

Asthma Across the Ages: Adults



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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

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List of Design Committee Members: Paula J. Busse, MD, Vanessa M. McDonald, PhD, Juan P. Wisnivesky, MD, DrPH, and Peter G. Gibson, MBBS (authors); David A. Khan, MD (editor)

Learning objectives:

1. To describe how key life events (pregnancy, occupation) modify the expression of asthma.
2. To describe how comorbidities change the clinical expression of asthma.
3. To describe how treatment considerations are modified by life stage in adults with asthma.

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Asthma is a common disease affecting approximately 300 million people worldwide, across all age ranges. Despite advances in asthma outcomes of the last few decades, there remains room for

improvement in asthma management and for patient outcomes, particularly in older patients. The heterogeneity of asthma is now well recognized, and is known to complicate response to

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Abbreviations used

BHR- Bronchial hyperresponsiveness
BMI- Body mass index
COPD- Chronic obstructive pulmonary disease
CVD- Cardiovascular disease
EOA- Early-onset asthma
ICS- Inhaled corticosteroid
OR- Odds ratio
SARP- Severe Asthma Research Program
T- Type

treatment and patient behavior and impact health outcomes. Asthma and its heterogeneity change according to age. Asthma affects people differently across the life span. In adults, prevalence is highest among those in middle age; however, mortality is greater in the older age group. In this clinical commentary, we describe how age impacts asthma prevalence and incidence, outcomes, disease expression, and approach to management in adulthood and in older patients. © 2020 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;8:1828-38)

Key words: Asthma; Aging; Management

INTRODUCTION

Asthma is highly prevalent, and can affect people at all stages of life, from infancy through childhood and adulthood, and into older ages (>66 years old).^{1,2} Although asthma can cause a negative impact on a patient's quality of life through loss of work, interruption of daily life activities, emergency room visits and hospitalizations, and potentially death in some, in particular older patients, it is treatable.^{3,4} However, there are important differences in the underlying pathophysiology and consequently, presentation of asthma through younger (age 20–40 years) and middle (age 41–65 years) adulthood and in the aged (age >66 years, “older adults”) that must be recognized to decrease its associated morbidity and mortality (Table I). This article describes our understanding of how aging impacts the epidemiology of, exacerbation risk of, phenotypes of, and diagnostic approach to asthma. Key elements include modification of the host response by age, different exposures that might occur at different stages of life, and different comorbidities that may emerge and impact asthma at different ages. This article does not focus on the effect of aging on the response to asthma therapies, which is reviewed elsewhere.^{1,6}

EPIDEMIOLOGY

Prevalence

Asthma prevalence is highest in those aged 45 to 64 years (Figure 1).^{5,8} There are also significant differences in asthma prevalence with sex across ages. In Australia, among children (aged 0–14 years), the prevalence was higher for males than for females, but among those older than 15 years, current asthma was more prevalent in females (10.9%) than in males (8.9%). Among males, the highest prevalence was in those aged 5 to 9 years (15.1%; CI, 11.0%–19.3%), whereas among females it was highest in those older than 75 years (13.4%; CI, 10.3%–16.5%).⁵ These trends are similar across nations.^{1,8,9}

Incidence

Although asthma is often considered a disease of childhood onset, it can develop in adulthood, even after the age of 65 years.⁹ The incidence of asthma in adulthood over a 10-year period was evaluated using data from prospective cohorts, involving 8 countries across Europe, and a total population of 23,704 participants. In these studies, asthma incidence varied from 2.9/1000/y to 8.3/1000/y.^{10,11} The risks for new-onset adult asthma were (asymptomatic) bronchial hyperresponsiveness (BHR), allergic rhinitis (twice as common among participants with incident asthma compared with those without asthma), female sex, respiratory infections in early life, aspirin-exacerbated respiratory disease, high-risk occupations (less likely in those aged >65 years), environmental pollutants, stressful life events, and obesity.^{12,13} Although new-onset allergic sensitization precipitating asthma is more common in younger adults, it can occur in the aged.^{13–17}

Asthma remission in adulthood

Asthma can also go into remission in adult life. Westerhof et al¹⁸ reported that 1 in 6 patients with adult-onset asthma experience a remission of his or her asthma within the first 5 years of disease onset. The Respiratory Health in Northern Europe study reported an overall remission rate of 20.2 per 1000 person-years among adults aged 26 to 53 years, meaning that approximately 20% of people experienced a clinical remission of asthma during a 10-year period.¹⁹ Similarly, a Swedish study reported a 10-year remission rate of asthma of 14.6% among adults aged 20 to 69 years,²⁰ and Sozener et al²¹ reported remission in 11.3% of adults.

Younger age, younger age of asthma onset, atopy, allergic rhinitis, and fewer comorbidities are linked to a greater possibility of remission.²¹ Patients with asthma persistence tend to be older, have worse asthma control, require higher doses of inhaled corticosteroids (ICSs), have more severe BHR, higher frequency of nasal polyps, and higher levels of blood neutrophils as compared with patients who experience clinical remission. In patients with moderate to severe BHR and nasal polyposis, the chance of remission is close to 0.^{18,22,23}

ASTHMA MORBIDITY AND EXACERBATION RISK THROUGH THE AGES

Asthma morbidity/mortality through the ages

Older adults have high rates of asthma morbidity and mortality when compared with younger adults.^{3,4,8} Adults older than 65 years presenting to the emergency department for asthma had the highest rate of hospitalization (~25% admission rate compared with 7.9% for all ages) and the longest length of stay.^{3,4,8} These poorer outcomes in the aged are likely multifactorial and include alteration in lung structure, increased presence of comorbidities, cognition (discussed later), and alteration of inflammation with aging (discussed later).

Exacerbation risk across the ages

Asthma exacerbations are responsible for a significant disease burden across adult life. There are changes across the age spectrum in the rate and pattern of asthma exacerbations, with the highest rate seen in the oldest age group. In a large population-based study in the United Kingdom, the rate of exacerbations was highest in the oldest cohort and lowest in the 5 to 17 years cohort. The exacerbation rate per 10 person-years (95% CI) in

TABLE I. Impact of asthma risk factors across adulthood

Risk factors	Age (y)			
	20-40	41-65	66-75	>75
Airway caliber			Age-related airflow limitation confounds diagnosis Lung aging Reduced FEV ₁ response to treatment	Age-related airflow limitation confounds diagnosis Lung aging Reduced FEV ₁ response to treatment
Airway inflammation	T2 asthma is prevalent Neutrophilic asthma ~10%	Late-onset eosinophilic asthma develops Age-related increase in airway neutrophils	Inflammaging and reduced corticosteroid response Increase in airway neutrophils	Inflammaging and reduced corticosteroid response Increase in airway neutrophils
Triggers	Occupational exposures	Occupational exposures		
Comorbidities	Allergic rhinitis Obesity	Nasal polyps Obesity	Comorbidity prevalence increases Obesity	Comorbidity prevalence increases Obesity
Life events	Occupation relevant Pregnancy can worsen asthma Menstrual cycle and perimenstrual exacerbations	Occupation relevant Menopause: variable effects possible Menstrual cycle and perimenstrual exacerbations	Retirement*	Social isolation
Treatment			Reduced response to corticosteroids Medication polypharmacy—drug-drug interactions	Cognitive impairment limits inhaler device choice, and adherence Medication polypharmacy—drug-drug interactions
Self-management	Adherence	Adherence	Adherence Increased age-related factors affecting inhaler technique (Figure 2)	Adherence Increased age-related factors affecting inhaler technique (Figure 2) Cognitive impairment

*Retirement is expected to be associated with reduced occupational triggers, and retirees report reduced perception of asthma triggers.⁵

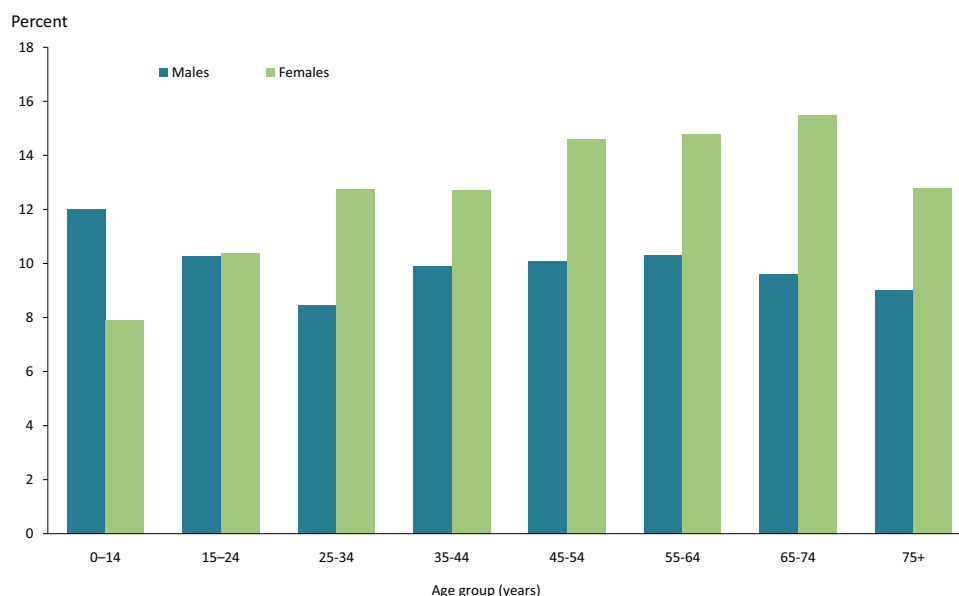


FIGURE 1. Prevalence of asthma, by age and sex (2017-2018). Refers to people who self-reported that they were diagnosed by a doctor or nurse as having asthma (current and long-term). From Australian Institute of Health and Welfare.⁷

adults aged 18 to 54 years was 3.22 (3.21-3.24), and in adults 55 years and older was 9.40 (9.37-9.42). Asthma severity was a common risk factor for asthma exacerbations across the different age ranges. The frequent-exacerbator phenotype was present in 2% of adults with asthma.^{24,25}

ASTHMA PHENOTYPES ACROSS ADULTHOOD

Data from large multicenter studies including the Severe Asthma Research Program (SARP) and the Leicester study (UK) have provided important insights into young and middle-aged adult asthma phenotypes.^{26,27} Although not designed to target older populations, these studies included some participants up to 80 years old. A smaller cross-sectional cluster study (Detroit, Mich) recruiting patients (mean age, 65.9 years) with asthma has also provided phenotypic data in the aged.²⁸ Despite differences in cohorts studied, methodology, and numbers of clusters identified, these studies have suggested that adult asthma can be broadly categorized into early-onset asthma (EOA) (generally before age 12 years) or adult-onset asthma.

Early-onset asthma

EOA is primarily differentiated into mild allergic and moderate to severe allergic EOA on the basis of lung function, dosage of controller medications, health care use for asthma, and the need for oral corticosteroid bursts.²⁹ Those subjects in SARP with milder disease were predominantly female and had a body mass index (BMI) of 23.6 to 28 kg/m².²⁶ These patients tended to have eosinophilic asthma, although the mild allergic UK cohort also had a higher sputum neutrophil count.²⁷ Data characterizing patients with moderate to severe EOA are less consistent. In SARP, the subjects were more likely to be black males with a slightly earlier age of asthma onset, and a higher BMI (31 kg/m²); despite a baseline FEV₁ of 57% predicted, they had good airway reversibility.²⁶ In the UK data, subjects were more likely to be female with a lower BMI (~27.6 kg/m²).²⁷ This group had higher sputum eosinophils than the milder EOA group.

The Detroit study identified 2 clusters of older patients with EOA, both with high rates of atopic sensitization (74% and 68%).²⁹ The first had a slightly younger age of asthma onset, a prebronchodilator FEV₁ of 69.8% predicted, with relatively high rates of fixed airway obstruction (45.7%) and poor disease control (Asthma Control Test score, 17.5). The second was more severe, with a prebronchodilator FEV₁ of 37.8% predicted, and even higher rates of fixed airway obstruction (72%) and poorer asthma control (Asthma Control Test score, 14.7). Importantly, asthma control in the overall population was low (Asthma Control Test score, 17.5).²⁹ Whether the 2 groups of EOA identified in the older population persist from those identified in younger adults requires further research.

Adult-onset asthma

Adult-onset asthma can be loosely subdivided into long-standing asthma developing in the late teens or early 20s, and later-onset asthma beginning after age 40 years. A consistent finding of adult-onset asthma is a lower rate of atopy, and a higher BMI and frequency of comorbidities compared with adults with EOA.¹⁶ In SARP, those developing asthma at age approximately 42 years were mainly females.²⁶ Despite a shorter asthma duration, they had high rates of health care utilization for asthma including oral corticosteroid bursts, which were out of proportion compared with their degree of airflow obstruction. In the UK study however, these subjects with later-onset asthma were more likely to be male and have a lower BMI (27 kg/m²), but they also had high uses of health care resources for asthma.²⁷ This cluster tends to be eosinophil predominant, with higher numbers than with EOA.³⁰ Amelink et al³⁰ also reported that in middle-age adult patients with late-onset asthma (age ~41 years), those with more severe disease had more nasal symptoms and nasal polyposis, higher blood neutrophil counts, and higher sputum eosinophilia than those with less severe disease.

The Detroit aging cohort identified 2 groups of adult-onset asthma, one with a later onset and the other with longer-standing disease.²⁹ The group with later onset (ie, shorter

duration of disease) had had a lower FEV₁, higher rates of fixed obstruction (23%), and a high BMI (32.0 kg/m²). The longer-standing group had a higher FEV₁%, no fixed airway obstruction, and a lower BMI. Data on sputum analysis were not captured.

Progression to chronic obstructive pulmonary disease/severe asthma

The coexistence of asthma and chronic obstructive pulmonary disease (COPD) is common, particularly in older populations. Estimates suggest that this overlap occurs in approximately 20% of patients with airway disease,⁵¹ with a higher prevalence in those older than 50 years. In a New Zealand population-based survey, a subgroup of 469 participants older than 50 years underwent complete pulmonary function testing; 96 (20.5%) were defined as having COPD, and 53 of 96 (55%) exhibited features of both asthma and COPD.³²

Although exposure to noxious particles is recognized as the most important risk factor for the development of COPD, there are other factors. Childhood asthma itself increases the susceptibility to COPD. In a longitudinal analysis of the European Community Respiratory Health Survey I and II cohorts, both childhood asthma (men: odds ratio [OR], 10.48, 95% CI, 6.10-18.03, *P* = .001; women: OR, 3.74; 95% CI, 1.55-9.02, *P* = .003) and paternal asthma were associated with COPD development. The risk increased with the number of childhood disadvantage factors such as maternal asthma, paternal asthma, childhood asthma, respiratory infections, and maternal smoking. The OR was 1.7 (95% CI, 1.1-2.6) and 1.6 (95% CI, 1.01-2.6) for males and females, respectively, when 1 childhood disadvantage factor was present. This increased to an OR of 6.3 (95% CI, 2.4-17) for men and 7.2 (95% CI, 2.8-19) for women when 3 or more factors were present.³³

IMPACT OF AGING ON INFLAMMATION

With increasing age, there are potential alterations of aging on the innate and adaptive immune responses that can occur simultaneously. "Immunosenescence" is a "blunted" response after a pathogenic threat or tissue injury. Despite an inability to proliferate, some senescent cells remain alive, functioning at an altered capacity. This results in "inflammaging," an increased low-grade basal systemic inflammation (eg, IL1- β , IL-6, and TNF- α) in the absence of an overt infection.³⁴ These immune alterations with aging must be taken into account when measuring inflammatory markers in older adults with asthma. For example, there is an age-related increase in sputum neutrophil counts, regardless of the presence of airway disease.³⁵⁻³⁷ In adults older than 20 years, there appears to be an increase of 0.46% per year in neutrophil percentage.³⁸

Induced sputum represents a criterion standard test for the measurement of airway inflammation, although it is mainly a research tool. The inflammatory asthma phenotypes and endotypes in older patients have not been as well characterized as in younger adults. However, there is emerging evidence that there may be some important inflammatory subsets of older patients with asthma. A type (T)2-ultrahigh group (diagnosed by elevated sputum RNA sequencing) was more prevalent in older adults with asthma. These patients have high levels of sputum eosinophils and neutrophils, elevated fractional exhaled nitric oxide, elevated blood eosinophils (470 cells/ μ L), and low IgE, and respond poorly to corticosteroids.^{39,40} In addition, there appears

to be another subset of older patients with asthma with a mixed T1/T2 component, characterized by elevated sputum neutrophils and eosinophils, IL-5, IL-6, IL-8, which was not secondary to the effect of aging.³⁵ Increased sputum neutrophils and IL-6 in the older population were related to decreased asthma control and increased use of health care resources for asthma. Strong data exist in studies with patients (~58 years old) with asthma that neutrophilic asthma is associated with increased systemic inflammation, identified by increased C-reactive protein.^{41,42} Systemic IL-6 is also associated with poorer asthma outcomes (decreased FEV₁ and increased exacerbations).⁴³ In another study comparing older than 55 years patients with asthma, COPD, and asthma/COPD overlap, no statistical differences were seen between sputum neutrophil and eosinophil counts, or serum IL-6 or high sensitivity C-reactive protein.⁴⁴ Therefore, some older patients with asthma likely have an important systemic inflammatory component of their disease, much like COPD. These similarities also highlight the additional complexities for older people with asthma. The changes in inflammation with aging and obstructive lung disease may be associated with an increased risk of ICS treatment failure with aging, although this requires additional study.⁴⁵

IMPACT OF SEX AND AGING

The relationships between sex hormones, aging, and asthma are complex and can impact both early-onset and late-onset asthma. Menopause may have a protective role in EOA. Asthma exacerbations are reported in relation to the menstrual cycle, typically in the week preceding the onset of menstruation. The probability of having severe asthma is higher in males after age 45 years, but not in females of the same age.^{46,47} In the National Inpatient Samples 2011-2012, the risk of asthma-related respiratory failure continued to rise in men after 60 years, but not in females.⁴⁷ The underlying mechanisms of these differences are likely multifactorial and include sex differences in asthma symptom perceptions or health-seeking behaviors.^{48,49} However, new-onset asthma during or after menopause is more likely to be severe and less responsive to anti-inflammatory treatment.⁵⁰

Pregnancy

Pregnancy leads to poor asthma control in one-third of women,⁵¹ increasing the risk of acute attacks,⁵²⁻⁵⁵ which may lead to adverse fetal outcomes.⁵²⁻⁵⁵ Optimized management of asthma during pregnancy, through appropriate pharmacotherapy and self-management education, leads to improved health outcomes for the offspring.^{52,53} A personalized approach to managing asthma therapy in pregnancy based on a fractional exhaled nitric oxide-guided treatment algorithm compared with symptom-based management led to a 50% reduction in acute attacks during pregnancy. In addition, the incidence rate ratio of doctor-diagnosed asthma for the offspring of women treated with a fractional exhaled nitric oxide protocol compared with symptom-based alone was significantly lower in the former (*P* = .04), potentially contributing to a primary prevention strategy for reducing the incidence of childhood-onset asthma.⁵⁶

CONFOUNDING FACTORS ACROSS ADULTHOOD

There are several important comorbidities, or "treatable traits," often associated with aging, which increase rates of asthma hospitalizations and emergency room visits.^{57,58}

McDonald et al⁵⁹ reported a cross-sectional study involving 100 patients older than 55 years (recruited from a tertiary care respiratory clinic) with obstructive airway diseases who underwent a multidimensional assessment to characterize their treatable traits. Those with asthma expressed a mean of 10.3 ± 1.9 treatable traits, not different from those with COPD (11.3 ± 2.8) and asthma/COPD overlap.⁴⁴ Subjects undergoing multidimensional treatment of their traits, compared with those receiving usual care, had improved asthma outcomes and measures of inflammation (eg, sputum and systemic).⁵⁹ Consequently, a comprehensive and multidisciplinary approach is necessary for middle-aged and older patients with asthma.

Cardiovascular

Cardiovascular diseases (CVDs) are more prevalent in older than younger adults. The presence of CVD worsens asthma outcomes and is more prevalent in patients with asthma, in particular those with severe airway disease.⁶⁰⁻⁶² Conversely, recent studies have suggested that asthma (including late-onset disease), particularly if uncontrolled,⁶³ is an independent risk factor for new-onset CVD.⁶⁴⁻⁶⁶ A decreasing FEV₁ may predict future CVD, especially in patients with known obstructive lung disease.⁶⁷

There are potential mechanisms to explain the link between asthma and CVD. Increasing systemic IL-6 is associated with the presence of CVD with poorer outcomes.⁶⁸⁻⁷⁰ A subset of older patients with asthma appear to have a strong IL-6 component.³⁵ Frequent oral corticosteroid use can also worsen CVD. A recent study suggested that in adults older than 70 years, those who had the apolipoprotein E allele (associated with CVD and atherosclerosis)⁷¹ had a greater decline in FEV₁ and FEV₁/forced vital capacity.⁷² Apolipoprotein E-deficient antigen-sensitized and antigen-challenged mice developed airway hyperresponsiveness and mucous cell metaplasia.^{73,74} The apolipoprotein E $\epsilon 4$ allele is associated with an increased innate response, thereby altering systemic and potentially airway inflammation.^{73,75} Moreover, eosinophils promote thrombus growth and are able to be activated by oxidized low-density lipoprotein to activate macrophages from M2 to M1.⁷²

Obesity

Older persons with asthma, compared with aged matched without asthma, are more likely to be obese, with increased abdominal adipose tissue.^{76,77} The relationship between obesity, aging, and asthma outcomes is likely multifactorial. Two studies of older patients with asthma reported that with increased BMI, there was a significant loss of asthma control.^{78,79} However, when analysis was adjusted for depression and lower income in one of the studies, the relationship between obesity and asthma outcomes was lost, suggesting a complex relationship between these factors in the aged.⁷⁹

There are many reasons why obese patients with asthma have poorer outcomes; however, whether aging affects these mechanisms is not clear. Obesity is associated with increased systemic T1 inflammation (ie, TNF- α , IL-1 β , IL-6), released from activated adipocytes and adipose tissue-resident cells, which “spill over” into the lungs.^{80,81} Elevated sputum NLRP3, IL-1 β , and neutrophils are increased in obese patients with asthma, and after consumption of saturated fatty acids.^{81,82} The relationship between obesity and neutrophilic asthma in females may only be

important for patients younger than 50 years, suggesting that sex hormones are an major component with obesity.⁸³

Physical inactivity

Physical inactivity is an important modifiable risk factor associated with poor outcomes in the general population, including increased mortality.⁸⁴ Physical inactivity is observed at higher rates in asthma compared with nonasthma control populations. The populations at a higher risk of physical inactivity in asthma are females and older people.⁸⁵ This is important because increased physical activity in asthma is associated with improved outcomes. In a cross-sectional study that evaluated physical activity in severe asthma, median age 59 years (range, 43-68 years), steps per day were strongly and independently associated with better exercise capacity (coefficient, 0.0169; 95% CI, 0.008-0.025; $P < .001$).⁸⁶ A systematic review reported similar results in patients with asthma over different severities.⁸⁵ Improving physical activity in asthma, and particularly in older people with asthma, is a priority.

DEPRESSION

Depression is highly prevalent in female patients with asthma, particularly in the aged.^{58,76,87,88} The impact of depression on asthma morbidity is substantial in this age group, associated with poor asthma control, more severe airway obstruction, poorer quality of life, and increased health care utilization.⁸⁸⁻⁹⁰ There are several mechanisms by which depression can exacerbate asthma, and whether these mechanisms differ with age is not clear at the present. The severity of depression has been associated with increased systemic T1 inflammation (ie, IL-1 β , IL-6, TNF- α) and markers of inflammation (ie, C-reactive protein),^{91,92} often seen in patients with a more “neutrophilic” asthma. In other chronic diseases such as rheumatoid arthritis, coronary disease, and atherosclerosis, depression increases systemic inflammation⁹³⁻⁹⁶ and peripheral neutrophilia.⁹⁷ Although not specifically targeting older patients, in a study of 24 participants with asthma (mean age, 44.45 years), depression was associated with increased sputum and serum IL-1 β and IFN- γ , which were inversely associated with impaired bronchodilator response.⁹⁸ Lower adherence to ICSs in older patients with asthma was strongly associated with depressive symptoms.⁹⁹

Chronic rhinosinusitis and nasal polyposis

Nasal polyposis is typically a disease of adult life. Up to 10% of the population reports nasal polyposis,¹⁰⁰ whereas imaging studies identify a prevalence of between 3% and 6.4% when using objective criteria.¹⁰¹ Nasal polyposis is a risk factor for adult-onset asthma,¹⁰² difficult-to-control asthma, asthma exacerbations, and increased mortality.¹⁰³ Analyses identify both eosinophilic and noneosinophilic types of nasal polyposis,^{104,105} with noneosinophilic forms having better surgical outcomes.¹⁰⁵ Aspirin-exacerbated respiratory disease has a prevalence of 9.6%, increasing to 40% in patients with allergic fungal sinusitis.¹⁰⁶ Therapeutic options for chronic rhinosinusitis with nasal polyposis include intranasal corticosteroid use, systemic corticosteroids, sinonasal surgery,¹⁰⁷ and T2-directed mAb therapy such as dupilumab.¹⁰⁸

Multiple medications for other comorbidities

Older people with multiple morbidities may experience adverse effects from medication interactions.¹⁰⁹ In older people

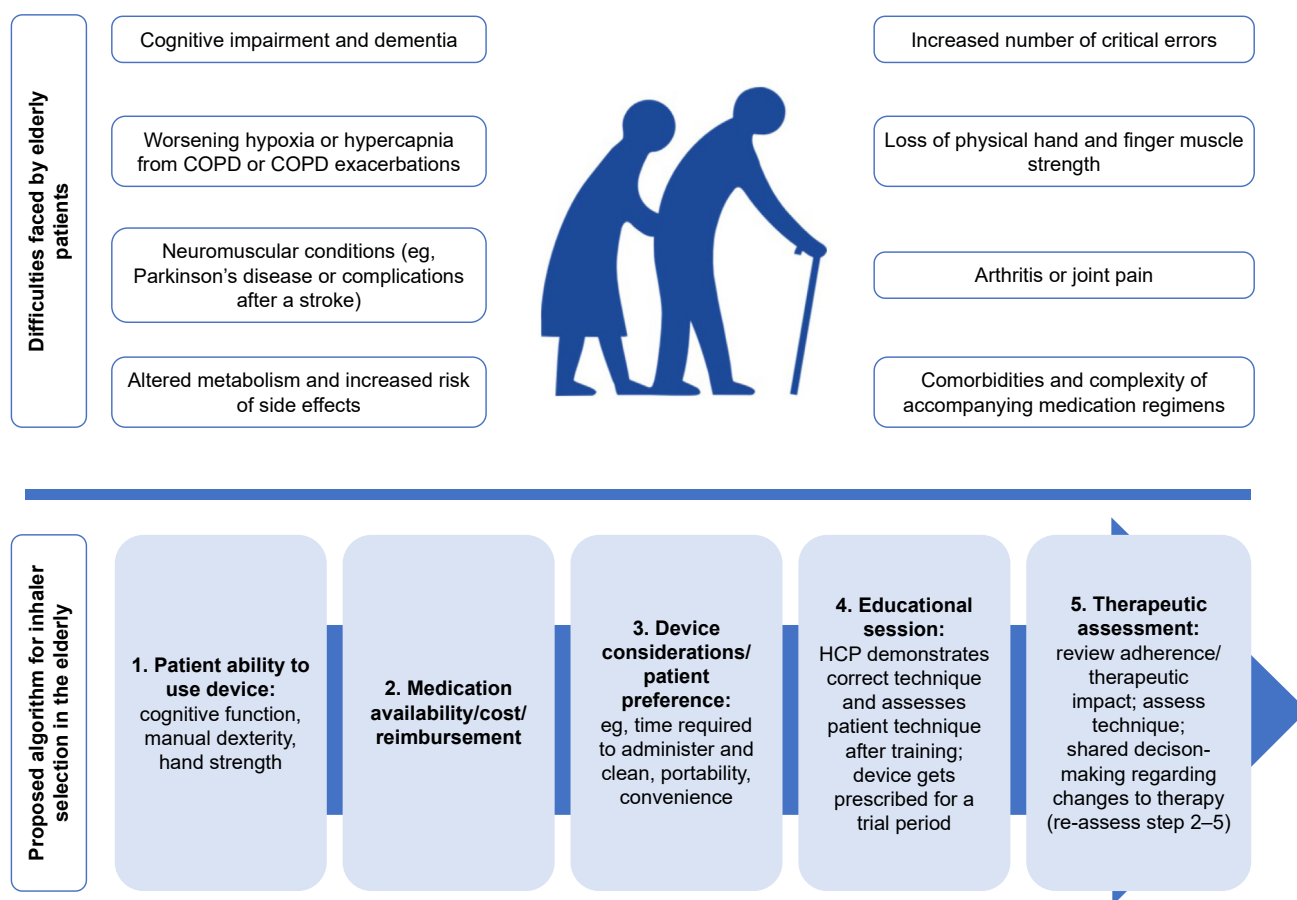


FIGURE 2. Challenges with the use of inhalation therapy in elderly patients with asthma, and an algorithm for appropriate inhaler device selection. *HCP*, Health care professional. Reprinted with permission from Usmani.¹³¹

with multiple comorbidities and polypharmacy there is an increased risk of adverse drug effects that relate not only to drug-drug interactions (eg, statins and macrolides) but also to drug-disease interactions (eg, beta blockers in asthma). In addition to drug interactions other factors related to multiple medications impact asthma in older individuals. A prospective, multicenter Korean study reported that fewer medications for comorbidities predicted improved asthma control in patients with asthma (OR, 0.863; $P = .004$).¹¹⁰ Furthermore, the use of more medications to treat comorbid conditions is associated with an increase in suboptimal treatment adherence.¹¹¹

Smoking

Smoking is a particularly important risk factor for patients with asthma irrespective of age, but there are some populations more likely to smoke. Smoking prevalence in patients with asthma overall is similar to that in the general population (~15%).^{112,113} Adults with late-onset asthma have higher smoking rates compared with those with EOA.¹¹⁴

Smoking significantly complicates asthma. It is associated with higher treatment requirements for ICSs with reduced responsiveness,¹¹⁵ accelerated lung function decline,¹¹⁶ and increased risk of severe attacks.^{112,117} Smoking cessation is a priority and strategies should be personalized to the asthma population taking into account the age of the patient.¹¹³

Cognition and asthma self-management

Asthma self-management, including adherence to controller medications, correct use of inhaler devices, trigger avoidance, use of asthma action plans, and peak flow monitoring, is an important determinant of asthma control. Unfortunately, studies have consistently reported that less than half of adult patients with asthma are adherent to these key self-management behaviors and that low adherence is associated with worse disease outcomes.^{118,119} Older adults with asthma face even greater barriers and appear to have lower rates of adherence to self-management compared with younger individuals.¹²⁰

Two factors that can negatively impact asthma self-management in older adults are low health literacy and impaired cognitive function.^{121,122} Health literacy is defined as the ability to gather, process, and understand the health information needed to make health care–related decisions. Low health literacy is more prevalent among adults older than 65 years (affecting up to 60% of individuals) and has been associated with lower adherence to asthma medication as well as worse asthma control and poorer quality of life.^{122–124} Similarly, age-related cognitive decline (particularly memory problems and decreased executive function) is related to decreased ability to self-manage asthma.¹²⁵ Difficulties remembering health care provider instructions for self-management, problems handling complex medication regimens (common among older patients),

and challenges managing acute attacks are some of the barriers to effective self-management faced by patients with asthma with cognitive decline. Moreover, illness beliefs (eg, conceptualizing asthma as an acute illness present only when having symptoms) and concerns about medications (eg, ICSs cause dependence or are toxic) are strong predictors of lower adherence to asthma medications and may explain, in part, the relationship between low health literacy and cognitive problems with self-management.^{126,127} This knowledge has led to the development of effective comprehensive personalized asthma self-management interventions for older patients with asthma, targeting these beliefs and other key barriers to asthma control.¹²⁸

Inhaler device selection

Inhaled medication is the cornerstone of asthma pharmacotherapy. Unfortunately, suboptimal use of inhaler therapy is frequently observed in people with asthma, and age significantly compounds this issue. In a group of patients with airway disease (aged 55-87 years), 48.5% had inadequate inhaler technique and 50% were using several different types of inhalation devices, termed inhaler device polypharmacy.⁴⁴ Older patients with decreased cognition and health literacy are at particular risk of poor inhaler technique.^{129,130} Factors that should be considered when prescribing inhaled medications include efficacy, safety, and proficiency. In addition to adherence, cost, and patient preference, the assessment of proficiency should incorporate age-related factors such as peak inspiratory flow rate, manual dexterity, coordination and handling capacity, and comorbidities that affect device use such as cognitive and vision impairment.^{131,132} Figure 2 highlights the difficulties faced by older people and presents an algorithm for device selection.

DIFFERENCES IN DIAGNOSTIC APPROACH ACROSS ADULTHOOD

Asthma symptoms

Many of the asthma symptoms in younger adults (ie, episodic wheezing, shortness of breath, cough, and chest tightness) are characteristic of those in older adults. However, in older patients, dyspnea is a common symptom of other disorders including cardiac disease, anemia, or other lung diseases; therefore, asthma as an etiology of these symptoms may be overlooked. In addition, some older patients may limit their activity to avoid getting dyspneic. Older patients often have a decreased perception of asthma symptoms despite significant airway obstruction.¹³³

Lung function testing

There are age-related factors that must be considered when interpreting lung function measurements. Changes in the structure of the aging lung decrease the FEV₁/forced vital capacity ratio; age-adjusted values are recommended to avoid overdiagnosis of obstruction.¹³⁴ Aging increases BHR to methacholine¹³⁵; therefore, provocation testing may be overinterpreted. Although more than 80% of older persons can achieve American Thoracic Society—acceptable results to perform spirometry, it may be difficult for those who are frail.¹³⁶ Poor coordination and muscle weakness in some patients may produce inaccurate readings of peak expiratory flow.¹³⁷

CONCLUSIONS

Asthma is a common condition that affects individuals across the life span. Despite improvement in outcomes for people with

asthma over the last few decades, outcomes remain poor, particularly for certain age groups including older people. The impacts of asthma in adulthood vary according to age, and include pathophysiological and biological changes, self-management and behavioral traits, and increasing prevalence and severity of comorbidity, which are impacted by advancing age. Life events such as pregnancy and behaviors such as smoking are some of the features that affect individuals with asthma during younger age. Recognizing the needs of individuals with asthma according to their life stage will enable a more personalized approach to patient care and improve patient outcomes.

REFERENCES

1. Braman SS. Asthma in the elderly. *Clin Geriatr Med* 2017;33:523-37.
2. Ebmeier S, Thayabaran D, Braithwaite I, Benamara C, Weatherall M, Beasley R. Trends in international asthma mortality: analysis of data from the WHO Mortality Database from 46 countries (1993-2012). *Lancet* 2017;390:935-45.
3. Tsai CL, Delclos GL, Huang JS, Hanania NA, Camargo CA Jr. Age-related differences in asthma outcomes in the United States, 1988-2006. *Ann Allergy Asthma Immunol* 2013;110:240-6. 246.e1.
4. Tsai CL, Lee WY, Hanania NA, Camargo CA Jr. Age-related differences in clinical outcomes for acute asthma in the United States, 2006-2008. *J Allergy Clin Immunol* 2012;129:1252-1258.e1.
5. Karvala K, Uitti J, Taponen S, Luukkonen R, Lehtimäki L. Asthma trigger perceptions are associated with work disability. *Respir Med* 2018;139:19-26.
6. Benfante A, Principe S, Battaglia S, Scichilone N. Are biological drugs effective and safe in older severe asthmatics? *Expert Opin Drug Saf* 2019;18:369-80.
7. Australian Institute for Health and Welfare. Asthma in Australia 2011: Australian Centre for Asthma Monitoring 2011. Canberra, Australia: Australian Institute for Health and Welfare; 2011.
8. Moorman JE, Akinbami LJ, Bailey CM, Zahran HS, King ME, Johnson CA, et al. National surveillance of asthma: United States, 2001-2010. *Vital Health Stat* 2012;3:1-58.
9. Winer RA, Qin X, Harrington T, Moorman J, Zahran H. Asthma incidence among children and adults: findings from the Behavioral Risk Factor Surveillance system asthma call-back survey—United States, 2006-2008. *J Asthma* 2012;49:16-22.
10. Hansen S, Probst-Hensch N, Keidel D, Dratva J, Bettchart R, Pons M, et al. Gender differences in adult-onset asthma: results from the Swiss SAPALDIA cohort study. *Eur Respir J* 2015;46:1011-20.
11. Burte E, Bousquet J, Siroux V, Just J, Jacquemin B, Nadif R. The sensitization pattern differs according to rhinitis and asthma multimorbidity in adults: the EGEA study. *Clin Exp Allergy* 2017;47:520-9.
12. de Nijs SB, Venekamp LN, Bel EH. Adult-onset asthma: is it really different? *Eur Respir Rev* 2013;22:44-52.
13. Anto JM, Sunyer J, Basagana X, Garcia-Esteban R, Cerveri I, de Marco R, et al. Risk factors of new-onset asthma in adults: a population-based international cohort study. *Allergy* 2010;65:1021-30.
14. Jaakkola MS, Ieromnimon A, Jaakkola JJ. Are atopy and specific IgE to mites and molds important for adult asthma? *J Allergy Clin Immunol* 2006;117:642-8.
15. Coumou H, Westerhof GA, de Nijs SB, Amelink M, Bel EH. New-onset asthma in adults: what does the trigger history tell us? *J Allergy Clin Immunol Pract* 2019;7:898-905.e1.
16. Agondi RC, Andrade MC, Takejima P, Aun MV, Kalil J, Giavina-Bianchi P. Atopy is associated with age at asthma onset in elderly patients. *J Allergy Clin Immunol Pract* 2018;6:865-71.
17. Jacquemin B, Siroux V, Sanchez M, Carsin AE, Schikowski T, Adam M, et al. Ambient air pollution and adult asthma incidence in six European cohorts (ESCAPE). *Environ Health Perspect* 2015;123:613-21.
18. Westerhof GA, Coumou H, de Nijs SB, Weersink EJ, Bel EH. Clinical predictors of remission and persistence of adult-onset asthma. *J Allergy Clin Immunol* 2018;141:104-9.e3.
19. Holm M, Omenaas E, Gislason T, Svane C, Jogi R, Normann E, et al. Remission of asthma: a prospective longitudinal study from northern Europe (RHINE study). *Eur Respir J* 2007;30:62-5.
20. Nwaru BI, Ekerljung L, Radinger M, Bjerg A, Mincheva R, Malmhall C, et al. Cohort profile: the West Sweden Asthma Study (WSAS): a multidisciplinary population-based longitudinal study of asthma, allergy and respiratory conditions in adults. *BMJ Open* 2019;9:e027808.

21. Sozener ZC, Aydin O, Mungan D, Misirligil Z. Prognosis of adult asthma: a 7-year follow-up study. *Ann Allergy Asthma Immunol* 2015;114:370-3.
22. Busse P, Wechsler ME. Identification of remission in adult-onset asthma. *Lancet Respir Med* 2018;6:417-8.
23. Wang J, Pindus M, Janson C, Sigsgaard T, Kim JL, Holm M, et al. Dampness, mould, onset and remission of adult respiratory symptoms, asthma and rhinitis. *Eur Respir J* 2019;53.
24. Bloom CI, Nissen F, Douglas JJ, Smeeth L, Cullinan P, Quint JK. Exacerbation risk and characterisation of the UK's asthma population from infants to old age. *Thorax* 2018;73:313-20.
25. Bloom CI, Palmer T, Feary J, Quint JK, Cullinan P. Exacerbation patterns in adults with asthma in England: a population-based study. *Am J Respir Crit Care Med* 2019;199:446-53.
26. Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med* 2010;181:315-23.
27. Halder P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;178:218-24.
28. Baptist AP, Hao W, Karamched KR, Kaur B, Carpenter L, Song PXX. Distinct asthma phenotypes among older adults with asthma. *J Allergy Clin Immunol Pract* 2018;6:244-249.e2.
29. Kaur R, Chupp G. Phenotypes and endotypes of adult asthma: moving toward precision medicine. *J Allergy Clin Immunol* 2019;144:1-12.
30. Amelink M, de Groot JC, de Nijs SB, Lutter R, Zwiderman AH, Sterk PJ, et al. Severe adult-onset asthma: a distinct phenotype. *J Allergy Clin Immunol* 2013;132:336-41.
31. Gibson PG, McDonald VM. Asthma-COPD overlap 2015: now we are six. *Thorax* 2015;70:683-91.
32. Marsh SE, Travers J, Weatherall M, Williams MV, Aldington S, Shirlcliffe PM, et al. Proportional classifications of COPD phenotypes. *Thorax* 2008;63:761-7.
33. Svanes C, Sunyer J, Plana E, Dharmage S, Heinrich J, Jarvis D, et al. Early life origins of chronic obstructive pulmonary disease. *Thorax* 2010;65:14-20.
34. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *J Gerontol A Biol Sci Med Sci* 2014;69:S4-9.
35. Busse PJ, Birmingham JM, Calatroni A, Manzi J, Goryachovskiy A, Fontela G, et al. Effect of aging on sputum inflammation and asthma control. *J Allergy Clin Immunol* 2017;139:1808-1818.e6.
36. Simpson JL, McDonald VM, Baines KJ, Oreo KM, Wang F, Hansbro PM, et al. Influence of age, past smoking, and disease severity on TLR2, neutrophilic inflammation, and MMP-9 levels in COPD. *Mediators Inflamm* 2013;2013:462934.
37. Carpagano GE, Turchiarelli V, Spanevello A, Palladino GP, Barbaro MP. Aging and airway inflammation. *Aging Clin Exp Res* 2013;25:239-45.
38. Brooks CR, Gibson PG, Douwes J, Van Dalen CJ, Simpson JL. Relationship between airway neutrophilia and ageing in asthmatics and non-asthmatics. *Respirology* 2013;18:857-65.
39. Peters MC, Ringel L, Dyjack N, Herrin R, Woodruff PG, Rios C, et al. A transcriptomic method to determine airway immune dysfunction in T2-high and T2-low asthma. *Am J Respir Crit Care Med* 2019;199:465-77.
40. Peters MC, Kerr S, Dunican EM, Woodruff PG, Fajt ML, Levy BD, et al. National Heart, Lung and Blood Institute Severe Asthma Research Program 3. Refractory airway type 2 inflammation in a large subgroup of asthmatic patients treated with inhaled corticosteroids. *J Allergy Clin Immunol* 2019;143:104-113.e14.
41. Fu JJ, Baines KJ, Wood LG, Gibson PG. Systemic inflammation is associated with differential gene expression and airway neutrophilia in asthma. *OMICS* 2013;17:187-99.
42. Simpson JL, Phipps S, Baines KJ, Oreo KM, Gunawardhana L, Gibson PG. Elevated expression of the NLRP3 inflammasome in neutrophilic asthma. *Eur Respir J* 2014;43:1067-76.
43. Peters MC, McGrath KW, Hawkins GA, Hastie AT, Levy BD, Israel E, et al. Plasma interleukin-6 concentrations, metabolic dysfunction, and asthma severity: a cross-sectional analysis of two cohorts. *Lancet Respir Med* 2016;4:574-84.
44. McDonald VM, Simpson JL, Higgins I, Gibson PG. Multidimensional assessment of older people with asthma & COPD: clinical management and health status. *Age Ageing* 2011;40:42-9.
45. Dunn RM, Lehman E, Chinchilli VM, Martin RJ, Boushey HA, Israel E, et al. Impact of age and sex on response to asthma therapy. *Am J Respir Crit Care Med* 2015;192:551-8.
46. Zein JG, Dweik RA, Comhair SA, Bleecker ER, Moore WC, Peters SP, et al. Asthma is more severe in older adults. *PLoS One* 2015;10:e0133490.
47. Zein JG, Udeh BL, Teague WG, Koroukian SM, Schlitz NK, Bleecker ER, et al. Impact of age and sex on outcomes and hospital cost of acute asthma in the United States, 2011-2012. *PLoS One* 2016;11:e0157301.
48. McCallister JW, Holbrook JT, Wei CY, Parsons JP, Benninger CG, Dixon AE, et al. Sex differences in asthma symptom profiles and control in the American Lung Association Asthma Clinical Research Centers. *Respir Med* 2013;107:1491-500.
49. Chhabra SK, Chhabra P. Gender differences in perception of dyspnea, assessment of control, and quality of life in asthma. *J Asthma* 2011;48:609-15.
50. Balzano G, Fuschillo S, De Angelis E, Gaudiosi C, Mancini A, Caputi M. Persistent airway inflammation and high exacerbation rate in asthma that starts at menopause. *Monaldi Arch Chest Dis* 2007;67:135-41.
51. Middleton PG, Gade EJ, Aguilera C, MacKillop L, Button BM, Coleman C, et al. ERS/TSANZ Task Force Statement on the management of reproduction and pregnancy in women with airways diseases. *Eur Respir J* 2020;55:1901208.
52. Murphy VE, Namazy JA, Powell H, Schatz M, Chambers C, Attia J, et al. A meta-analysis of adverse perinatal outcomes in women with asthma. *BJOG* 2011;118:1314-23.
53. Murphy VE, Wang G, Namazy JA, Powell H, Gibson PG, Chambers C, et al. The risk of congenital malformations, perinatal mortality and neonatal hospitalisation among pregnant women with asthma: a systematic review and meta-analysis. *BJOG* 2013;120:812-22.
54. Namazy JA, Murphy VE, Powell H, Gibson PG, Chambers C, Schatz M. Effects of asthma severity, exacerbations and oral corticosteroids on perinatal outcomes. *Eur Respir J* 2013;41:1082-90.
55. Wang G, Murphy VE, Namazy J, Powell H, Schatz M, Chambers C, et al. The risk of maternal and placental complications in pregnant women with asthma: a systematic review and meta-analysis. *J Matern Fetal Neonatal Med* 2014;27:934-42.
56. Morten M, Collison A, Murphy VE, Barker D, Oldmeadow C, Attia J, et al. Managing Asthma in Pregnancy (MAP) trial: FENO levels and childhood asthma. *J Allergy Clin Immunol* 2018;142:1765-1772.e4.
57. Patel MR, Janevic MR, Heeringa SG, Baptist AP, Clark NM. An examination of adverse asthma outcomes in U.S. adults with multiple morbidities. *Ann Am Thorac Soc* 2013;10:426-31.
58. Hsu J, Chen J, Mirabelli MC. Asthma morbidity, comorbidities, and modifiable factors among older adults. *J Allergy Clin Immunol Pract* 2018;6:236-243.e7.
59. McDonald VM, Clark VL, Cordova-Rivera L, Wark PAB, Baines KJ, Gibson PG. Targeting treatable traits in severe asthma: a randomised controlled trial. *Eur Respir J* 2020;55.
60. Rogliani P, Sforza M, Calzetta L. The impact of comorbidities on severe asthma. *Curr Opin Pulm Med* 2020;26:47-55.
61. Bourdin A, Fabry-Vendrand C, Ostinelli J, Ait-Yahia M, Darnal E, Bouee S, et al. The burden of severe asthma in France: a case-control study using a medical claims database. *J Allergy Clin Immunol Pract* 2019;7:1477-87.
62. Sweeney J, Patterson CC, Menzies-Gow A, Niven RM, Mansur AH, Bucknall C, et al. Comorbidity in severe asthma requiring systemic corticosteroid therapy: cross-sectional data from the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry. *Thorax* 2016;71:339-46.
63. Cepelis A, Brumpton BM, Laugsand LE, Dalen H, Langhammer A, Janszky I, et al. Asthma, asthma control and risk of acute myocardial infarction: HUNT study. *Eur J Epidemiol* 2019;34:967-77.
64. Bang DW, Wi CI, Kim EN, Hagan J, Roger V, Manemann S, et al. Asthma status and risk of incident myocardial infarction: a population-based case-control study. *J Allergy Clin Immunol Pract* 2016;4:917-23.
65. Tattersall MC, Guo M, Korcarz CE, Gepner AD, Kaufman JD, Liu KJ, et al. Asthma predicts cardiovascular disease events: the multi-ethnic study of atherosclerosis. *Arterioscler Thromb Vasc Biol* 2015;35:1520-5.
66. Ferrari M, Piccinno E, Marcon A, Marchetti P, Cazzoletti L, Pirina P, et al. Chronic bronchitis without airflow obstruction, asthma and rhinitis are differently associated with cardiovascular risk factors and diseases. *PLoS One* 2019;14:e0224999.
67. Duong M, Islam S, Rangarajan S, Leong D, Kurmi O, Teo K, et al. Mortality and cardiovascular and respiratory morbidity in individuals with impaired FEV₁ (PURE): an international, community-based cohort study. *Lancet Glob Health* 2019;7:e613-23.
68. Ridker PM, Libby P, MacFadyen JG, Thuren T, Ballantyne C, Fonseca F, et al. Modulation of the interleukin-6 signalling pathway and incidence rates of atherosclerotic events and all-cause mortality: analyses from the Canakinumab

- Anti-Inflammatory Thrombosis Outcomes Study (CANTOS). *Eur Heart J* 2018;39:3499-507.
69. Aulin J, Siegbahn A, Hijazi Z, Ezekowitz MD, Andersson U, Connolly SJ, et al. Interleukin-6 and C-reactive protein and risk for death and cardiovascular events in patients with atrial fibrillation. *Am Heart J* 2015;170:1151-60.
70. Cainzos-Achirica M, Enjuanes C, Greenland P, McEvoy JW, Cushman M, Dardari Z, et al. The prognostic value of interleukin 6 in multiple chronic diseases and all-cause death: the Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis* 2018;278:217-25.
71. Liu S, Liu J, Weng R, Gu X, Zhong Z. Apolipoprotein E gene polymorphism and the risk of cardiovascular disease and type 2 diabetes. *BMC Cardiovasc Disord* 2019;19:213.
72. Kulminski AM, Barochia AV, Loika Y, Raghavachari N, Arbeev KG, Wojczynski MK, et al. The APOE epsilon4 allele is associated with a reduction in FEV₁/FVC in women: a cross-sectional analysis of the Long Life Family Study. *PLoS One* 2018;13:e0206873.
73. Gao S, Wang C, Li W, Shu S, Zhou J, Yuan Z, et al. Allergic asthma aggravated atherosclerosis increases cholesterol biosynthesis and foam cell formation in apolipoprotein E-deficient mice. *Biochem Biophys Res Commun* 2019;519:861-7.
74. Yao X, Fredriksson K, Yu ZX, Xu X, Raghavachari N, Keeran KJ, et al. Apolipoprotein E negatively regulates house dust mite-induced asthma via a low-density lipoprotein receptor-mediated pathway. *Am J Respir Crit Care Med* 2010;182:1228-38.
75. Gale SC, Gao L, Mikacenic C, Coyle SM, Rafaels N, Murray Dudenkov T, et al. APOε4 is associated with enhanced in vivo innate immune responses in human subjects. *J Allergy Clin Immunol* 2014;134:127-34.
76. de Roos EW, Lahousse L, Verhamme KMC, Braunstaal GJ, Ikram MA, In't Veen J, et al. Asthma and its comorbidities in middle-aged and older adults: the Rotterdam Study. *Respir Med* 2018;139:6-12.
77. Song WJ, Kim SH, Lim S, Park YJ, Kim MH, Lee SM, et al. Association between obesity and asthma in the elderly population: potential roles of abdominal subcutaneous adiposity and sarcopenia. *Ann Allergy Asthma Immunol* 2012;109:243-8.
78. Epstein TG, Ryan PH, LeMasters GK, Bernstein CK, Levin LS, Bernstein JA, et al. Poor asthma control and exposure to traffic pollutants and obesity in older adults. *Ann Allergy Asthma Immunol* 2012;108:423-428.e2.
79. Xu KY, Wisnivesky JP, Martynenko M, Mhang G, Busse PJ, Wolf MS, et al. Assessing the association of obesity and asthma morbidity in older adults. *Ann Allergy Asthma Immunol* 2016;117:33-7.
80. Peters U, Dixon AE, Forno E. Obesity and asthma. *J Allergy Clin Immunol* 2018;141:1169-79.
81. Wood LG, Li Q, Scott HA, Rutting S, Berthon BS, Gibson PG, et al. Saturated fatty acids, obesity, and the nucleotide oligomerization domain-like receptor protein 3 (NLRP3) inflammasome in asthmatic patients. *J Allergy Clin Immunol* 2019;143:305-15.
82. Li Q, Baines KJ, Gibson PG, Wood LG. Changes in expression of genes regulating airway inflammation following a high-fat mixed meal in asthmatics. *Nutrients* 2016;8:E30.
83. Scott HA, Gibson PG, Garg ML, Upham JW, Wood LG. Sex hormones and systemic inflammation are modulators of the obese-asthma phenotype. *Allergy* 2016;71:1037-47.
84. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet* 2012;380:219-29.
85. Cordova-Rivera L, Gibson PG, Gardiner PA, McDonald VM. A systematic review of associations of physical activity and sedentary time with asthma outcomes. *J Allergy Clin Immunol Pract* 2018;6:1968-1981.e2.
86. Cordova-Rivera L, Gibson PG, Gardiner PA, Powell H, McDonald VM. Physical activity and exercise capacity in severe asthma: key clinical associations. *J Allergy Clin Immunol Pract* 2018;6:814-22.
87. Wainwright NW, Surtees PG, Wareham NJ, Harrison BD. Psychosocial factors and asthma in a community sample of older adults. *J Psychosom Res* 2007;62:357-61.
88. Patel PO, Patel MR, Baptist AP. Depression and asthma outcomes in older adults: results from the National Health and Nutrition Examination Survey. *J Allergy Clin Immunol Pract* 2017;5:1691-1697.e1.
89. Krauskopf KA, Sofianou A, Goel MS, Wolf MS, Wilson EA, Martynenko ME, et al. Depressive symptoms, low adherence, and poor asthma outcomes in the elderly. *J Asthma* 2013;50:260-6.
90. Ross JA, Yang Y, Song PX, Clark NM, Baptist AP. Quality of life, health care utilization, and control in older adults with asthma. *J Allergy Clin Immunol Pract* 2013;1:157-62.
91. Haapakoski R, Ebmeier KP, Alenius H, Kivimäki M. Innate and adaptive immunity in the development of depression: an update on current knowledge and technological advances. *Prog Neuropsychopharmacol Biol Psychiatry* 2016;66:63-72.
92. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat Rev Immunol* 2016;16:22-34.
93. Parissis JT, Adamopoulos S, Rigas A, Kostakis G, Karatzas D, Venetsanou K, et al. Comparison of circulating proinflammatory cytokines and soluble apoptosis mediators in patients with chronic heart failure with versus without symptoms of depression. *Am J Cardiol* 2004;94:1326-8.
94. Nikkheslat N, Zunszain PA, Horowitz MA, Barbosa IG, Parker JA, Myint AM, et al. Insufficient glucocorticoid signaling and elevated inflammation in coronary heart disease patients with comorbid depression. *Brain Behav Immun* 2015;48:8-18.
95. Mason DR, Beck PL, Muruve DA. Nucleotide-binding oligomerization domain-like receptors and inflammasomes in the pathogenesis of non-microbial inflammation and diseases. *J Innate Immun* 2012;4:16-30.
96. Penninx BW. Depression and cardiovascular disease: epidemiological evidence on their linking mechanisms. *Neurosci Biobehav Rev* 2017;74:277-86.
97. Pan S, Liu ZW, Lv Y, Song WQ, Ma X, Guan GC, et al. Association between neutrophilic granulocyte percentage and depression in hospitalized patients with heart failure. *BMC Psychiatry* 2016;16:446.
98. Zhang L, Zhang X, Zheng J, Liu Y, Wang J, Wang G, et al. Depressive symptom-associated IL-1β and TNF-α release correlates with impaired bronchodilator response and neutrophilic airway inflammation in asthma. *Clin Exp Allergy* 2019;49:770-80.
99. Krauskopf K, Sofianou A, Martynenko M, Goel M, Wolf MS, Halm E, et al. Depression and increased asthma morbidity in the elderly: poor adherence may be a key factor. *J Gen Intern Med* 2012;27:S156.
100. Palmer JN, Messina JC, Bilech R, Grosel K, Mahmoud RA. A cross-sectional, population-based survey of U.S. adults with symptoms of chronic rhinosinusitis. *Allergy Asthma Proc* 2019;40:48-56.
101. Dietz de Loos D, Lourijsen ES, Wildeman MAM, Freling NJM, Wolvers MDJ, Reitsma S, et al. Prevalence of chronic rhinosinusitis in the general population based on sinus radiology and symptomatology. *J Allergy Clin Immunol* 2019;143:1207-14.
102. Aarab R, Vijverberg SJH, Prins M, Snijder MB, van Ree R, Fokkens WJ, et al. Prevalence of and factors associated with adult-onset asthma in different ethnic groups: the HELIUS study. *Respir Med* 2019;150:113-9.
103. Alt JA, Thomas AJ, Curtin K, Wong J, Rudmik L, Orlandi RR. Mortality risk in patients with chronic rhinosinusitis and its association to asthma. *Int Forum Allergy Rhinol* 2017;7:591-9.
104. Wu D, Bleier BS, Li L, Zhan X, Zhang L, Lv Q, et al. Clinical phenotypes of nasal polyps and comorbid asthma based on cluster analysis of disease history. *J Allergy Clin Immunol Pract* 2018;6:1297-1305.e1.
105. Kim JW, Huh G, Rhee CS, Lee CH, Lee J, Chung JH, et al. Unsupervised cluster analysis of chronic rhinosinusitis with nasal polyp using routinely available clinical markers and its implication in treatment outcomes. *Int Forum Allergy Rhinol* 2019;9:79-86.
106. Philpott CM, Erskine S, Hopkins C, Kumar N, Anari S, Kara N, et al. Prevalence of asthma, aspirin sensitivity and allergy in chronic rhinosinusitis: data from the UK National Chronic Rhinosinusitis Epidemiology Study. *Respir Res* 2018;19:129.
107. Rix I, Hakansson K, Larsen CG, Frendo M, von Buchwald C. Management of chronic rhinosinusitis with nasal polyps and coexisting asthma: a systematic review. *Am J Rhinol Allergy* 2015;29:193-201.
108. Bachert C, Han JK, Desrosiers M, Hellings PW, Amin N, Lee SE, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet* 2019;394:1638-50.
109. Boyd CM, Darer J, Boulton C, Fried LP, Boulton L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple co-morbid diseases. *J Am Med Assoc* 2005;294:716-24.
110. Ban GY, Ye YM, Lee Y, Kim JE, Nam YH, Lee SK, et al. Predictors of asthma control by stepwise treatment in elderly asthmatic patients. *J Korean Med Sci* 2015;30:1042-7.
111. Rolnick SJ, Pawloski PA, Hedblom BD, Asche SE, Bruzek RJ. Patient characteristics associated with medication adherence. *Clin Med Res* 2013;11:54-65.
112. Tonnesen P, Marott JL, Nordestgaard B, Bojesen SE, Lange P. Secular trends in smoking in relation to prevalent and incident smoking-related disease: a prospective population-based study. *Tob Induc Dis* 2019;17:72.

113. Perret JL, Bonevski B, McDonald CF, Abramson MJ. Smoking cessation strategies for patients with asthma: improving patient outcomes. *J Asthma Allergy* 2016;9:117-28.
114. Tan DJ, Walters EH, Perret JL, Burgess JA, Johns DP, Lowe AJ, et al. Clinical and functional differences between early-onset and late-onset adult asthma: a population-based Tasmanian Longitudinal Health Study. *Thorax* 2016;71:981-7.
115. Bellia V, Battaglia S, Catalano F, Scichilone N, Antonelli R, Imperiale C, et al. Aging and disability affect misdiagnosis of COPD in elderly asthmatics. *Chest* 2003;123:1066-72.
116. James AL, Palmer LJ, Kicic E, Maxwell PS, Lagan SE, Ryan GF, et al. Decline in lung function in the Busselton Health Study: the effects of asthma and cigarette smoking. *Am J Respir Crit Care Med* 2005;171:109-14.
117. Price DB, Rigazio A, Campbell JD, Bleecker ER, Corrigan CJ, Thomas M, et al. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. *Lancet Respir Med* 2015;3:849-58.
118. Williams LK, Peterson EL, Wells K, Ahmedani BK, Kumar R, Burchard EG, et al. Quantifying the proportion of severe asthma exacerbations attributable to inhaled corticosteroid nonadherence. *J Allergy Clin Immunol* 2011;128:1185-1191.e2.
119. Williams LK, Pladevall M, Xi H, Peterson EL, Joseph C, Lafata JE, et al. Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma. *J Allergy Clin Immunol* 2004;114:1288-93.
120. Bozek A, Jarzab J. Adherence to asthma therapy in elderly patients. *J Asthma* 2010;47:162-5.
121. Apter AJ, Wan F, Reisine S, Bender B, Rand C, Bogen DK, et al. The association of health literacy with adherence and outcomes in moderate-severe asthma. *J Allergy Clin Immunol* 2013;132:321-7.
122. Federman AD, Wolf MS, Sofianou A, Martynenko M, O'Connor R, Halm EA, et al. Self-management behaviors in older adults with asthma: associations with health literacy. *J Am Geriatr Soc* 2014;62:872-9.
123. Paasche-Orlow MK, Riekert KA, Bilderback A, Chanmugam A, Hill P, Rand CS, et al. Tailored education may reduce health literacy disparities in asthma self-management. *Am J Respir Crit Care Med* 2005;172:980-6.
124. Gazmararian JA, Baker DW, Williams MV, Parker RM, Scott TL, Green DC, et al. Health literacy among Medicare enrollees in a managed care organization. *JAMA* 1999;281:545-51.
125. Kroll JL, Steele AM, Pinkham AE, Choi C, Khan DA, Patel SV, et al. Hippocampal metabolites in asthma and their implications for cognitive function. *NeuroImage Clin* 2018;19:213-21.
126. Halm EA, Mora P, Leventhal H. No symptoms, no asthma: the acute episodic disease belief is associated with poor self-management among inner-city adults with persistent asthma. *Chest* 2006;129:573-80.
127. Soones TN, Lin JL, Wolf MS, O'Connor R, Martynenko M, Wisnivesky JP, et al. Pathways linking health literacy, health beliefs, and cognition to medication adherence in older adults with asthma. *J Allergy Clin Immunol* 2017;139:804-9.
128. Federman AD, O'Connor R, Mindlis I, Hoy-Rosas J, Hauser D, Lurio J, et al. Effect of a self-management support intervention on asthma outcomes in older adults: the SAMBA study randomized clinical trial. *JAMA Intern Med* 2019;179:1113-21.
129. O'Connor R, Muellers K, Arvanitis M, Vicencio DP, Wolf MS, Wisnivesky JP, et al. Effects of health literacy and cognitive abilities on COPD self-management behaviors: a prospective cohort study. *Respir Med* 2019;160:105630.
130. Allen SC, Jain M, Ragab S, Malik N. Acquisition and short-term retention of inhaler techniques require intact executive function in elderly subjects. *Age Ageing* 2003;32:299-302.
131. Usmani OS. Choosing the right inhaler for your asthma or COPD patient. *Ther Clin Risk Manag* 2019;15:461-72.
132. Gibson PG, McDonald VM, Marks GB. Asthma in the older adult. *Lancet* 2010;374:803-13.
133. Quadrelli SA, Roncoroni A. Features of asthma in the elderly. *J Asthma* 2001;38:377-89.
134. Vaz Fragoso CA, McAvay G, Van Ness PH, Casaburi R, Jensen RL, MacIntyre N, et al. Phenotype of normal spirometry in an aging population. *Am J Respir Crit Care Med* 2015;192:817-25.
135. Cuttitta G, Cibella F, Bellia V, Grassi V, Cossi S, Bucchieri S, et al. Changes in FVC during methacholine-induced bronchoconstriction in elderly patients with asthma: bronchial hyperresponsiveness and aging. *Chest* 2001;119:1685-90.
136. Allen SC, Yeung P. Inability to draw intersecting pentagons as a predictor of unsatisfactory spirometry technique in elderly hospital inpatients. *Age Ageing* 2006;35:304-6.
137. Enright PL, McClelland RL, Buist AS, Lebowitz MD. Correlates of peak expiratory flow lability in elderly persons. *Chest* 2001;120:1861-8.