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Review article on epidemiology, etiology and risk factors, phenotypes, diagnosis and treatment of asthma.

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ABSTRACT:

All age groups are impacted by the clinical illness known as asthma. The last several years have seen a sharp rise in the prevalence of asthma worldwide. According to recent data, the prevalence of asthma has continued to rise in some parts of the world, but it has plateaued and even declined in others. Numerous risk factors have been linked to asthma, and variations in these risk factors' distributions may account for variations in prevalence. In this we aim to provide a comprehensive review on epidemiology of asthma, etiology and risk factors, asthma phenotypes, diagnoses and treatment.

KEYWORDS: Epidemiology of asthma, prevalence, COPD, WHO, Hygiene hypothesis, aeroallergens, endotypes, wheezing.

INTRODUCTION:

Asthma is a chronic inflammatory lung disease that can lead to recurrent bouts of coughing, wheezing, and trouble breathing.

The lung's airway lining swells and becomes irritated during an acute asthma attack. Moreover, the muscles around the airway spasm and the airway itself produce mucus. When combined, this results in less airflow.

Asthma symptoms include:

• Inflammation of the airways: The lining of the airway's swells, narrows, and turns red.

• Airway obstruction: When the muscles around the airway contract, the airway narrows, and it becomes more difficult for air to enter and exit the lungs.

• Hyperresponsiveness of the airways: The muscles surrounding the airways react more forcefully and rapidly to a minor number of allergens and irritants.

One of the most prevalent major non-communicable diseases, asthma significantly lowers quality of life for many people. By disability-adjusted life years, asthma ranks 16th globally among the primary causes of years lived with disability and 28th among the leading causes of disease burden. Asthma affects over 300 million individuals globally, and by 2025, another 100 million people could probably be impacted. The prevalence, severity, and mortality of asthma vary greatly between regions. Although the prevalence of asthma is higher in high-income nations, low- and middle-income nations account for most asthma-related deaths.

The available data points to asthma as a complex multifactorial illness, with host variables, environmental exposures, and genetic predisposition all playing a role in its etiology. These include host variables (obesity, nutritional deficiencies, infections, allergic sensitization), environmental factors (pollens, mold and other aeroallergens, weather), and genetic factors (genes linked to asthma susceptibility loci). The fundamental processes of asthma remain incompletely known; however, they might involve modulating airway responsiveness and inflammation. Furthermore, it is increasingly understood that asthma may be a collection of diverse phenotypes with varying etiologies and prognoses rather than a single illness (1).

EPIDEMIOLOGY:

Collecting information of the epidemiology, prevalence, pathophysiology, and etiology of asthma, as well as the similarities and differences definition study-base between asthma in children and adults, have a huge difference. Nevertheless, the study employed in large population and less population-based studies are made more complex by variance in asthma (2).

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. Even though some of these definitions can seem to be almost identical, the variety in how the primary outcome is defined might significantly affect the projected prevalence and risk variables. For instance, the study mentioned above demonstrates that, overall, there was only a relatively low 61% agreement between four seemingly very similar and widely used definitions, and that, depending on the definition, more than a third of the children in the study could be classified as "controls" or "asthma cases" (3). When understanding the findings of asthma epidemiology meta-analyses, these distinctions must be considered.

While certain epidemiological definitions are more specific and sensitive than others, both situations can result in the incorrect designation of an asthmatic's state. As an illustration, definition of epidemiology it is the distribution and determinant of health-related issue like asthma (4). Therefore, compared to clinical criteria, which may also include objective measurements such the co-presence of bronchial hyperreactivity, survey definitions that embrace wheezy breathing effectively estimate higher prevalence of asthma (5).

It's also critical to take the participants' ages into account. wheezing may represent the early stages of asthma in many cases. However, it can be challenging to distinguish between the onset of true asthma in young children and transient wheezing caused by viral infections, especially for early childhood cohort studies. Retrospective recall usually misclassifies recurrent childhood asthma as late-onset asthma and preferentially favors those with more severe childhood disease (6). For adults, prospectively gathered data on childhood asthma status can limit the possibility of recall bias. It may be challenging to distinguish an asthma diagnosis in elderly patients at risk for co-morbidity from other conditions that cause dyspnea, such as chronic obstructive pulmonary disease (COPD), and heart failure.

Given the growing consensus in the research community that "asthma" is an umbrella term for several diseases with similar clinical manifestations but distinct underlying pathophysiological mechanisms (7), often referred to as "asthma endotypes" (8,9), a unified definition of asthma may not be desirable. Asthma symptoms, such coughing or wheezing, and objective measurements, like lung

function and biomarkers in blood, exhaled air, sputum, and/or urine, should be considered observable characteristics, or "phenotypes," in this context (10,11). It is crucial to remember, though, that while distinct phenotypes in different patients may arise from the same underlying mechanism, different mechanisms may give birth to similar or nearly identical observable features (12).

The framework of asthma endotypes is still only a theoretical idea as of right now (8), but it could also be useful in creating precise definitions of the condition to aid in the further investigation of its underlying mechanisms. The term "asthma" should be completely banned due to the growing interest in endotypes. Nevertheless, the term "asthma" offers a useful and functional framework for scientists to investigate mechanisms and for clinicians to manage patients. Therefore, before eliminating the term, we must first suggest more meaningful and useful terminology, which can only be achieved by developing a deeper understanding of asthma endotypes.

According to estimates from the World Health Organization (WHO), asthma affects 300 million people globally, posing a serious risk to health and negatively impacting everyday activities and quality of life. In 2009, this illness claimed the lives of 250,000 individuals in low- and middle-income nations. In addition, asthma is the most common chronic respiratory illness affecting children globally, and its incidence is rising. According to estimates from the Centers for Disease Control and Prevention (CDC), the number of Americans suffering with asthma has increased significantly by 12.3% since 2001. Asthma affected 24.6 million individuals in 2009, up from 20.3 million at the start of the decade, according to statistical data. The cost of medical bills and missed productivity because of this rise is $56 billion to society. However, no convincing reason for this rise in prevalence has been found, particularly considering the overall decline in smoking and secondhand smoke exposure that has resulted

from the enactment of smoking bans. Outside the US, the same circumstances are reported. Asthma prevalence increased in the UK between 1955 and 2004, according to Anderson and colleagues' metanalysis of data from routine statistics and demographic surveys.

The reasons why some people get asthma and others do not, as well as the reasons why asthma has become a public health concern in certain groups earlier than in others, remain poorly understood despite a huge number of research investigations. Focusing on the epidemiology of asthma presents a major challenge in attempting to harmonize the extensive findings of several epidemiologic research conducted across the globe by addressing an appropriate operational definition. The results focus on asthma symptoms and their highly subjective representations because it is necessary to come up with a concrete and workable definition of asthma for use in large-scale questionnaire-based epidemiologic research.

When conducting questionnaire surveys, the presence of asthma is frequently determined by answering questions about recent episodes of wheezing, "wheeze ever," and a doctor's diagnosis of the condition. Although this method has demonstrated high short-term repeatability, it may not be as specific, especially when applied to younger patients, as other causes of wheezing sickness, such as viral infections, may be mistakenly identified as asthma. When focusing on symptoms, the most typical clinical presentation is coughing, chest tightness, wheezing, and dyspnea, especially throughout the night, along with periods of asymptomatic breathing. The introduction of critical patient education programs and the pharmacological treatment of asthma symptoms may be delayed due to the Non specificity and diversity inherent in individual perceptions of respiratory trouble. Individual differences in clinical manifestations mean that a significant exacerbation of asthma requiring immediate medical attention may not be identified at first, which could result in a delay in receiving necessary treatment and a worsening of the condition.

The prevalence rates of asthma that are reported vary greatly. Even though epidemiologic data are hard to agree upon, multiple studies have demonstrated that the prevalence of asthma is rising globally, affecting 7% to 10% of the population at minimum. The noteworthy variations in worldwide rates reported in current research are a result of data collected using nonstandard approaches (questionnaires versus definition agreement) in most epidemiologic studies to evaluate asthma prevalence.

In contrast to statistics published for Western populations, this discovery has little bearing on the geographic distribution of asthma, for which rates remain relatively low in many rural areas. In industrialized nations, pollution preys silently on vulnerable respiratory systems, causing asthma in those who already have specific respiratory conditions. A "hygiene hypothesis" has been put up to explain why children are more likely to acquire asthma, a condition that may be related to early life exposure to fewer microbes. (13)

ETIOLOGY AND RISK FACTOR:

Asthma is associated with its own genesis, presentation, and pathophysiology. There are three types of asthma phenotypes that are known to have risk factors: host, environmental, and genetic. Despite being widespread, a family history of asthma does not guarantee the development of asthma. (14) The idea that environmental changes are a major contributing factor to the current asthma epidemic is supported by the significant increases in the incidence of asthma over the previous few decades. Furthermore, the relevant risk factors for asthma may vary over time, and environmental triggers may impact a person differently depending on when in their life they experience them.

Studies examining risk variables conducted over short periods of time may indicate a lower probability of asthma, while longer-term follow-up may link the same factors to a higher risk. This pattern might be related to the overlap of several early childhood wheeze phenotypes, only some of which develop into asthma in later childhood and adulthood. This phenomenon leads us to investigate the risk factors for chronic asthma at several life stages, including pregnancy, infancy, childhood, and, in a nutshell, adulthood. (15)

Parent risk factor:

Prenatal risk factors are complex and multifaceted. The range of wheezing diseases that can arise in childhood and infancy, only some of which progress to classical asthma, complicates assessment. (16,17)

Additionally, there is a correlation between pregnant mothers who smoke and higher chances of food allergies, cytokine responses in the cord blood, and nitric oxide concentrations in the breathed air of newborns. (18) Research has demonstrated the unmistakable effects of smoking during pregnancy; the effects are amplified when postnatal smoke exposure is included.

Diet and Nutrition:

Foods high in antioxidants like vitamin E and zinc, as well as foods with anti-inflammatory qualities like omega-3 fatty acids, have been the focus of observational studies looking at prenatal nutrition levels or dietary interventions and the later development of atopic disease. Higher prenatal fish or fish oil consumption has been linked to a lower risk of atopic disease (eczema and atopic wheezing, in particular) up to age six, according to several studies. (19-21)

Early wheezing is linked to respiratory infections in children, but it's not known if infections on their own contribute to the development of chronic asthma. Persistent wheeze may be caused by a severe viral illness, such as respiratory syncytial virus (23) however other research has found no connection. (24) Daycare attendance is linked to a higher prevalence of early wheeze but a lower incidence of persistent wheeze and is thought to serve as a proxy for viral infections. (25)

Exposure to Animal:

Studies on the effects of early exposure to farm animals have shown a decreased risk of developing asthma and atopy, but results regarding the effects of early exposure to domestic cats and dogs have been conflicting.(26,27) According to certain research, there is a higher chance of allergy sensitization when exposed to cats.(28) Being around dogs may help prevent the development of particular sensitization to the dog allergen (28,29), as well as other sensitizations (such dust mites in the home) and asthma.

Occupational exposure:

Workplace asthma is frequently caused by common, frequently underdiagnosed asthma Gen or sensitizing agent exposures. Work-aggravated/exacerbated asthma (WEA), which affects people with pre-existing asthma, and occupational asthma (OA), which affects those without a history of asthma, are the two separate subtypes of WRA. Generally, OA is divided into two categories: occupational asthma caused by irritants (10%) and immunoglobulin (Ig)-E-mediated or sensitizer-induced OA (90%) (140). An objective diagnosis of asthma with symptoms temporally connected to the patient's place of employment is necessary for the diagnosis of WRA (15).

Food:

Food allergies and asthma have long been contentious issues, making it challenging to establish their connection in young patients. According to the parents' observations, the children appear to do well when the alleged food allergy is avoided. Based only on historical data, our poll revealed that 19.75% of children appear to have asthma connected to food, according to their parents. I suspected grapes (57%), bananas (53%), guavas (51%), citrus fruits (28%), ice cream (21.5%), fried meals (19%), tomatoes (12.5%), and other food items that are suspected to be less common. These are the most implicated food items. Aeroallergens: Research indicates that as kids become older, they become more susceptible to indoor allergies. Research has indicated that when children get older in an indoor environment, they become more susceptible to allergies. Research has additionally demonstrated that sensitivity, which is 1.5% at age I, rises to 90% at age 8–11. The house dust mite is the main indoor allergen. For sensitivity to occur, 100 mites are needed per gram of dust, and for wheeze, 500 mites per gram of dust. During the most humid months, there are 4-5 thousand dust mites per gram of dust in Bangalore households. (30) Dust mites are the cause of 50% of chronic asthma cases) 7 In youngsters older than six years old, skin testing for mold and pollen sensitivity revealed only 7.5%. In Bangalore, cockroach sensitivity was found in 25% of cases. e. irritants: For six percent of youngsters, the triggers include cooking smells, smoke, sprays, and burning mosquito coils. According to a study by Cherian E, children between the ages of 10 and 17 smoked their first cigarette in 41.4% of urban children and 21.86% of rural children. Women who frequent clubs had a higher smoking rate (36.2%) than women from the rural agricultural labor class (2%), who view smoking as a status symbol. About 6 Asthma is triggered by cigarette smoke, which has been observed to cause an increase in cases from 6% in 1994 to 7.5% in 1999. We are grateful for the laws that forbid smoking tobacco in public areas. (31)

ASTHMA PHENOTYPES:

It was long believed that there were two main varieties of asthma: atopic or "extrinsic" asthma and non-atopic or "intrinsic" asthma. Early-onset atopic asthma is more common in childhood and early adulthood; later age groups are more likely to have non-atopic asthma after that. A hypothesis-based method was used to create additional asthma phenotypes, which included factors such as disease severity, symptom triggers, age at beginning, inflammatory patterns, exacerbations, and airflow obstruction, and categorized patients into broad categories based on a single variable (32,33). This approach had a significant drawback in that several of the categories overlapped and were unable to differentiate between the groups.

On the other hand, the most recent methods have employed a systems biology paradigm that reduces the impact of preexisting notions. To explain and forecast clinical phenotypes as well as the molecular mechanisms underlying asthma, these cluster studies have employed algorithms that incorporate the impact of numerous interacting components in sizable cohorts and some Program (SARP) (34-36). Even though clusters differed, there was agreement on certain subgroups. T2-high and non-T2-high groups are the two main categories they belong to. (37) However, the latest techniques have used a systems biology perspective, which lessens the influence of previous ideas. These cluster studies have used algorithms that consider the influence of multiple interacting factors in large cohorts to explain and predict clinical phenotypes as well as the molecular pathways driving asthma. These include the Airways Disease Endo typing for Personalized Therapeutics (ADEPT) (35), the Severe Asthma Research Program (SARP) (36), and the Unbiased Biomarkers for the Prediction of Respiratory Disease Outcome (U-BIOPRED) (34). Although there were differences among the clusters, there was consensus for several subgroups. They fall into two basic categories: T2-high and non-T2-high. (37).

FUTURE DIRECTION IN PHENOTYPING:

Distinctive from conventional hypothesis-based methods of phenotyping asthma, the use of cluster analysis in asthma has garnered growing interest. The "-omics" approach, which refers to a sizable dataset generated from a single sample, is used to carry out this study to shed light on previously unknown molecular host-environment interactions and disease causes. For asthma, reports of minimally invasive analytical methods using blood, sputum, or bronchial brushings have been made. To discover asthma phenotypes, several datasets use clustering algorithms to analyze the behavior of several clinical parameters (such as blood eosinophils, lung function, BMI, ACQ, atopy, and demographics) in large cohorts. The Severe Asthma Research Program (SARP) is also among one of those research programmed (36). (34). These cutting-edge "-omics" technologies employ a heuristic approach that eschews imposing preconceived notions and permits latent phenotypes to emerge from the data. Thus, this method removes investigator prejudice and encourages the development of new paradigms.

DIAGNOSE:

Asthma diagnosis needs objective demonstration of variable airflow restriction in addition to a history or current presence of respiratory signs and symptoms associated with asthma. Variable airflow obstruction refers to an obstruction that varies with time, therapy, and exposure to asthma triggers. It does not always signify that the blockage is present. When a patient has a normal history of asthma and responds well to treatment, the diagnosis of asthma is supported. (39). However, objective confirmation of the fluctuating airflow obstruction characteristic of asthma by peak expiratory flow monitoring or spirometry is necessary, particularly for patients whose symptoms do not strongly imply asthma and whose response to treatment is unsatisfactory. (40-43)

For all patients, spirometry is advised to confirm the diagnosis of asthma prior to starting potentially lifelong medication. Because of the broad range of projected values for peak flow rates, this type of objective testing is chosen over peak flow measurement. As a result, a diagnosis based on peak flow monitoring, or a therapeutic trial is less accurate. Unfortunately, a lot of medical professionals diagnose asthma without objective testing to support the diagnosis. As a result, misdiagnosis and improper treatment—especially overtreatment—are frequent. (44,45).

Although it can be done well in primary care clinics as well, pulmonary function laboratories are where spirometry is most frequently performed. (46) In comparison to laboratory-based spirometry equipment, portable hand-held spirometers facilitate screening for blockage (47) and may be more convenient to use for this purpose. Spirometry performed outside of the office may take longer, which makes it less appealing to patients. Additionally, because feedback is delayed, it may not be as appealing to doctors as spirometry performed in general care and specialty settings (48-51). Spirometry must be carried out in accordance with the correct protocols, no matter where it is done. Following manufacture, all spirometers should be calibrated on a regular basis and standardized (53-56).

The maximum amount of air that can be exhaled (FVC) and the forced vital capacity (FEV1), from which the FEV1/FVC ratio can be computed, are measured by spirometry. The patient is told to inhale as deeply as they can, to close their lips around the spirometer's mouthpiece, and to exhale as quickly and completely as they can. This needs to be completed consistently and with all you might. (57)

TREATMENT:

Bronchodilator Therapy

When treating acute asthma, the goal of bronchodilator therapy is to undo any bronchial smooth muscle spasm, buying time until the corticosteroid's anti-inflammatory effects take effect, which usually takes six to twelve hours. It is essential to attain a maximal or nearly maximum response with minimal systemic side effects given the severity of airway restriction. High dosages of inhaled β2-adrenoceptor agonists, such salbutamol, are commonly acknowledged as the first-line treatment for bronchodilators; nevertheless, the nebulizer's function in delivery has become more questionable. There is controversy around the role of intravenous salbutamol or aminophylline and the usage of supplemental bronchodilator therapy with inhaled anticholinergics.

Pharmacotherapy is still the mainstay of asthma treatment today. The two main classes of medications are bronchodilators, like SABA, which relax ASM and provide quick symptom relief, and control medicines, which limit inflammation and are represented by inhaled corticosteroids (ICS) (58). Additional biologic therapy can considerably lower severe acute exacerbations and ICS exposure when treating severe asthma (58). Additionally, when evaluating a patient with asthma, clinicians may consider treating other type 2 coexisting conditions such as allergic rhinitis, eczema/atopic dermatitis, urticaria, etc., as these conditions are linked to a higher risk of exacerbations and lower asthma control (59). Asthma onset and persistence are significantly influenced by the immune response of Th cells, and pharmacological therapies that target cytokines and pathways are continuously being developed. Pembrolizumab, dupilumab, mepolizumab, and other biologics that have received FDA approval are primarily indicated for "Type-2 high" asthma, which is characterized by severe eosinophilic asthma and/or asthma that is dependent on oral corticosteroids. The GINA pocket guide decision tree (60) has typical eligibility requirements for each category as well as indicators of a strong response. Patients in the ALLIANCE cohort showed a T2-high phenotype, which is typified by atopy and eosinophilia, across all age groups, with school-aged children and young adults having the highest prevalence of T2-high asthma. Patients with T2-high asthma can be detected at any age using readily available biomarkers. (61-62)

In clinical studies, astegolimab had a comparable result (63). Several clinical trials have yielded poor outcomes for other biologics that target Th1 or Th17. Since "Th1, Th17" are known to have important roles in "Type-2-low" asthma, a more thorough investigation of the pathogenic mechanism and the appropriate patient population selection based on the related clinical signs may result in a positive outcome. To find out which asthma phenotypes benefit most from biologics that target Th17 and Th1-related cytokines, larger research is required. Based on repeated injections or sublingual delivery of specific allergens to allergic patients to establish immunological tolerance, AIT is the only asthma treatment that modifies the condition and may even be preventive (64). Treg cells, which produce the cytokines TGF-β and IL-10 to suppress allergic inflammation, are the main players in the mechanism of AIT (64). AIT inhibits the expression of pro-inflammatory CXCL8, IL24, and CCL26 mRNA and reduces local airway inflammation (65). Furthermore, Th2 cells exposed to persistent allergens expressed high levels of CTLA-4 and PD-1, and the long-lasting effects of AIT treatment may be explained by the persistence of pro-allergic Th2 cells with a depleted phenotype throughout AIT (66). The production of allergen-specific IgG, IgG4 and IgA in serum, the suppression of local Th2/ILC2 cell numbers or the secretion of type 2 cytokines, the increase in Th1 cell, Treg or Bregs numbers, and the induction of a recently introduced anti-inflammatory mediator, secretoglobin 1A1, in the local environment are just a few of the biomarkers that have been identified as potential indicators of the clinical efficacy of AIT (65,67). Three sequential phases of AIT—an initiation, a conversion, and a tolerance mounting phase—were proposed by an intriguing study. According to this study, a potential decision point for treatment modification prior to long-term

treatment is the ratio of Th17 cells to IL-10 B-cells at the early starting phase, which correlated with symptom improvement after three years of treatment (68). AIT as a developing field of asthma care still needs to be understood. (69)

CONCLUTION:

Chronic asthma is a serious illness that can cause clinically significant morbidity, missed work or school days, high hospital and emergency room expenses, and occasionally even death. The current treatment for asthma helps manage the condition and may even stop patients with asthma from developing permanent airway abnormalities.

The incidence and prevalence of asthma have increased over the past two to three decades, according to numerous cross-sectional studies. However, there is still much to learn about the underlying immunologic, genetic, and environmental mechanisms that underlie the development of this condition and its increased expression, particularly in the developed world. However, a few risk variables have recently been consistently and unambiguously established. For example, refraining from smoking throughout pregnancy and the first few days after giving birth, as well as avoiding known occupational sensitizers, can be highly recommended. However, more recent research has cast doubt on the conventional wisdom that breastfeeding for the maximum amount of time and avoiding animals will lower the likelihood of developing asthma. Detailed investigations into epigenetics and gene-by-environment interactions will probably eventually sort out the contradictions between the numerous possible exposures and results. Even while there are signs that the rise in asthma cases has leveled off, at least in the most prevalent nations, there are still many unanswered questions regarding the epidemiology and risk factors associated with asthma. One of the main objectives of asthma care is risk reduction, which may potentially involve actual primary prevention of asthma.

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