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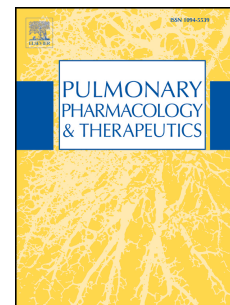
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Is Aging a Comorbidity of Asthma?

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Overview

The aging population is growing at an unparalleled rate. Asthma is common in the elderly (age over 65 years) and can be more severe with little chance for remission. Asthma in older individuals is often under-diagnosed, misdiagnosed and frequently under-treated. Concomitant medical and psychosocial conditions are more prevalent in the elderly and can obfuscate the presentation of asthma and make it more difficult to assess and manage. While these comorbidities are important in understanding elderly asthma, aging itself can be considered a "comorbidity" since it impacts structural and functional changes in the lung. Structural changes of the aging lung may worsen physiologic function in asthma. The immune system also changes with age, with increased vulnerability to pathogens and differences in airway inflammation, leading to variability in how asthma manifests and responds to treatment. The fact that aging can influence the severity and presentation of asthma along with its diagnosis and management is important for the treating physician to understand. This article will discuss the multitude of factors that justify considering aging as a comorbidity of asthma.

1. Epidemiology of Aging and Asthma

As of 2016, 8.5 percent of people worldwide (617 million) were aged 65 and older. That proportion is projected to increase to nearly 17% (1.6 billion) by 2050. This aging population is living longer with chronic diseases, including asthma. In the Global Burden of Disease update in 2017[1], asthma ranked number sixteen in highest causes of years lived with disability. Observational studies of asthma in the elderly estimate its prevalence to range from 4.5% to 12.7%[2-15].

Not only are people living longer with asthma, but also incident disease is increasingly recognized and diagnosed later in life. In a large French cohort of elderly adults, 23% were diagnosed after age 65[16]. Other population studies in multiple countries have demonstrated that asthma incidence increases with age[17-21].

Compared to other age groups, older asthmatics in the United States had the highest asthma-related death rate at 5.8 deaths per 10,000 persons with asthma[2]. In other age groups, the asthma mortality rate is decreasing, while in the elderly it has been constant over time[2].

2. The Effects of Aging on Lung Structure and Function Can Worsen Asthma

Aging influences all aspects of human biology and has predictable effects on lung structure and function [22]. Most age-related functional changes of the lung result from decreased compliance of the chest wall, decrease in static elastic recoil pressure, and reduced strength of respiratory muscles[23]. Approximately 30% of chest wall compliance is lost by age 75[24]. There is stiffening of the ribs[25], and calcification of cartilage, including costal and chondrosternal junctions, which contribute to chest wall rigidity[26]. Loss of bone mineral density leads to decreased vertebral body height and even fracture[27]. This results in kyphoscoliosis to varying degrees, with only 23% of healthy subjects age 75 to 93 years having normal curvature of the spine[26]. Kyphosis and increased convexity of the sternum may result in an increase in the anterior-posterior diameter of the chest. These changes in chest wall compliance result in a disruption in the normal mechanics of breathing.

In addition to skeletal changes, there are alterations in the collagen fiber network that coils around the alveolar ducts. The result is dilation of the ducts, enlargement of alveoli, decrease in alveolar surface tension and a more compliant lung[27, 28]. Increased lung compliance reduces elastic recoil which in turn affects expiratory flows and lung volumes. Healthy nonsmokers have a loss in forced expiratory volume in one second of approximately 30 milliliters per year beginning after age 30[27, 29] with a concomitant decrease in forced vital capacity. This decline accelerates after age 65[30], even more so in the presence of asthma[31]. The normal flow-volume curve for a healthy elderly individual appears more "obstructed" compared to that of his or her younger counterpart.

There is early airway closure due to both decreased lung elastic recoil and reduced chest wall compliance [23, 27, 32, 33]. This leads to an increase in residual volume and functional residual capacity, and this air trapping and hyperinflation contribute to the decreased curvature of the diaphragm[32], further impeding the operation of the aging lung. There are changes in the respiratory muscles themselves that occur with aging. Sarcopenia is the loss of muscle mass and function seen with aging and other processes, which is

thought due to reduced muscle protein synthesis, increased proteolysis, motor neuron loss, and increased muscle fat content[34]. There is an age-related reduction in maximal inspiratory and maximal expiratory pressures[35]. For example, a 50 year-old man of average height has a maximal inspiratory pressure of 111 cm H₂O, compared to 70 cm H₂O for a man aged 80[35]. This reduction in muscle strength is due to both impaired respiratory mechanics and sarcopenia.

Taken together, the decreased compliance of the thoracic skeleton, the decrease in elastic recoil of the lung and the decreased strength of the respiratory muscles that occur with aging, impact normal pulmonary mechanics and alter lung function. Loss of elastic recoil has also been reported in chronic asthma [36] along with the characteristic features of airway inflammation and remodeling. Combined with these pathophysiologic changes attributable to asthma itself, the aging process can lead to more severe disease and worse outcomes (Figure 1)[37].

Aging has been associated with increased bronchial reactivity in response to methacholine in some studies[38-40]. Smaller airway caliber due to altered airway mechanics may lead to an enhanced tendency toward bronchoconstriction[39]. A diminished bronchodilatory response to deep inspiration with aging may also be of mechanistic importance[41]. Given that asthma is associated with decreased airway caliber and with an impaired bronchodilatory response to deep inspiration, the elderly asthmatic might be particularly vulnerable to excessive airway narrowing and more severe asthma outcomes.

3. The Effects of Aging on Immune Function Can Impact Asthma

Immunosenescence refers to the decline in immune function seen with aging[42, 43] that affects innate, adaptive and humoral immunity. This can result in increased susceptibility to pathogens and manifests as more frequent infections[44]. There is also chronic, systemic inflammation termed "inflamm-aging" found in many older individuals that is characterized by increased serum IL-6, TNF- α [45] and is linked to increased mortality[46].

The ability to kill phagocytosed organisms is reduced in older individuals compared to younger[47], perhaps due to impaired reactive oxygen species production signaling[48]. Natural killer (NK) and natural killer T (NKT) cells play pivotal roles in pathogen clearance, particularly of viruses. The number and

function of NK and NKT cells are altered with aging[49, 50], suggesting the ability to clear viruses may be diminished. Involution of the thymus is complete by age 70[51], leading to a shift to memory T-cells and fewer circulating naïve T cells. There is less receptor diversity and a decline in T-helper cell activity[52]. In murine models, these changes lead to decreased response to antigen and decreased viral clearance[53]. B-cell populations, though unchanged in absolute numbers, decrease in diversity and quality[48]. In the setting of new antigen exposure, these changes may impact the ability to clear and protect against pathogens. Immunosenescence may thus affect the ability of older adults to clear viruses, leading to a more prolonged inflammatory state. Among elderly patients with asthma, viral infection was reported by 58% of patients as causing wheezing and other asthma symptoms, as compared to only 30% reporting animal allergies as the trigger[54]. Additionally, the diagnosis of asthma in the elderly is often preceded by upper respiratory symptoms, suggesting a role of viruses in the development of late-onset asthma[55] due to changes in immune function. Figure 2 delineates aspects of the relationship between immunosenescence and asthma.

There is an age-related increase in neutrophilia and CD4+ T cells in bronchoalveolar lavage fluid[56]. In older asthmatic subjects, the neutrophilia is associated with increased neutrophil mediators, such as matrix metalloproteinase-9 and neutrophil elastase, which are thought to play a role in neutrophil-predominant severe asthma[57, 58]. Thus there may be a role of increased airway neutrophilia with aging that contributes to asthma severity in the elderly and diminishes response to standard anti-inflammatory therapy.

While eosinophils are likely important in elderly asthma, age-related changes in eosinophil number and function independent of asthma are not well-understood. Mathur and colleagues[59] demonstrated decreased eosinophil degranulation in response to IL-5 stimulation in patients with asthma, aged 55-80 compared to patients aged 20-40[59]. Despite this apparent decline in eosinophil function, an elevated peripheral blood eosinophil count was associated with more chronic respiratory symptoms and airway hyperresponsiveness in men older than 60 who were enrolled in the Normative Aging study[60].

Total Immunoglobulin E (IgE) declines with age, peaking by age 20[61, 62] as demonstrated in cross-sectional, population-based studies. Among older individuals with asthma, lower total IgE levels, fewer positive skin prick tests, and less concomitant allergic rhinitis or atopic dermatitis are seen compared to a

younger cohort[63]. Nevertheless, 28%-74% of older patients with asthma are sensitized to at least one antigen[64, 65], and a history of atopy is the strongest predictor of asthma diagnosis in the elderly[66].

In summary, immunosenescence increases vulnerability to respiratory pathogens, alters the inflammatory milieu, and affects allergic response to antigen. Waning immunity in the elderly may be linked to late-onset asthma. In patients with pre-existing asthma, immunosenescence, may increase the risk of viral-related asthma exacerbations and may lead to more difficult-to-control disease.

4. Aging Affects Diagnosis of Asthma and Severity of Disease

Asthma in older individuals is often under-diagnosed or misdiagnosed. Whether aging should be considered a disease state or normal physiology is a long-standing debate[67]. Regardless of one's stance on this matter, with age come physiologic changes that influence asthma diagnosis and severity. There is less perception of bronchoconstriction induced by methacholine challenge testing, which may reflect decreased sensitivity to mechanoreceptors or chemoreceptors[32]. This decreased perception occurs even though elderly may be prone to increased bronchial responsiveness[39]. There is also decreased perception of spontaneous bronchoconstriction (i.e., related to environmental factors). Older individuals may adopt a sedentary lifestyle that contributes to underestimation of respiratory symptoms[68]. The "paradox of well-being" affects some elderly individuals and refers to the notion that despite age-related changes in circumstances, including health, one's subjective well-being remains the same. This can coexist with lower health expectations, and leads to delayed diagnosis and worse asthma outcomes[69]. These age-related changes in perception of symptoms suggest that the symptom-based diagnosis and management of asthma in the elderly may lead to under-diagnosis and under-treatment[16, 54].

Comorbid disease becomes more prevalent with age[70] and can delay asthma diagnosis, cause incident asthma[71], worsen asthma severity and even become part of the asthma phenotype. Congestive heart failure is a disease of predominantly older individuals that may masquerade as asthma but may also obscure its identification. Chronic obstructive pulmonary disease (COPD) and bronchiectasis can co-exist with asthma, are more common in the elderly, and can make asthma diagnosis and treatment more difficult. These lung diseases as well as gastro-esophageal reflux disease may contribute to exacerbations

and may worsen asthma severity[72]. Obesity affects more than one third of those over age 65[73]. It increases the risk of developing asthma and can lead to poor outcomes and exacerbations[74]. As in younger patients, chronic rhinosinusitis is associated with asthma in the elderly[75]. Sleep disordered breathing is more prevalent in elderly with asthma compared to younger patients[76] and age-matched controls[77]. Depression is common in older individuals and can mask or worsen symptoms particularly by reducing adherence to treatment[78, 79]. Because many of the co-morbidities of asthma are more prevalent with aging, older age itself may be considered an asthma co-morbidity.

Delayed diagnosis of asthma in the elderly may also occur because the health care provider does not have a high degree of suspicion for the disease in this population or does not order proper testing. Asthma is under-diagnosed in older persons even in the setting of reversible airflow obstruction on spirometry[72]. Pulmonary function testing is difficult to perform for some elderly individuals due to the need for repeated forced exhalations in the setting of fatigue or cognitive dysfunction. However, If appropriately screened, including for the ability to understand and participate in testing, up to 80% of older patients can successfully perform spirometry[80]. Reference values for spirometry have recently been improved and expanded to include a wider age range, though data remains sparse in individuals over age 80[81].

Adjunctive testing modalities can be used to support the diagnosis of asthma in the elderly. Exhaled nitric oxide (NO) levels help predict response to corticosteroids[82] but do not necessarily correlate with disease activity, symptoms, lung function, or exacerbations[83]. Exhaled NO levels increase with age in patients with asthma in some studies[84, 85], but exhaled NO is not used alone for diagnosis. The forced-oscillation technique is a diagnostic modality used to assess airway impedance in different regions of the lung. It can be used to assess bronchodilator response[86] and to identify distal airways disease[87]. This modality can be particularly useful in elderly populations because it is effort-independent and simply requires quiet breathing. However, the forced-oscillation technique is not yet widely available or accepted by most practitioners.

Asthma is often under-treated in the elderly[54, 72, 88] for a multitude of reasons including minimization of symptoms by the patient, misinterpretation of the symptoms by the provider, inability to properly use the therapy and concern for increased susceptibility to adverse effects. Elderly individuals are frequently not included in clinical trials, leading to limited data on safety and efficacy of novel therapies.

Anticholinergic medications may be particularly poorly tolerated, increasing the risk for falls, urinary outlet obstruction, and closed-angle glaucoma[89], though these side effects are not well-established for inhaled therapy. Aging patients are more prone to increased fracture risk, cataracts, and loss of bone mineral density with oral and even inhaled corticosteroid use[90, 91]. Beta agonists may be inappropriately withheld from the elderly asthmatic patient due to provider discomfort when the patient is concurrently receiving beta blockade for comorbid disease. Polypharmacy is more prevalent among older adults, and aging affects pharmacokinetics of other medications[92], in part due to occult renal[93] disease. Some elderly individuals receive sub-therapeutic doses of inhaled medication due to decreased muscle strength and loss of the coordination required to activate delivery devices. Due to perceived side effects and risks by both the patient and physician, fewer asthma medications may be prescribed than needed for effective disease control.

5. Conclusion

The aging population is burgeoning. Asthma is a common disease of older individuals, although it is often under-diagnosed, misdiagnosed and under-treated. The morbidity and mortality of asthma is increased in the elderly. Aging can be considered a “comorbidity” of asthma since the physiologic and immunologic changes imposed on the lung by the aging process combine with the features of asthma to produce a more severe disease phenotype (Table 1). Other lung diseases such as COPD and bronchiectasis are more prevalent in the elderly and can coexist with asthma, worsening symptoms and making management more difficult. Heart failure, GERD, obesity, sinus disease, and sleep-disordered breathing can all contribute to disease severity. In addition, depression and cognitive dysfunction can impact recognition of symptoms and adherence to treatment and can lead to delay in care. A greater understanding of the impact of aging on all aspects of asthma presentation and management is needed.

Figure Legend

Figure 1. The effects of normal aging on lung structure and function can compound the pathophysiologic changes of asthma to lead to more refractory disease. *Modified from Skloot. Annals of the American Thoracic Society. 2016.*

Figure 2. Cellular changes in the immune system with aging that decrease viral clearance may increase the risk for late-onset asthma and lead to asthma exacerbations.

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Table 1. Features of Normal Aging that Make it a Comorbidity of Asthma

Feature	Why it Worsens Asthma
Underestimation of symptoms Decreased symptom perception Paradox of well-being	Delayed diagnosis and under-treatment
Health care provider does not suspect asthma in elderly	Delayed diagnosis and under treatment
Elderly unable to perform pulmonary function testing	Under-diagnosis and treatment
Elderly individuals not included in asthma trials	Unknown optimal treatment of elderly
Increased susceptibility to medication side effects	Under treatment
Change in Lung Structure and Function Decreased compliance of chest wall Decrease in elastic recoil of lungs Reduced respiratory muscle strength	Compromised respiratory mechanics with decreased airflow and increased air trapping and hyperinflation
Immunosenescence Decreased clearance of pathogens Changes in airway cellularity and inflammation	Trigger for asthma exacerbations Possible diminished response to standard anti-inflammatory therapy
Comorbidities become more common with age	Delayed diagnosis, cause incident asthma or worsen asthma severity, impact phenotype

Figure 1.

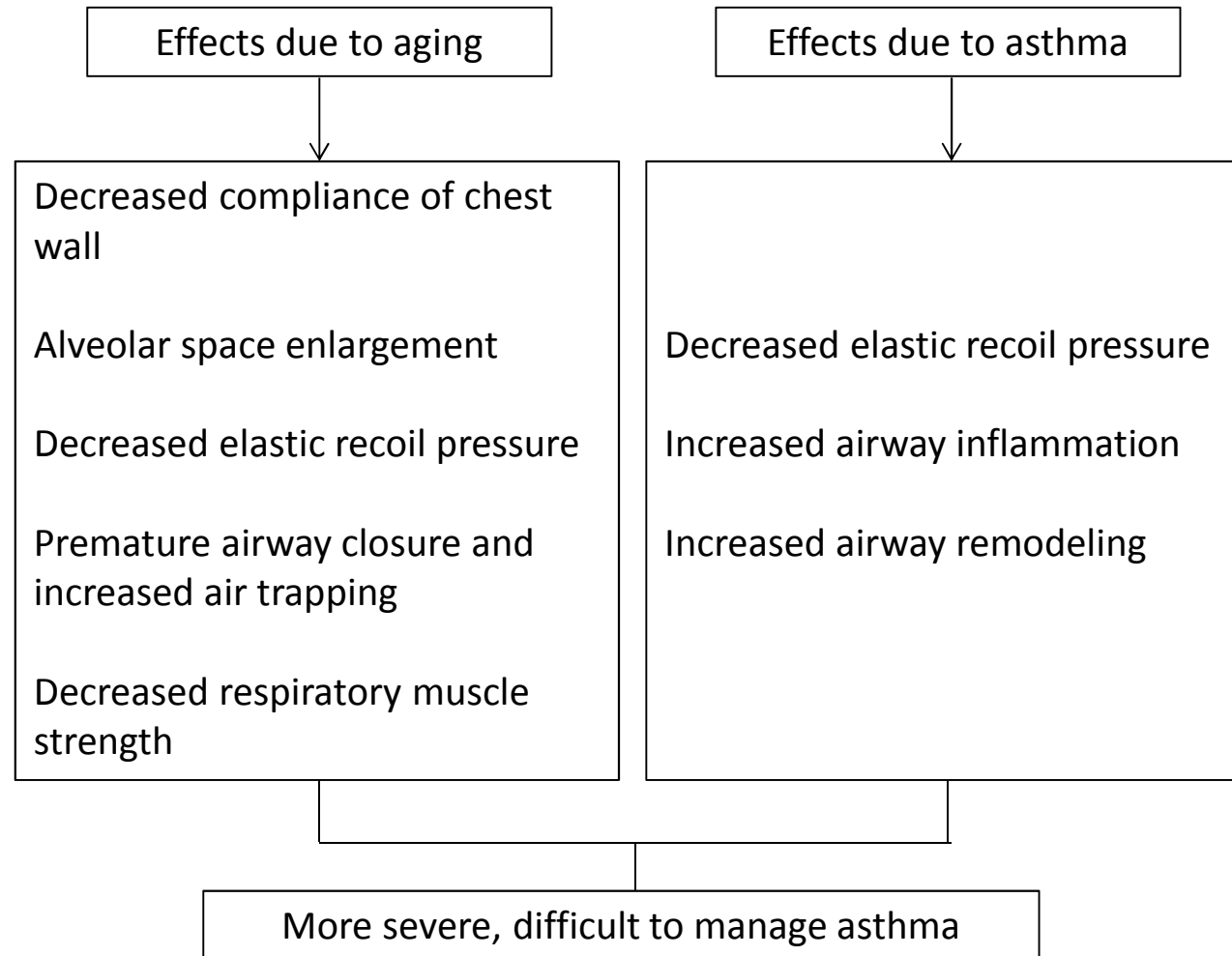


Figure 2.

