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Asthma predisposing factors and comorbidities: Their influences on asthma control levels

Faiza Chairunisa [1,*], Arief Bakhtiar [2] and Purwo Sri Rejeki [3]

[1] *Bachelor of Medicine Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.*
[2] *Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.*
[3] *Department of Physiology and Medical Biochemistry, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.*

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Abstract

Asthma remains a concerning global health problem, interferes with the life of around 300 million people of all ages around the world, and results in approximately 1000 deaths each day. Its prevalence, exceptionally among children, is soaring in many countries with asthma-caused deaths mostly occur in low- to middle-income countries inflicting undesirable burden on healthcare systems. Ages, sexes, body mass index, socioeconomic status, allergic and smoking history are some of the associated predisposing factors. Some of the most frequently reported asthma-related comorbidities are rhinitis, obstructive sleep apnea, gastroesophageal reflux disease, psychopathologies, and hormonal disorders. The Global Initiative Health for Asthma through asthma control levels defines the extent to which asthma features can be observed. Poor symptom control, one of two domains in which asthma control can be assessed, escalates the risk of exacerbations. This review will break down asthma-related predisposing factors and comorbidities as well as discuss the potential correlations between predisposing factors, comorbidities, and asthma control levels. Uncovering this relationship can lead to ideal and novel preventative and therapeutic interventions. Nonetheless, interdisciplinary approaches are deemed essential in elucidating the full mechanisms of these interactions to be able to pursue high-precision and efficacious preventative and therapeutic strategies for asthma.

Keywords: Asthma control levels; Predisposing factors; Comorbidities; Literature review

1. Introduction

Asthma is a heterogenous respiratory disease generally associated with chronic airway inflammation and hyperresponsiveness [1]. Around 1 – 29% population of adults in various countries have experienced asthma symptoms [2]. Chest tightness, breath shortness, wheeze, and various cough along with variable limitation of expiratory airflow are some of the respiratory symptoms commonly define asthma. One or more of these symptoms can predominate [3]. GINA-defined asthma control levels have been widely used to observe and classify asthma features according to its control-based management, yet uncontrolled cases of asthma are still found in around 4% of the overall world population of people with asthma [4].

Estimated by the Global Asthma Report in their collaboration with the Global Burden of Disease, asthma has caused around 455 thousand deaths each year despite asthma-caused death considered preventable. By 2024, at least 300 million people worldwide have suffered from asthma with a higher prevalence in high-income countries. This number is predicted to increase by a hundred million in 2025 [1]. People with uncontrolled asthma are at a higher risk of exacerbations, hospitalizations, deaths including premature deaths, and—often times—poor quality of life [5]. Reported by GINA, asthma is ranked 24th as the leading cause of chronic disability and 34th as the leading cause of burden disease

* Corresponding author: Faiza Chairunisa

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measured by disability adjusted life years (DALYs). In maintaining asthma control levels, a standard control-based therapy needs to be provided in accordance with asthma management cycle, which includes assessment, both pharmacological and non-pharmacological treatment adjustment, and response review [3]. However, with the current significantly high prevalence of people with uncontrolled asthma despite the implementation of the respective management, a further explanation of the correlation between predisposing factors, comorbidities, and asthma control levels is required.

The pathogenesis of asthma is mainly driven by inflammatory components, where an airway inflammation occurs due to an abnormal accumulation of inflammatory cells in bronchioles. Asthma, also known as a condition of bronchial hyperactivity, is also associated with increased responsivity of the tracheobronchial to various stimuli including both singular and combined stimuli. This condition creates an increase of resistances during expiration, involving bronchospasms, airway inflammations, mucous edema and obstruction which further leads to air-trapping, increased dead spaces, and hyperinflation [6]. Though asthma exacerbations can happen as a repercussion of a single cause, it is more common that they come from a combination of causes resulting in induction of intricate inflammatory pathways and airway obstruction. Besides its direct repercussion, viral infection as a major precipitant can also synergize with allergen sensitization and link with atypical bacteria in inducing exacerbations [7]. Studies have shown that predisposing factors play a significant role in the manifestation of asthma exacerbations. Continuous smoking has been proven to trigger the development of asthma besides influencing the acceleration of lung function loss over time. Metabolic consequences of obesity including insulin resistance, type-2 diabetic, and metabolic syndrome tend to contribute in the pathogenesis of obese asthma. There is a higher number of airways hyperresponsiveness (AHR) in female during adulthood—a stark contrast compares to in childhood, where AHR is a more common occurrence in male [8]. Other predisposing factors expected to invoke asthma which among them are premature birth and prenatal stress, metabolic and immunity function, microbiome factors, allergen and pollutant exposure, ethnicity and socioeconomic status (SES), as well as airway infection [9]. Asthma can also be triggered by genetical factors; prenatal factors such as cigarette consumption, nutrition and dietary, stress, the use of antibiotics, and specific childbirth procedures for pregnant women; childhood factors such as asthma phenotype, breastfeeding, lung function, family structure, SES, the use of antibiotics, history of infection, allergic sensitivity, cigarette smoke exposure, animal exposure, genetic interaction with environment, sex and gender; as well as the risk of workplace exposure in adulthood which can lead to occupation asthma [10]. Even so, how exactly these factors along with comorbidities can correlate to asthma control levels remain unclear hence the necessity of a thorough observation and further explanation.

To answer the aforementioned problems, this literature review aims to extensively appraise the influences of predisposing factors and comorbidities on asthma control levels. It will thoroughly break down how major asthma predisposing factors including ages, sexes, body mass index, socioeconomic status, allergic and smoking history affect the manifestations and severity of asthma. In addition, it will also address the roles of comorbidities and control-based management in determining clinical outcomes. Furthermore, this review is expected to bring forth valuable insights as well as premises for future researches in the development and improvement of both preventative and therapeutic strategies through diagnostic and management for people with asthma.

2. Review content

2.1. Asthma

2.1.1. Definition and Classification

Asthma is a heterogenous obstructive respiratory tract disease caused by a reversible constriction. Once in a while, this reversibility may wear off, causing new constrictions to only disappear with the help of treatments [11]. Both environmental and genetic factors play major roles in the development of asthma. It is marked by a chronic inflammation of the respiratory tract, which causes hyperresponsivity of bronchial, remodelling of tissues, narrowing of lumens, and an excessive production of mucus—particularly due to the collaborative action of immune system cells and epithelial cells [12]. Asthma is followed with the presence of respiratory symptoms such as wheezing, shortness of breath, increased chest pressure, and/or coughs varying in intensity and over time. This variation of coughs can be triggered by several factors including exercise, exposure to allergens and irritants, changes in weather, or viral infections. These symptoms are often accompanied by various limitation of expiratory flow which is likely to become persistent over time [3].

Recent studies have highlighted on the heterogeneity of asthma, recognizing how the disease covers multiple phenotypes. These phenotypes act for distinct groups of the disease through certain characteristics and various expressions [13]. According to these phenotypes, GINA classifies asthma into allergic asthma, non-allergic asthma,

cough variant and cough predominant asthma, adult-onset (late-onset) asthma, asthma with persistent airflow limitation, and asthma with obesity. Moreover, as recommended by the Task Force American Thoracic Society/European Respiratory Society (ATS/ERS), asthma is levelled based on its severity into mild, moderate, and severe asthma. Mild asthma is defined as a condition where step 1 and 2 of asthma treatment, such as low-dose inhalers and controllers, are essential in sustaining asthma well-controlled. Moderate asthma refers to the necessity of step 3 treatment, such as low-dose ICS/LABA, to keep asthma well-controlled. Severe asthma requires step 4 and 5 which involve high dose asthma treatment in order to prevent asthma in becoming uncontrolled or resistant [1].

2.1.2. Epidemiology

In 2024, about 300 million people worldwide were affected by asthma. This prevalence has perpetually risen along the years, suggesting an expected increase by 100 million people in 2025 [1]. Epidemiological data showed that there was nearly a double in the number of asthma cases throughout decades [14]. Asthma has become the most chronic disease in children by affecting around 24% of this population as well as impacting approximately 19% of teenagers. Nearly 455 thousand deaths were caused by asthma [4]. There is a wide geographic variation in the prevalence, severity, and mortality caused by asthma. While asthma prevalence reached its highest number in high-income countries, most asthma-related deaths took place in middle- to low-income countries [15]. Albeit the number of hospitalizations and deaths caused by asthma have slumped in some countries, it still inflicts undesirable burden on healthcare systems as well as the society by causing loss of workplace productivity and a significant increase in treatment costs [1]. The financial burden caused by asthma surpassed the combination of tuberculosis and HIV/AIDS-related costs globally [16] However, solely 4.3% of asthma cases around the world were able to get diagnosed according to the World Health Survey (WHS) indicating that this disease remains underdiagnosed [17].

2.1.3. Physiology of Respiratory

The respiratory system consists of two main processes—external and internal respiration. Oxygen absorption and carbon dioxide discharge happen during the external respiration. The internal respiration comprises the usage of oxygen, carbon dioxide production by cells, along with gas exchange between cells and their liquid medium. Respiratory process involves organs including lungs in charge of gas exchange and some other “pumps” accommodating lungs in running their respiratory function. These pumps refer to chest cavity, respiratory muscles leading the expanding and deflating of chest cavity, area in brain which controls the movement of these muscles, as well as tractus and nerves connecting brain to muscles. After going through a process in which it gets warmed and evaporated in nasal passages and faring, inspired air goes through trachea, bronchioles, respiratory bronchioles, alveolar duct, and the alveoli for gas exchange [18].

2.1.4. Pathophysiology of Asthma

According to type 1, 2, and 17 major T helper (Th) classifications of immunity, pathophysiological mechanism of asthma comprises Th2-type immune responses, involving high concentrations of allergen-specific immunoglobulin E (IgE), eosinophilia, hyperreactivity, and remodeling of airway. These mechanisms are strongly associated with type I hypersensitivity reactions or also known as allergy and orchestrated by intracellular signaling of effector cells, including eosinophils and lymphocytes [19]. Asthma attack mainly caused by the stimulation of bronchospasm due to one of three mechanisms—IgE-involved cell mast degranulation; non-IgE-involved cell mast degranulation which triggers the release of a slow-acting anaphylactic substance called histamine and kinin causing bronchoconstriction; and a direct stimulation to bronchial muscle without the involvement of cell mast [11].

2.1.5. Management

The principle of asthma management aims to control the symptoms and reduce the risks of asthma. Controlling the symptoms means to be able to reach a certain symptom control level and maintain normal activities in asthmatic person. Reducing the risks of asthma is expected to lower the risk of exacerbations, persistent airflow limitation, or other side effects due to asthma treatment including asthma-related deaths. A control-based management is essential to adjusts therapies and is proven to improve outcomes on a population level by using the presence of asthma symptoms [1]. This management covers both pharmacological and non-pharmacological interventions in a continuous cycle of assessment, adjustment, and review of response. Assessment records the necessary confirmation of asthma diagnose, symptom control and modifiable risk factors such as lung function, comorbidities, inhaler technique and adherence, as well as patients and parents’ preferences or goals. Adjustment is required to treatment of modifiable risk factors and comorbidities, non-pharmacological strategies, asthma medications whether to adjust down or up, and education and skills training. The cycle settles with a review of symptoms, exacerbations, side-effects, lung function, and the satisfactory levels of patients and parents [3].

2.1.6. Comorbidities

Comorbidities in asthma may vary with disease severity and ages, due to asthma being a heterogenous disease with various phenotypes and clinical courses. Most frequently reported asthma-related comorbid conditions are rhinitis, sinusitis, hypertension, obstructive sleep apnea (OSA), gastroesophageal reflux disease (GERD), obesity, chronic obstructive pulmonary disease (COPD), hormonal and psychiatric disorders, respiratory infections, smoking or nicotine dependence, as well as hyperventilation for instance caused by glottic dysfunction. Although there is no apparent link with asthma, other conditions—among them are atopic dermatitis, allergic bronchopulmonary aspergillosis (ABPA), and bronchiectasis—have been found with a considerable high prevalence among people with asthma [20, 21]. A study also found that COPD, ischemic heart, and cerebrovascular disease have the strongest effect on asthma control. These comorbidities also increase the overall risk of uncontrolled asthma [17]. Adults with asthma significantly tend to have more comorbidities than the general population such as allergic rhinitis, respiratory infections, and high impact/high prevalence of chronic conditions (HIHPCCs) including depression. Albeit having a lower burden of comorbidities compares to adults, at least 12.6% of children with asthma are associated with chronic medical condition [22].

2.2. Asthma Predisposing Factors

2.2.1. Age

Study has shown that allergic asthma is at its peak during childhood and consistently decreases with age. However, the number of non-allergic asthma incidents tends to be low in this period before it reaches its peak in late adulthood. After the age of forty, asthma incidents are mostly dominated by non-allergic type [23]. Asthma in elderly shows a specific phenotype. It is also proven that ageing can influence asthma in terms of clinical characteristics, inflammation features, exacerbations, and responses to treatment. In adulthood, there is an important transformation of innate and adaptive immune responses, also known as immunosenescence. Ageing is also associated with increased chronic low-level systemic inflammation—inflammaging—which is recognized by the presence of increased IL-6 and TNF-alpha. Elderly asthmatic people also tend to have even more comorbidities, such as COPD, hypertension, diabetes, and osteoarthritis [24].

2.2.2. Sex

Asthma is a heterogeneous disease which prevalence and severity may differ among male and female with various age groups. During childhood, the prevalence of asthma in males tends to increase, whereas for females it tends to rise along with its severity during adulthood. In adult females, sex hormone levels fluctuation in puberty, menstruation cycle, and pregnancy are associated with asthma pathogenesis. Albeit the intricacy in determining gender and sex-specific asthma risks due to the potential for comorbidities, it is found that a complex and relevant role of sex hormone results in an increase of T2 inflammation. T2 asthma is known to be more prevalent during pro-androgenic period in both males and females—including in males who experience late puberty and females who experience luteal phase of perimenopause and post-menopause—with a tendency of asthma manifestations to worsen due to low level of androgen [25].

2.2.3. Body Mass Index (BMI)

Since the late 1990s, correlation between obesity and asthma have been reported. Several studies have shown that obesity or an increase in BMI is associated with new-onset asthma in women. Overweight in adolescence initiates asthma and bronchial hyperreactivity in girls. However, other researches claimed that obesity only significantly affects asthma in boys and children with no allergic history. It is also known to increase the risk of late-onset asthma in both men and women by around 50%. This condition specifically refers to those who do not have allergic history. Asthmatic people with obesity are also known to have worse asthma control [26].

2.2.4. Socioeconomic Status (SES)

SES is defined by a person's levels of economic and education. A worsening in asthma control and increased exacerbation rates commonly happen to people with asthma who live in remote or underdeveloped areas. This evident SES gap of people with asthma even widens in older population and minority ethnic groups [27]. Despite educational level was not independently associated with asthma, there was a statistically significant odds ratio for the observed asthma prevalence in people with economic hardships [28].

2.2.5. Allergic History

Allergic asthma, known as the most common asthma phenotype, is also defined as aeroallergen-induced asthma. This sensitization triggers asthma symptoms and inflammation of the respiratory tract. The onset of allergic asthma commonly occurs during childhood and is often accompanied by comorbidities, such as atopy dermatitis and allergic rhinitis (hay fever). This type of asthma can often be persistent, though its severity may vary [29].

2.2.6. Smoking History

Smoking for people with asthma is known to be able to significantly increase the rate of morbidity and mortality compares to those who do not smoke. The prevalence of active smoker in adults with asthma in low to middle-income countries has reached around 25%, increasing the risks of severe symptoms and decreasing the responsivity to steroid treatment. Over time, continuous smoking can lead to asthma development and is associated with accelerated loss of lung function in adult-onset asthma [8].

2.3. Asthma Control Levels

Asthma control levelling is a range in which with the help of these levels, manifestations in people with asthma can be observed, reduced, or entirely removed with treatments. It is determined by the interaction of genetic background, the underlying process of disease manifestation, on-going treatment, environment, along with psychosocial factors of people with asthma. Asthma control has two general principles of management, which are symptoms controlling and adverse outcomes risk alleviation. Furthermore, these levels divide asthma into three stages based on asthma control score from clinical visits of adults, teens, and children of age 6 – 11 years old with asthma according to GINA. Classification of these stages or symptom control levels of people with asthma is explained on the table below [3].

Table 1 Asthma Symptom Control [1]

In the past 4 weeks, has the patient had:			**Asthma Symptom Control**		
			Well controlled	**Partially controlled**	**Uncontrolled**
1.	Daytime asthma symptoms more than twice/week?	Yes/No	None of these	1 – 2 of these	3 – 4 of these
2.	Any night waking due to asthma	Yes/No			
3.	SABA* reliever for symptoms more than twice/week?	Yes/No			
4.	Any activity limitation due to asthma	Yes/No			

2.4. Correlation Between Predisposing Factors, Comorbidities, and Asthma Control Levels

In conformity with International Asthma Guidelines, the main purpose of asthma treatment is to achieve the optimum asthma control, which defined by its control level through symptom control assessments. Primarily, optimum asthma control is the main purpose of each level of asthma severity. Asthma control is known to be affected by a number of factors in which are also included in asthma predisposing factors along with diseases accompanying asthmatics condition or what is called as comorbidities. Studies have shown that middle-class economy tends to be associated with poor asthma control and high numbers of hospitalization due to asthma. It is also known that smokers have a higher frequency of experiencing disturbing asthma symptoms, asthma attacks, and higher asthma severity compares to those who do not smoke. Better knowledge in key relationship of factors affecting asthma control is expected to help determine preventive calculation targets efficiently [30].

3. Conclusion

In line with previous studies, asthma control levels in asthma management is critical in maintaining clinical outcomes, which can be affected by various aspects including asthma-related predisposing factors such as age, sex, BMI, socioeconomic status, allergic, and smoking history along with comorbidities. This review was able to highlight possible influences of aforementioned specific factors and comorbidities on the severity and incidents of asthma. Albeit it has been found that some of these variables do actually have direct effects of which can further reflects on asthma control levels, insignificancies were also spotted in some of them. This suggests that further multidisciplinary investigations into these complex relationships are integral to elucidate the mechanisms of these interactions, which in turn can result in higher precision and more efficacious preventative and therapeutic strategies for asthma.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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