, and accounts for approximately **13 million** days of missed school annually.
- Thus, **focused attention** on patients with poorly controlled asthma may **significantly reduce** the socioeconomic burden of disease.

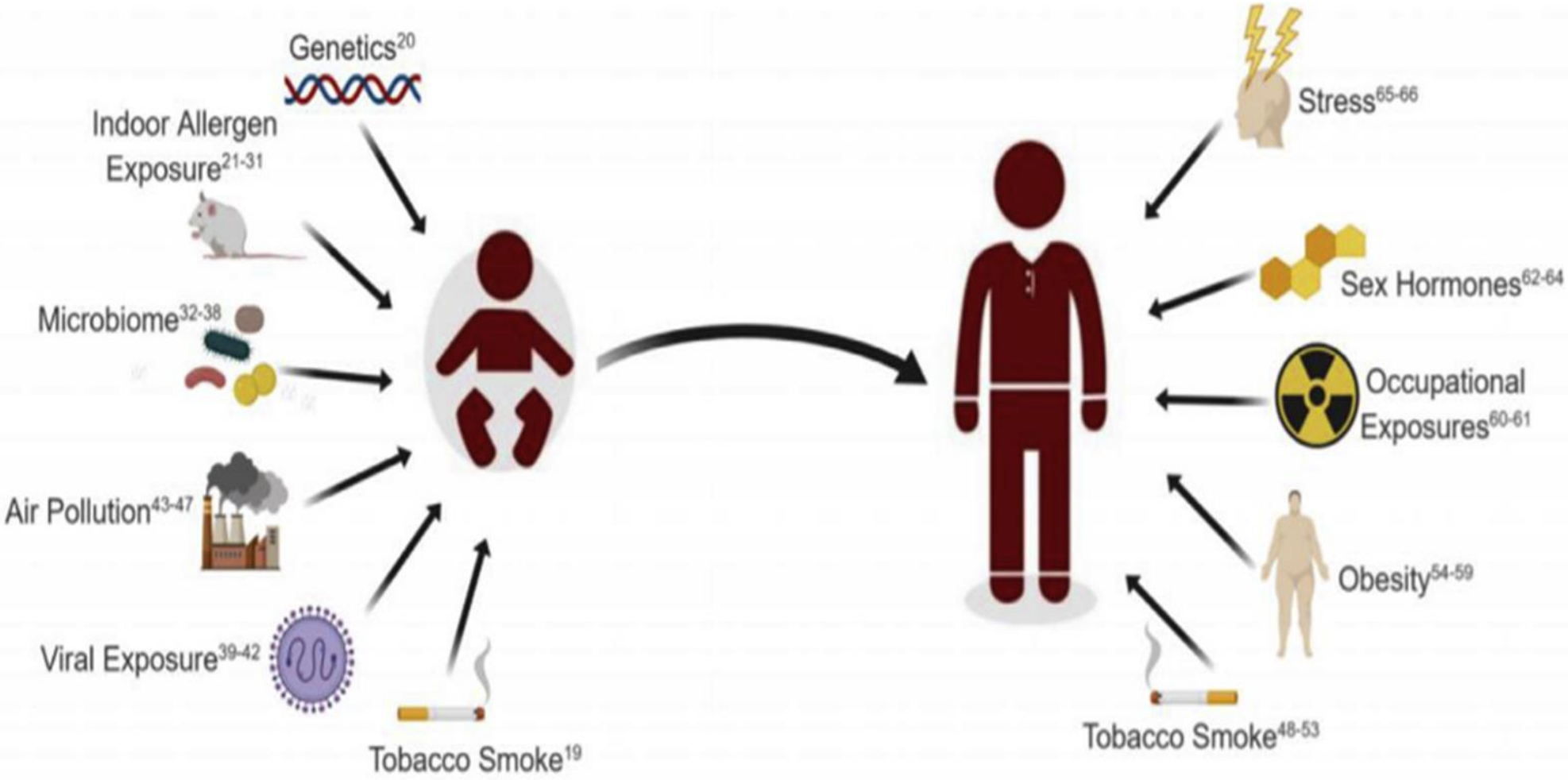
Risk factors

- Despite **therapeutic advances**, the continued rise in asthma prevalence suggests that the **fundamental cause**s of asthma are yet **poorly understood**.

- There is an **extensive degree of overlap** between risk factors for **childhood and adult** onset asthma.

- Childhood onset asthma
- Genetics
- Indoor allergen exposure
- Microbiome exposures
- Respiratory viruses
- Environmental tobacco smoke (ETS)
- Air pollution
- Obesity

- Adult onset asthma
- Smoking
- Occupational exposures
- Sex hormones
- Stress events
- Very late onset asthma
- Medication related asthma triggers


Genetics[20]
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Genetics

- A **strong genetic basis** for asthma has long been established. In **monozygotic twins**, asthma concordance is approximately 50%.
- The combined risk for all these genetic variants is estimated to predict ~10% of asthma heritability and prevalence.
- Involved genes incriminate epithelial barrier function abnormalities as contributory to asthma.
- In the Avon Longitudinal Study of Parents and Children, this genetic locus posed the strongest risk for persistent wheeze in children with a relative risk ratio of 1.6

- Shngle nucleotide polymorphisms (SNPs) in the ch17q21 region have also been reproducibly associated with severe acute asthma flares requiring oral steroids and/or hospitalization.

- It is well known that epigenetic modifications regulate the expression of cytokines and transcription factors responsible for T-cell differentiation. In addition, epigenetic mechanisms, including DNA methylation, may influence childhood asthma by regulation of IgE levels and other asthma genes

Indoor allergen exposure

- The relationship between sensitization to inhalant allergens and onset of asthma is also well-recognized.
- A significantly increased risk of asthma occurs with aeroallergen sensitization at less than five years of age.
- Indoor allergens including house dust mite, mice, cockroach, animal dander, and fungi are of especial interest due to the possibility of intervention during childhood.
- Recent data suggests that exposure and allergic sensitization to mouse antigen is a stronger predictor of severe asthma than cockroach allergen.

- Overall, pet allergen exposure does not appear to increase atopic risk, with decreased asthma risk with cat exposure in one study .
- Fungal exposure is recognized to increase the risk for life-threatening asthma exacerbations possibly through the release of IL-33.
- Mold sensitization is common amongst patients with severe asthma requiring multiple hospital admissions
- However, there is also evidence that increased fungal diversity may actually be protective against allergic disease .This mirrors the protective effects conferred by diversity in the human microbiome

Microbiome exposures

- The hygiene hypothesis implicates our microbial environment in early life as integral to immune development, and protective against atopy and asthma.
- In the past decade, several studies have investigated the protective effects of being raised on a farm as opposed to rural communities or cities
- Microbial exposures from living in proximity with domestic animals in early life appear to afford protection against development of atopic asthma

Gender also
appears to influence the impact of exposure with lower cumulative incidence of asthma in girls raised on a farm as compared to boys

- The risk of asthma is similarly greater in children born via cesarean section, implicating microbial colonization pattern in these children versus vaginal delivery .

Respiratory viruses

- Respiratory syncytial virus (RSV) and human rhinovirus (HRV) are the most common respiratory viruses associated with wheeze in early childhood.
- Influenza has also been associated with exacerbation of ongoing disease.
- In one series, influenza A virus was detected in 2.6% of hospitalized children and 14.1% ($P < .001$) of ambulatory-treated patients with asthma flares.
- HRV induced asthma flares also increase in severity parallel with the degree of mouse and dust mite sensitization
- On the other hand, RSV induced wheeze during infancy was associated with non-atopic asthma at 7 years of age.
- ~50% of infants with RSV induced wheeze during infancy developed persistent asthma when followed up to 7 years [

Environmental tobacco smoke (ETS)

- Environmental tobacco exposure (ETS) is well recognized to increase the risk for asthma in early life.
- Both prenatal and postnatal maternal smoking significantly increased the incidence of asthma at all ages
- Paternal smoking was also associated with a significantly increased odds of asthma in 5–18 year olds

Air pollution

- Epidemiologic studies of air pollution and asthma have identified increased risk of both exacerbation of lung disease with acute exposure as well as development and/or impairment of asthma with chronic exposure to ambient air pollutants.

- Various pollutants have been incriminated including ozone, nitrogen dioxide (NO2), particulate matter (PM) and others, even at levels less than the current National Ambient Air Quality Standards.

- Genetics also factor into determining susceptibility to air pollution, the most well-known being glutathione-S-transferase polymorphisms that are involved in antioxidant defenses.

- Global warming has been incriminated in increasing the duration and intensity of the pollen season
- This increased exposure to allergens com- bined with pollutants acts synergistically to enhance the allergic response.
- Children who live near major roadways and exposed to traffic-related air pollution have increased susceptibility to asthma.
- In general, the burden of air pollution related asthma is associated with a lower socioeconomic status, and is thus a health equity issue

Smoking

- It is clear that asthmatics who smoke have significantly increased morbidity and mortality than non-smokers.
- The prevalence of active smoking in adult asthmatics from low- and middle-income countries is ~25% placing them at particularly increased risk of severe symptoms and reduced response to steroid therapy.
- The burgeoning use of e-cigarettes has prompted investigation of their deleterious effects [69], and recent data demonstrates that chronic use alters the bronchial epithelial proteome of the human airway.
- Similarly, smoking e-cigarettes during pregnancy has equivalent risk to conventional cigarettes for asthma development
- Thus, cessation of all forms of smoking is essential to the management of asthmatics.

Obesity

- Obesity increases the risk for late onset asthma in both men and women by approximately 50% ,especially in non-allergic individuals with a more pronounced effect in females.

- Obese asthmatics are known to have worse asthma control and increased rates of healthcare utilization due to asthma

Occupational exposures

- Approximately 10–25% of adult-onset asthma is estimated to drive from work related exposures that may be sensitizers or irritants in nature .
- Exposure to laboratory animals was most robustly associated with development of occupational asthma.
- The acute exposure to high levels of irritants also cause asthma through non-immunologic inhalation injury.
- Most cases of OA require cessation of exposure, and even with avoidance does not warrant complete recovery.

Sex hormones

- In the Epidemiology and Natural history of asthma: 71% of adult patients were women in contrast with 34% of children.

- Although boys have increased onset of atopic asthma compared to girls during early childhood, there is a recognized switch in asthma prevalence from males to females that coincides with the onset of puberty.

- While the precise role for sex hormones in regulating asthma is not completely understood, overall ovarian hormones enhance and testosterone dampens airway inflammation in asthma.

Stress events

- The association of psychosocial stressors with asthma may reflect disproportionate exposure among those from lower socioeconomic classes and ethnic minorities.

- Stress can modulate lung development, as well neuroendocrine and autonomic responses, and potentiate reactivity to allergens and infections .

- Pediatric studies have previously reproduced a causal link between stress events and asthma onset . More recently, observational studies have confirmed this association in adults.

- Elucidation of these mechanisms may improve asthma outcomes particularly in ethnic minorities and the economically disadvantaged.

Very late onset asthma

- The age cutofffor the definition of very late-onset asthma varies but diagnosed as > 50 years in some papers and > 65 years in others
- The aging lung is associated with decreased lung function due to mechanical disadvantages and loss of elastic recoil.
- Emerging data suggest that older asthmatics have increased sputum neutrophilia secondary to Th1 and Th17 inflammation

Medication related asthma triggers

- Beta blockers have the potential to cause acute bronchoconstriction in asthma on a dose dependent basis, the risk of which is mitigated to some degree by the use of cardioselective agents.

- Their use in asthmatics should thus be contingent upon a risk benefit analysis in individual patients using the lowest dose possible.

- While ACE-inhibitors by themselves do not potentiate asthma, their possible side effect of cough may be confused for asthmatic symptoms.

Conclusion

- Despite advances in our understanding of asthma, it continues to be a significant global source of morbidity and mortality.
- The future of asthma appears largely reliant on precision medicine.
- Several strategies for prevention have been attempted in recent years, none of which have succeeded to date in decreasing morbidity.
- Longitudinal studies from pregnancy progressing through childhood and adulthood will further elucidate the complex pathways underlying asthma and facilitate personalized therapies.


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