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Review article

Epidemiology and risk factors for asthma

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1. Introduction

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 [1]. Assessment of the scope and burden of disease is however confounded by misdiagnosis and bias in surveillance reports that result in over- or underestimation of cases. Nonetheless, despite this heterogeneity in data collection, there is little doubt that asthma has markedly increased in the past 50 years in terms of both incidence as well as prevalence. In recent cohorts, up to 15–20% of the general population have a diagnosis of asthma in some countries which is highly concerning [2]. In fact, the World Health Organization, through extrapolation from existing data, predicts a further increase in the number of asthmatics by an additional 100 million in 2025 [3]. This highlights the need for application of standardized and validated methods to enable improved evaluation of temporal trends of asthma prevalence.

The objective of this review is to summarize the trends in asthma burden in the United States and internationally. Further, in view of the heterogeneity of severe asthma, we seek to highlight environmental exposures during early childhood and later in life that are potential stimuli for programming of asthma. Our search strategy included a systematic review of the existing English literature. The Pubmed electronic database (1970–2018) was screened including the search terms asthma, epidemiology, and risk factors ("asthma" [All Fields] AND "epidemiology" [MeSH Terms] AND "risk factors" [MeSH Terms]). (See Fig. 1)

2. International prevalence

The prevalence of asthma varies significantly in different regions of the world. Prevalence trends are best estimated through the repeated survey of large random samples in the same region, within the same age-range, using identical validated methods. Such studies are expensive to conduct and time consuming, however, a few studies that fulfill these criteria have delineated asthma trends among children and adults. The two largest global evaluations of asthma are the European Community Respiratory Health Survey (ECRHS) and International Study of Asthma and Allergy in Children (ISAAC). The ISAAC project is the most extensive international survey regarding asthma symptoms. Phase III of ISAAC reported a 12-month prevalence of asthma symptoms among adolescents ranging from 2.1% in Indonesia to 32.2% in the United Kingdom [4]. The highest 12-month prevalence of wheeze was found in Westernized, English speaking countries, but also in some Latin American countries (32.1% prevalence among 6–7-year old children in Costa Rica).

The European Community Respiratory Health Survey (ECHRS) is the only other comparable international asthma survey [5]. This study included male and female subjects between 20 and 44 years mostly from European centers. Among countries that overlapped with those in ISAAC, the ranking of asthma symptom prevalence was similar. The highest rates were found in the English-speaking countries and the lowest in Italy and Greece. Eder et al. collated data from epidemiological surveillance studies, which show overall robust increase in asthma prevalence in most countries during the second half of the 20th century through the 1990s [2]. Following this, the prevalence appears to have plateaued in some areas of the Western world, especially in Western/Northern Europe and Australia. However, it has been on the uprise in developing countries over recent decades of westernization, particularly childhood onset asthma.

While asthma is more prevalent in higher income countries, the relationship between gross national product (GNP) and asthma frequency is non-linear. Rather, there appears to be a threshold below which countries have lowest asthma rates. Within the population of a given GNP, there is a prominent urban to rural gradient in decreasing prevalence of asthma [6].

The importance of geographic location in the development of asthma has been highlighted by migration studies. While immigrants from developing countries initially demonstrate a lower prevalence of asthma than natives, this rises to similar rates proportional with increasing duration of residence [7]. These studies have also demonstrated higher rates of asthma in children of immigrants born in host countries [8].

International trends in mortality rates from asthma provide a barometer of asthma burden and the influences of changing management guidelines. For instance, asthma mortality epidemics between the

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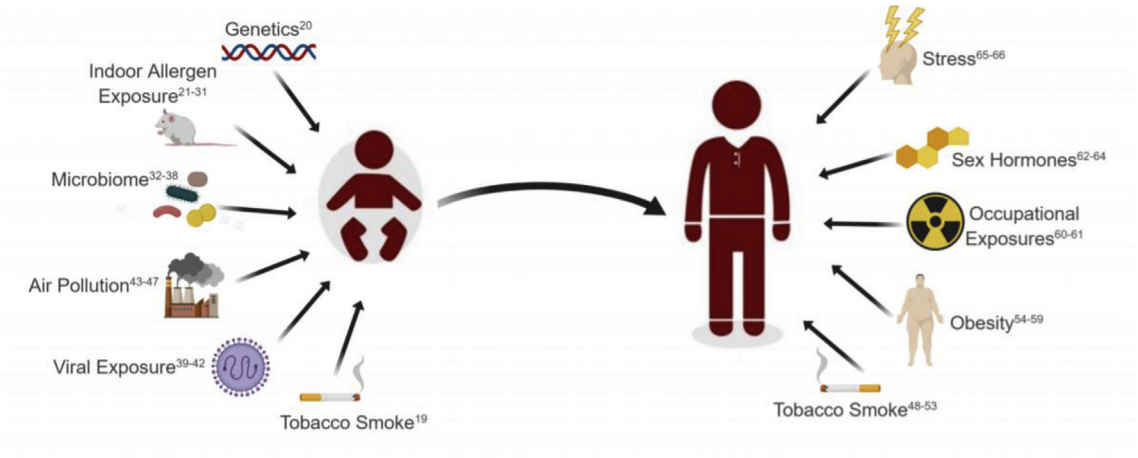

Fig. 1. Asthma Epi figure

1960s–1980s were identified to be secondary to overuse of high dose β2 agonists, that ended with their withdrawal. Between 1985 and 2005, the surge in use of inhaled corticosteroids (ICS) for asthma management led to a progressive decline in estimated asthma mortality. Ebmeier et al. collated asthma mortality rates in those aged 5–34 years from 46 nations using the online WHO Mortality Database, and demonstrated a fall in the estimated mean global asthma mortality rate by 57% (from 0.44 per 100,000 in 1993 to 0.19 per 100,000 in 2006) [9]. This is reflected in the decline of annual age-standardized disability adjusted life year (DALY) rates for asthma by 42.8% between 1990 and 2015 [1], most of which stems from a reduction in mortality.

However, the reductions in years lived with disability (YLDs) have been much smaller. Also, global asthma mortality rates in the past decade appear to have plateaued without further decline since 2006, indicating the need for novel strategies to achieve further reduction. Additionally, subjects with asthma have increased mortality from all causes [10].

3. United States prevalence

The Center for Disease Control and Prevention (CDC) has implemented various surveillance activities to determine the burden of asthma in terms of prevalence, health care utilization, and mortality. Much of this data is collected through National Center for Health Statistics (NCHS) surveys and the Vital Statistics System. The current prevalence within the United States according to CDC data for 2015 is 7.8%, and is almost equally pervasive in adults and children [11]. Overall, the CDC reports a decline in the annual age-adjusted asthma mortality rate per 1 million persons in the United States between 1999 and 2016 (13.59–9.34 in women, and 9.14 to 7.78 among men) [11].

Despite improved asthma outcomes on the whole, there is a disproportionate disease burden among children and ethnic minorities. A recent report from the TENOR observational study highlights racial disparities in pediatric asthma-related health outcomes [11]. It has been known for decades that inner city children are more likely to develop asthma as well as severe asthma symptoms. Black race and Puerto Rican ethnicity have become clear risk factors for asthma, although the extent of influence by urban environmental exposures as opposed to underlying genetic susceptibility alone remains unknown. While the degree of African ancestry has been associated with asthma [12], these analyses are frequently confounded by inherent social factors such as socioeconomic status, access to health care and medications, and further compounded by a host of environmental exposures which will be discussed further. Thus, the relative contributions of ethnicity versus poverty and other circumstantial neighborhood factors to inner city related asthma disparities remain unclear.

Overall, black or Puerto Rican ethnicity and household poverty are the major risk factors rather than residing in an urban area in itself. Poverty may increase susceptibility to asthma via several pathways, due to increased presence of smoking, prematurity, indoor allergens, stress, and exposure to pollution, in poorer households. Despite black children requiring a higher level of therapy, they fared worse than Caucasian children in terms of health care utilization parameters as well as patient reported outcome measures.

These findings are an extension of severe asthma outcomes in black and white adult populations. When categorized by ethnicity, the highest incidence for 2015 is recorded in non-Hispanic blacks (10.3%), followed by white non-Hispanic (7.8%), other non-Hispanic (6.9%), and Hispanic populations (6.6%), respectively. The mortality rate for that year approaches 1.1/100,000 population, with a three fold greater burden in non-Hispanic blacks as compared with other races. There has been a nearly 50% increase in asthma diagnosis among the black population over the past decade. African Americans are also known to have a higher asthma related mortality than other races [13]. More than a quarter of black adults report being unable to purchase their asthma prescriptions, and one in four black adult asthmatics indicated that they were unable to afford primary care physician visits [13].

There is also a distinct social gradient in asthma, with the occurrence rising with each successive level of poverty [14]. From 2001–10, asthma prevalence was 11.2% among persons with a family income less than 100% of the federal poverty threshold, as compared with 7.3% for those with incomes of greater than 200% of the poverty level. Financial barriers also account for medication non-adherence as evidenced by a 2009 study, in which the rates of filling asthma prescriptions declined with out-of-pocket costs of more than USD 12 per prescription [13]. This aligns with the finding that 40.3% of those without health insurance were unable to afford asthma medications as opposed to 11.5% of those with insurance not being able to afford therapy [15].

4. Financial impact

Despite stable prevalence in recent years, asthma expenditures have continued to progressively increase. The national medical expenditure secondary to adult asthma was calculated at USD 18 billion per year for 2003 to 2005 [16]. Estimates of total asthma related costs to the United States healthcare system continue to rise, and jumped from USD 53 billion for 2007 to USD 56 billion for 2009 [17], and most recently USD 82 billion in 2013 [18].

Patients with severe asthma are thought to represent between 5 and 10% of all subjects. Difficult to control asthma accounts for the bulk of

the socioeconomic burden associated with the disease. These include both direct health care related costs as well as indirect costs, in terms of lost productivity. In the TENOR cohort, there was a direct relationship between costs and loss of asthma control [19]. 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. 36,000 children miss school on a daily basis due to asthma in the US and this has been linked with poor academic performance especially among inner city youth [20]. Thus, focused attention on patients with poorly controlled asthma may significantly reduce the socioeconomic burden of disease.

5. Risk factors

Despite therapeutic advances, the continued rise in asthma prevalence suggests that the fundamental causes of asthma are yet poorly understood. Akin to prevalence data, the study of risk factors and protective relationships in asthma has proven difficult due to the myriad of related factors. Of note, there is an extensive degree of overlap between risk factors for childhood and adult onset asthma.

5.1. Childhood onset asthma

Recognition of the so called “asthma epidemic” has led to the initiation of over 150 birth cohorts on asthma around the world in the past three decades [21], and data gathered has significantly elucidated origins of childhood asthma. International collaborations have been implemented in recent years to better understand information from these birth cohorts, however, this has been hampered by differences in definition and methodology.

In view of the distinct predilection of the inner-city population for development of pediatric asthma, the Inner-City Asthma Network Program was established almost three decades ago to improve outcomes for these high-risk children in urban environments. While a wide breadth of variables influence disease, the two most significant drivers of asthma development were allergic sensitization and tobacco smoke exposure in a causal network analysis of an inner-city asthma cohort [22].

5.2. Genetics

A strong genetic basis for asthma has long been established. In monozygotic twins, asthma concordance is approximately 50%. Genome-wide association studies (GWAS) in large pediatric and adult cohorts have identified significant ($P < 10-8$) asthma related single nucleotide polymorphisms (SNPs) that have been replicated across studies [23]. These results have underscored the importance of genetic variants in genes recognized as contributory to asthma such as HLA-DQ, SMAD3, TSLP, IL1RL1/IL18R1, and IL33. Yet, the individual contributions of these genetic variants is generally modest (odds ratios ~1.2) even for the most replicated loci. The combined risk for all these genetic variants is estimated to predict ~10% of asthma heritability and prevalence.

The gasdermin B/orosomucoid like 3 (GSDMB-ORMDL3) locus on chromosome 17q21 has been most consistently replicated in GWAS of asthma. 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 [24]. SNPs in the ch17q21 region have also been reproducibly associated with severe acute asthma flares requiring oral steroids and/or hospitalization [25].

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 (ALOX15, CAPN14, and POSTN) [26,27].

5.3. 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 [28]. Indoor allergens including house dust mite, mice, cockroach, animal dander, and fungi are of especial interest due to the possibility of intervention during childhood.

The first of the Inner-City Asthma Networks was the National Cooperative Inner-City Asthma Study which sought to identify causal environmental factors in childhood asthma. This resulted in several key environmental observations, such as the association of cockroach, dust mite, and mouse sensitization with uncontrolled asthma [29]. In a pediatric cohort, dust mite sensitization at ages 1 and 2 were predictive of 3.3- and 6.4-times odds of wheezing at follow up in adolescence [30]. Two separate birth cohorts of at-risk children demonstrated a significant dose-response relationship between HDM exposure and related atopic asthma [31,32]. Conversely, in an early childhood study at three centers, there was no association between HDM-specific IgE and levels of exposure in early life in two of these cohorts, whereas a positive association was found in the third [33]. This may indicate that the dose-response relationship between allergen exposure and sensitization may differ according to geographical locale.

Cockroach exposure is an even more potent inducer of sensitization, with a threshold 10- to 100- fold lower than other indoor allergens [34]. Recent data suggests that exposure and allergic sensitization to mouse antigen is a stronger predictor of severe asthma than cockroach allergen [35]. In a US cohort of inner-city residences, 95% had detectable mouse allergen, increased levels being associated with cockroach infestation [36].

In contrast, the association between furred pet exposure and atopic risk is contradictory. Due to the ubiquity of cat and dog allergens, surveys that hinge upon presence of pets in the home alone may be insufficient to measure exposure [37]. Overall, pet allergen exposure does not appear to increase atopic risk, with decreased asthma risk with cat exposure in one study [38].

In the context of fungi, both qualitative and quantitative measures of fungal exposure have been linked with an enhanced allergy and asthma risk. The allergenic significance of domestic exposure to *Alternaria alternata* in urban settings is underrecognized relative to HDM, mouse and cockroach. Sensitization to *Alternaria* has been implicated in increased asthma-related morbidity independent of sensitization to other aeroallergens. Fungal exposure is recognized to increase the risk for life-threatening asthma exacerbations possibly through the release of IL-33 [39]. Mold sensitization is common amongst patients with severe asthma requiring multiple hospital admissions [40,41].

However, there is also evidence that increased fungal diversity may actually be protective against allergic disease [42]. This mirrors the protective effects conferred by diversity in the human microbiome, as detailed below.

On the other hand, the Urban Environment and Childhood Asthma (URECA) birth cohort was established over a decade ago to establish the influence of early life exposures on clinical outcomes in a high-risk urban population. Contrary to expectations, greater concentrations of mouse, cat and cockroach allergens during the first years of life were inversely related to asthma risk [43]. The authors postulated that this finding may be secondary to an altered indoor microbiome associated with pest and furred animals.

The second Inner City Asthma Network - the Inner-City Asthma Study (ICAS) - validated the role of environmental exposures by subsequent multifaceted intervention studies that demonstrated improved control with household remediation measures. ICAS enrolled children

with atopic asthma and sensitization to perennial allergens. Interventions targeted at reducing the predominant allergen incriminated in asthma morbidity within a community have translated into decreased asthma symptoms and to a lesser degree, acute asthma flares [44].

5.4. 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 [45,46]. These studies on farm life have provided a compelling argument in support of the hygiene theory. Microbial exposures from living in proximity with domestic animals in early life appear to afford protection against development of atopic asthma [46]. The generally accepted hypothesis is that the microbial diversity of the farm environment triggers protective immune responses. 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 [47].

Most recently, the prevalence of atopy and asthma was shown to be significantly lower in Amish, as opposed to Hutterite children despite similar lifestyle and ancestry [48]. This has been attributed to differences in farming practices and endotoxin levels which were 6.8 times higher in Amish homes. These surveys replicated stronger protection with exposure in utero and in early life. Similarly, Amish children have a much lower prevalence of atopic asthma compared with farm and non-farm children (5.2% vs 6.8% vs 11.2%, respectively) [49]. This makes the notion that the global increase in atopy and asthma is influenced by lifestyle and environment even more provocative.

This is supported by studies showing that reduced stool microbial diversity at 1 month of age is predictive of atopy at 2 and 6 years of age [50]. The risk of asthma is similarly greater in children born via cesarean section, implicating microbial colonization pattern in these children versus vaginal delivery [51]. In addition to vaginal delivery, increasing numbers of older siblings also appear to have favorable effects on the infant microbiome [52].

In the Canadian Healthy Infant Longitudinal Development (CHILD) study, Arrieta et al. found that the first 100 days of life are crucial in terms of microbiome establishment and the risk of asthma and atopy [53]. This focus on early life biodiversity has stimulated pregnancy and early childhood interventions for the prevention of atopy and asthma, however none have proven effective thus far.

5.5. Respiratory viruses

Respiratory viruses influence subsequent wheeze and asthma acting either independently or in conjunction with atopy. 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 [54]. 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 [55].

HRV triggered wheeze appears to confer particular predilection for future atopic asthma comparable with the risk associated with allergen sensitization when followed up at ages 7 and 13 in the Childhood Origins of Asthma (COAST) study [56]. HRV induced asthma flares also increase in severity parallel with the degree of mouse and dust mite sensitization [57]. On the other hand, RSV induced wheeze during infancy was associated with non-atopic asthma at 7 years of age. In another cohort, ~50% of infants with RSV induced wheeze during infancy developed persistent asthma when followed up to 7 years [58]. However, RSV triggered wheezing in the first three years of life was not associated with a similar risk of future asthma at 13 years in one study [28].

5.6. Environmental tobacco smoke (ETS)

Environmental tobacco exposure (ETS) is well recognized to increase the risk for asthma in early life. A meta-analysis of 79 papers evaluating ETS and asthma grouped studies by type and timing of ETS (prenatal maternal, postnatal maternal, postnatal paternal, or household) and the age at which outcomes were measured (≤ 2, 3–4, or 5–18 years) [59]. Both prenatal and postnatal maternal smoking significantly increased the incidence of asthma at all ages (OR 1.18–1.70). Paternal smoking was also associated with a significantly increased odds of asthma in 5–18 year olds (OR 1.39); limited data precluded analysis in children less than five.

5.7. 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 [60]. Living in specific locations with especially poor air quality such as near a highway confers a higher exposure risk. 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 climate change is also responsible for altered exposure to aeroallergens. Global warming has been incriminated in increasing the duration and intensity of the pollen season [61]. Pollutants also enhance early and delayed-phase responses to various allergens, and contribute to disease development through augmentation of primary sensitization to allergens. This increased exposure to allergens combined with pollutants acts synergistically to enhance the allergic response. Data from the National Allergen Bureau has shown significant recent increases in annual pollen exposures [62], which has been linked with pollutant induced production of plant-based pathogenic allergens [63]. There is also accumulating evidence about the possible effects of diesel exhaust particles, not just as a direct lung irritant but in relation to sensitization.

Children who live near major roadways and exposed to traffic-related air pollution have increased susceptibility to asthma. A recent study has shown that exposure to air ozone levels at sub-NAAQS thresholds is associated with pulmonary and systemic changes in African American adolescents with asthma [64]. In general, the burden of air pollution related asthma is associated with a lower socioeconomic status, and is thus a health equity issue [65]. Holistic strategies to minimize the effects of air pollutants on health are thus imperative.

5.8. Adult onset asthma

As opposed to pediatric asthma, there is a conspicuous absence of longitudinal studies on the adult side that track disease course from early adulthood for an adequate duration. However, there are well recognized risk factors for disease onset as well as exacerbation.

5.9. Smoking

It is clear that asthmatics who smoke have significantly increased morbidity and mortality than non-smokers. Continued smoking itself predisposes to developing asthma with an odds ratio of 2.0–2.6 [66] and has been linked with accelerated loss of lung function over time in adult onset asthma [67]. 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 [3].

A new diagnosis - asthma-COPD overlap syndrome (ACOS) - is now

used to classify those with clinical features of both entities, such as COPD patients with airway eosinophilia and asthmatic smokers with fixed obstruction or neutrophilic inflammation. Approximately 13% of 3500 patients in the COPD gene consortium met criteria for ACOS [68]. The proportion of patients with ACOS is expected to be even higher in an asthma population due to concomitant smoking and those with fixed airway obstruction.

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 [70]. Similarly, smoking e-cigarettes during pregnancy has equivalent risk to conventional cigarettes for asthma development [71]. Thus, cessation of all forms of smoking is essential to the management of asthmatics.

5.10. Obesity

Obesity increases the risk for late onset asthma in both men and women by approximately 50% [72], 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 [73].

There appears to be a gender bias in the interaction of obesity with asthma, which may be due to sex hormones (discussed later) or other gender-specific factors, such as inherent collapsibility of the distal airways in non-allergic obese females with adult-onset asthma [74]. This gender dimorphism is apparent from early childhood, where asthma has been linked with obesity only in young girls and not in boys [73]. Both the European Network For Understanding Mechanisms of Severe Asthma (ENFUMOSA) and Severe Asthma Research Program (SARP) found a higher female to male ratio (4.4:1) in severe asthma [75,76].

Several hypotheses have been postulated to explain the obesity-asthma relationship, such as oxidative stress and mechanical effects of obesity on the respiratory system [73]. Increased airway oxidative stress has been found especially in obese adults with late onset disease. The deficiency of dietary antioxidants further increases susceptibility to oxidative lung damage. Abdominal and mediastinal fat accumulation can alter respiratory mechanics, thus changing lung physiology and function.

The most recently proposed theory implicates inflammatory mechanisms including the effects of adipokines and inflammatory cytokines released from adipose tissue [75]. Adipokines are mediators that may be pro- (eg. leptin) or anti-inflammatory (eg. adiponectin) in function. Leptin has been implicated in the pathogenesis of asthma in obese females through Th1 mediated airway inflammation [77]. Among adolescents, higher leptin levels correlate inversely with lung function and the expression of visceral fat leptin correlates with airway hyperreactivity in adults. While the mechanisms of obesity related asthma are not fully understood, weight reduction interventions may improve asthma control.

The metabolic consequences of obesity including insulin resistance, type 2 diabetes, and the metabolic syndrome likely contribute significantly to the pathogenesis of “obese asthma” [78]. The association between obesity and asthma is even greater in the setting of insulin resistance [79]. Insulin resistance has also been linked with lower lung function among obese adolescents with asthma [80]. The literature also suggests a bidirectional relationship independent of obesity between T2DM and asthma.

5.11. 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 [81]. Occupational asthma (OA) may be caused by high molecular weight (HMW) proteins or low molecular weight (LMW) chemicals (eg. diisocyanates), which drive asthma via IgE and non-IgE mechanisms respectively. HMW factors from biological sources such as wheat allergens account for most cases of OA. In a recent review by Baur et al., exposure to laboratory animals was most robustly associated with development of OA [82]. 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.

5.12. Sex hormones

As previously discussed, gender is known to be differently distributed between adult and pediatric populations. In the Epidemiology and Natural history of asthma: Outcomes and treatment Regimens (TENOR) severe asthma cohort, 71% of adult patients were women in contrast with 34% of children. This parallels the observations of Zein et al. who noted a shift from male to female predominance of severe asthma post-adolescence [83]. 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 [84]. The Childhood Asthma Management Program (CAMP) study showed an increase in asthma symptoms parallel with the Tanner stages of puberty in girls [85]. 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 [86].

5.13. Stress events

The association of psychosocial stressors with asthma may reflect disproportionate exposure among those from lower socioeconomic classes and ethnic minorities. An accumulating body of evidence suggests a causal relationship between these stressors and asthma development as well as morbidity. Stress can modulate lung development, as well neuroendocrine and autonomic responses, and potentiate reactivity to allergens and infections [87]. There also appear to be specific pathways through which stress influences epigenetic activity in asthma related cells.

Pediatric studies have previously reproduced a causal link between stress events and asthma onset [87]. More recently, observational studies have confirmed this association in adults. In a longitudinal cohort study of 327 adolescents without asthma at age 16, an increase in stressful life events as measured by a validated questionnaire was associated with a 4-fold higher incidence of new asthma onset between 18 and 29 years [88]. Elucidation of these mechanisms may improve asthma outcomes particularly in ethnic minorities and the economically disadvantaged.

5.14. Very late onset asthma

The age cutoff for the definition of very late-onset asthma varies but diagnosed as > 50 years in some papers [89] and > 65 years in others [90]. The aging lung is associated with decreased lung function due to mechanical disadvantages and loss of elastic recoil. In addition to these consequences of normal aging, immunosenescence likely has important consequences in elderly asthmatics [91]. Emerging data suggest that older asthmatics have increased sputum neutrophilia secondary to Th1 and Th17 inflammation [92].

5.15. 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 [93]. 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.

6. 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.

Conflict of interest statement

None.

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