Thesis

Sex- and gender-specific differences in asthma

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Graz, 05.11.2024 *Lena Gattringer m.p.*

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“There is no duty more obligatory than the repayment of a kindness.”
– *(Quote from Marcus Tullius Cicero (1))*

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Zusammenfassung

Asthma ist eine der häufigsten chronisch entzündlichen Lungenerkrankungen, von der Menschen in allen Altersgruppen überall auf der Welt betroffen sind. Die Krankheit ist vor allem durch eine chronische Entzündung der Atemwege, die meist durch eine obstruktiv-reversible Bronchokonstriktion mit bronchialer Hyperreaktivität, und den damit verbundenen „asthma-typischen" Symptomen gekennzeichnet. Weltweit steigt die Inzidenz an Asthma zu erkranken stetig an. Während im Kindesalter Jungen häufiger an Asthma erkranken als Mädchen, dreht sich dieses Verhältnis im Erwachsenenalter durch fluktuierende Hormonspiegel, vor allem von Östrogen und Progesteron um, und mehr Frauen als Männer sind betroffen. Im fünften Lebensjahrzehnt steigt die Prävalenz von Asthma bei Männern wieder an, wenn ein Rückgang des Testosteronspiegels zu beobachten ist. Dies lässt unter anderem auf den Einfluss den Sexualhormone auf die Erkrankung haben rückschließen (Figure 1). Fluktuierende hormonelle Einflüsse wie beispielsweise während der Menstruation, einer Schwangerschaft oder in der Menopause, können sich unterschiedlich auf den Krankheitsverlauf und die Lebensqualität bei Frauen auswirken. Häufig sind die Beschwerden stärker ausgeprägt und das Risiko für Exazerbationen steigt durch Hormonschwankungen. Es ist daher wichtig diese Aspekte vor allem beim Management und der Therapie von Asthma bronchiale zu berücksichtigen.
Asthma ist ebenfalls ein komplexes Zusammenspiel aus Genetik und Umwelt. Geschlechtsspezifische Unterschiede sind daher nicht nur auf endo- und exogene Hormone und deren Zyklen zurückzuführen. Auch genetische Faktoren und Umwelteinflüsse scheinen eine wesentliche Rolle in Bezug auf die geschlechtsspezifischen Unterschiede bei Asthma zu spielen, jedoch gibt es in dieser Hinsicht noch eine Reihe unbeantworteter Forschungsfragen.

In diesem narrativen Literaturreview werden kurz die pathophysiologischen Grundlagen von Asthma bronchiale beschrieben und ein grober Überblick über die Diagnostik und Therapie gegeben, wobei hier auch die diesbezüglichen Unterschiede zwischen den Geschlechtern erörtert werden. Danach befasst sich die Arbeit genauer mit der aktuellen Literatur zu den unterschiedlichen hormonellen Einflüssen bei Frauen und Männern in Bezug auf die Erkrankung und

den damit verbundenen geschlechts-spezifischen Unterschieden hinsichtlich Prävalenz, Krankheitsverlauf, Diagnostik, Therapie und Auswirkungen auf die Lebensqualität.
In den meisten Arbeiten zu diesem Thema wird dem Sexualhormon Östrogen ein proinflammatorischer Effekt zugeschrieben, wohingegen Testosteron protektive Eigenschaften aufweist, was unter anderem die unterschiedliche Altersprävalenz erklären könnte. Einige Studien weisen jedoch auch auf einen womöglich positiven und protektiven Einfluss, den Östrogen auf den Entzündungsprozess, und damit auf den Krankheitsverlauf haben kann, hin. Viele Frauen erleben während der Menstruation oder einer Schwangerschaft, in denen es zu teils starken Hormonschwankungen kommen kann, eine Veränderung bezüglich ihrer Symptomatik und Asthmakontrolle. Das Risiko an „late-onset asthma“ zu erkranken, eine Art von Asthma, welches oftmals schwer zu behandeln ist, steigt vor allem bei (peri-) menopausalen Frauen stark an.
Welchen Einfluss äußerlich zugeführten Hormone, wie zum Beispiel bei hormoneller Kontrazeption oder einer Hormonersatztherapien in der Menopause oder bei einer Geschlechteranpassung von Transgenderpersonen haben, ist nicht eindeutig geklärt und weiterhin unter Forschenden umstrittenen.

Zusammenfassend kann gesagt werden, dass ein großer Forschungsbedarf besteht, um die verschiedenen Zusammenhänge zwischen der Erkrankung, den Hormonveränderungen und dem biologischen Geschlecht genauer zu verstehen, und damit das Asthmamanagement für Frauen und Männer, aber auch für transgeschlechtliche Menschen, individuell anpassen zu können. Ebenfalls bedarf es weiteren Langzeitstudien, die beispielsweise speziell für Frauen mit schwerem Asthma oder für Frauen während der Menopause ausgelegt sind. Zusätzlich sollten in Zukunft auch Guidelines bei Therapieempfehlungen vermehrt auf die geschlechts-spezifischen Unterschiede eingehen.

Abstract

Asthma is one of the most common chronic inflammatory lung diseases affecting people of all ages all over the world. The disease is characterized by chronic inflammation of the airways, usually due to obstructive-reversible bronchoconstriction with bronchial hyperreactivity and a heterogeneous group of resulting symptoms. The incidence of asthma is steadily increasing worldwide. While in childhood boys are more likely to develop asthma than girls, this ratio is reversed in adulthood with fluctuating hormone levels, particularly of estrogen and progesterone, and more women than men are affected. In the fifth decade the prevalence of asthma rises again in males, when a decrease in testosterone levels can be observed. This is partly due to the influence which sex hormones have regarding asthma (Figure 1). In women, fluctuating hormonal levels during menstrual cycle, pregnancy or menopause can have different effects on the course of the disease and quality of life. The symptoms are often more pronounced, and the risk of exacerbations increases due to hormonal changes. Therefore, it is important to take these aspects into account, especially in the management and treatment of asthma. However, sex and gender differences are not only due to endo- and exogenous hormones and their cycles. Asthma also is a complex interplay between genetics and the environment, but there are still several unanswered research questions in this regard.

This narrative literature review briefly outlines the pathophysiological fundaments of asthma and provides a short overview of diagnostic and therapy, including a brief reflection of the sex- and gender- differences in this context. Furthermore, it delves into recent literature on the different hormonal influences in women and men with asthma and evaluates gender-specific differences in terms of prevalence, diagnosis, disease progression, therapy, and effects on quality of life.
In most studies, the sex hormone estrogen is described as having a pro-inflammatory effect, whereas testosterone is attributed protective properties. These observations could explain the different age prevalence in women and men. However, some studies also point to a possible positive and protective influence of estrogen on the inflammatory process and, thus, the course of the disease. Many women experience a change in their symptoms and asthma control during

menstruation or pregnancy, both periods in which sex hormones underly fluctuations. The risk to develop "late-onset asthma", a type of asthma which is often difficult to treat, increases significantly, especially in (peri-) menopausal women. The influence of externally administered hormones, such as hormonal contraception or hormone replacement therapy during menopause or gender reassignment for transgender people, is not clearly understood and remains controversial among researchers.

In summary, there is a great need for further research to better understand the relationship between the disease, hormonal changes, and gender, in order to be able to individually adapt the management of asthma for women and men, but also for transgender people. In order to understand certain (patho-) mechanisms more precisely, further long-term studies are needed, e.g., specifically for women with severe asthma or for women during menopause. In future, guidelines should also take greater account of gender-specific differences in therapy recommendations.

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1 List of abbreviations

AERD	Aspirin-exacerbated respiratory disease
AIT	Allergen immunotherapy
BMI	Body mass index
BPA	Bisphenol A
COPD	Chronic obstructive pulmonary disease
DHEA	Dehydroepiandrosterone
DHEAS	Dehydroepiandrosterone sulphate
DHT	Dihydrotestosterone
ECRHS	European community respiratory health survey
e.g.	Example given
ERS	European respiratory society
ER-α	Alpha estrogen receptor
ER-β	Beta-estrogen receptor
E1	Estrone
E2	Estradiol
E3	Estriol
FeNO	Fractionated exhaled nitric oxide
FEV_1	Forced expiratory volume per second
FSH	Follicle stimulating hormone
FVC	Forced vital capacity
GINA	Global initiative for asthma
GnRH	Gonadotropin-releasing hormone
HC	Hormonal contraceptives
HRT	Hormone replacement therapy
ICS	Inhaled corticosteroids
IgE	Immunoglobulin E
IL	Interleukin
ILC	Innate lymphoid cells
LABA	Long-acting beta-agonist
LAMA	Long-acting muscarinic antagonist
LEAD	Lung, heart, social, body study
LH	Luteinizing hormone

LTRA	Leukotriene receptor antagonists
MHT	Menopausal hormone therapy
non-Th2	Non-Type 2 asthma
NSAID	Non-steroidal anti-inflammatory drug
OCS	Oral corticosteroids
PEF	Peak expiratory flow
PIAMA	Prevention and Incidence of Asthma and Mite Allergy
PMA	Perimenstrual asthma
SABA	Short-acting beta-agonist
SAMA	Short-acting muscarinic antagonist
SHBG	Sex hormone-binding globulin
SNP	singe nucleotide polymorphisms
Th2	Type 2 asthma
TNF-α	Tumor necrosis factor-α
TSLP	Thymic stromal lymphopoietin
XIST	X-inactive specific transcript gene

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4 Introduction

4.1 Definition

Asthma is a common chronic inflammatory lung disease affecting people of all ages. The disease is characterized by chronic inflammation of the airways, reversible bronchial obstruction with bronchial hyperresponsiveness and a heterogeneous group of symptoms. (2) Those symptoms range from mild to severe and can be triggered by various factors including allergens, exercise, stress, respiratory infections and other (environmental) irritants. (3)

The underlying cause of asthma is not fully understood up to now (status 2023), but it is believed that multiple factors such as genetics, sex, environmental exposure, lifestyle, and momentary health conditions (including risk factors like smoking or obesity) are involved in the disease's pathology. (4)

4.2 ICD classification

J45 - Asthma

- **J45.0**: predominantly allergic asthma (extrinsic asthma)
- **J45.1**: nonallergic asthma (intrinsic asthma)
- **J45.2**: mild intermittent asthma
- **J45.3**: mild persistent asthma
- **J45.4**: moderate persistent asthma
- **J45.5**: severe persistent asthma
- **J45.8**: mixed asthma (asthma with combined J45.0 and J.45.1)
- **J45.9**: other and unspecified asthma (including late-onset asthma)

(This review gives just a short overview of the current ICD classification and refers to https://icd.who.int/browse10/2019/en#/J45.0 for more details. In addition, this review does not go into detail with the individual classifications)

4.3 Overview of asthma

Worldwide an estimated 334 million people or around 4.2% of the world's population are affected by the disease. The prevalence varies significantly among different countries. In children, asthma is the most common chronic lung disease with a prevalence of over 10%, in adults the prevalence is up to 5% (5), with the highest in Scotland and New Zealand and the lowest in Eastern Europe and Asia. (6) According to the *LEAD* (Lung, hEart, sociAl, boDy) study, a longitudinal cohort study which among others tried to investigate respiratory health across the Austrian population (aged 6-82 years), the overall prevalence of current asthma was reported to be 4.4% of the general population of Vienna, with slight differences in females (4.8%) compared to males (4.3%). The highest prevalence for females in Austria was found to be between the age of 50-<60 years and for males at the age of 60-<70 years. (5)

Asthma is not a "single disease" but can be categorized into several subtypes ranging between a mild and severe form. (3) Allergic asthma typically starts in childhood, whereas non-allergic asthma tends to develop later in life. Among adults with asthma, around 30% have allergic asthma, while another 30% have non-allergic asthma. The remaining individuals often suffer from mixed forms of both. (6) Forms of asthma with a later onset mostly are more severe and difficult to control and associated with increased morbidity and mortality. (5,7) In most cases the intensity of asthma response is related to the underlying airway inflammation. Typical characteristics of asthma among others include chronic airway inflammation, airway hyperresponsiveness and reversible airflow obstruction. (6)

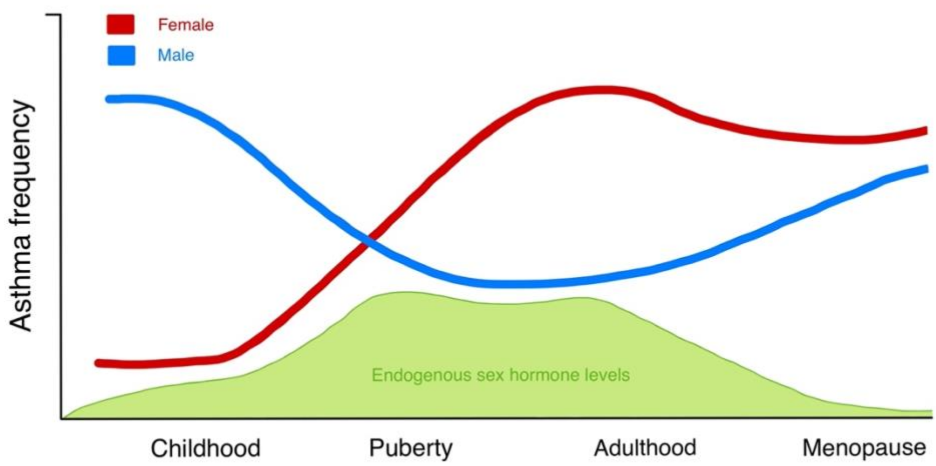

Figure 1 *Relation between asthma frequency and fluctuating endogenous sex hormone levels. During childhood, asthma prevalence is higher in boys than in girls. This ratio changes during puberty with the rise of endogenous sex hormone levels. Adapted from the publication "Sex hormones and asthma: The role of estrogen in asthma development and severity".* *(76)*

4.4 Sex differences in respiratory physiology and anatomy

Located in the chest, the lungs as paired organs, are responsible for the gas exchange. Physiologically during the active process of the inspiration phase the diaphragm contracts and moves down, while the intercostal muscles expand the chest cavity, creating a negative pressure in the pleural cavity and leading air to move in. During expiration (passive process) the diaphragm relaxes, and the chest cavity decreases in size, pushing the air out of the lungs again. Differences in lung physiology are primarily due to anatomical variations. (8,9)

On average, men tend to be taller than women, having larger lungs with greater absolute lung volumes. (8) However, relative lung volumes and capacities between the sexes are similar. For example, the ratio of functional residual capacity to total lung capacity is consistent between men and women, suggesting that elastic properties of the lung and chest wall do not depend on sex. (10) Differences in lung architecture and respiratory function between sexes have been linked to the disparities in the prevalence of lung diseases such as asthma. One factor that is observed and may possibly explain the higher prevalence of asthma in boys during prepuberty is dysanaptic lung growth. Especially in early life, dysanaptic lung growths, meaning disproportionate or differential growth of the airways and lung parenchyma, results in a lower number of alveoli relative to the number of airways. In girls, the growth of bronchial airways and lung tissue occurs more proportionally. (11) As soon as boys mature, they tend to develop larger airway diameters, increased lung volumes, greater maximum expiratory flow and a larger diffusion surface area compared to females. (8,12) After puberty women are affected more than men by respiratory symptoms due to certain lung diseases such as asthma. Smaller airway diameters and lung size in women can affect respiratory function and may lead to differences in how respiratory conditions manifest and are managed in females compared to males. Additionally, a higher BMI or pregnancy can significantly influence respiratory function. In summary, disparities in lung structure and function should be considered when evaluating and treating respiratory conditions in females. (8)

4.5 Pathophysiology

Asthma is characterized by chronic airway inflammation which results throughout a complex interplay between immune cells, mediators, and structural airway cells. In general, the disease affects the small airways obstructing especially the small bronchioles. In most asthmatics the process often begins with the exposure to a specific trigger or an inhaled irritant such as an allergen (e.g., dust or pollen) or other stimuli like cold air or stress, which leads to a bronchial hypersensitivity reaction. This results in narrowing of the airways which leads to airway obstruction and variable airflow limitation. Asthma patients often experience respiratory symptoms like shortness of breath, chest tightness, coughing and wheezing, mostly accompanied by an increased mucous production. (6)

During an early (or acute) phase, (often when exposed to a trigger) certain epithelial mediators such as interleukin 25 (IL-25), interleukin 33 (IL-33) or thymic stromal lymphopoietin (TSLP) are released. These cytokines initiate multiple signaling pathways to maintain inflammation and recruit and activate immune cells. TSLP primes dendritic cells to promote the differentiation of naïve CD4+ T-cells (a type of lymphocytes) into T2-helper cells (Th2). These Th2 cells produce various cytokines which activate B-cells. B-cells differentiate into plasma cells which produce IgE, an antibody which in turn is important for the activation of mast cell responses to allergens. (7) Immunoglobulin E (IgE) cross-links with the antigen and binds among others to mast cells, causing mast cell degranulation and subsequently the release of mediators such as histamine, prostaglandin D2, and interleukins. These mediators attract other immune cells and lead to airway smooth muscle contraction. (13) Innate lymphoid cells (ILCs), especially type 2 ILC (ILC2), which are located on mucosal surfaces such as the lungs, contribute to the pathogenesis of (allergic) asthma by also producing type 2 cytokines such as IL-5 and IL-13. (14) This immune reaction together with the neural pathway (activation of the nervous system) causes an acute bronchoconstriction of the smooth lung muscles.

The early phase is followed by a late phase reaction, where the innate and adaptive immune response leads to a further inflammation reaction. This delayed reaction is especially characterized by inflammatory cells, such as T-lymphocytes, neutrophils, eosinophils, and associated interleukins such as IL-4, IL-5 and IL-13 in Type 2 high asthma or IL-6, IL-8 and IL-17A in Type 2 low asthma. These inflammatory cells start infiltrating the airways, causing further responses such as vasodilatation with subsequent oedema and increased mucus production. (13)

4.5.1 Airway remodeling

Due to chronic inflammation and repetitive repair processes, structural changes in the airways occur, also referred as airway remodeling. Mechanisms of remodeling include thickening of the airway wall due to increased bronchial smooth muscle mass, collagen deposition and changes in the epithelial layer. These smooth muscle cells can produce inflammatory cytokines which further promote the inflammatory process. Over time, these changes can lead to persistent airflow limitation and increased severity of asthma symptoms, making it more difficult to manage asthma effectively. Also, airway remodeling can have an impact on lung function, which over time might decline. If not treated appropriately, these changes might be permanent. Therefore, early and effective management is crucial to prevent remodeling and enhance lung function and asthma control. (15,16)

4.6 Types of asthma

Asthma cannot be seen as a single entity but rather as an umbrella term for several types or subgroups. Also, in some patients certain pheno- and endotypes of asthma might overlap, making the diseases management more challenging. (7) (This review gives a short overview of the most common types of asthma) Categorizing asthma into subgroups is important since different asthma types do not respond equally to the same therapeutic interventions and therefore require different medications and therapy regimes. Special treatments target specific cytokines of different molecular pathways. Severe asthma for example often requires the use of specific targeted biologic therapies but might not respond to corticosteroids.(7) Researchers categorize asthma phenotypes and endotypes based on the underlying biological mechanisms and biomarkers of each pathway (*Figure 2).*

Phenotypes can be classified into Type 2 (T2)-high phenotypes, including early-onset allergic asthma, late-onset eosinophilic asthma and aspirin-exacerbated respiratory disease (AERD) and T2-low phenotypes such as smoking- and obesity-associated asthma, and very-late onset asthma (asthma due to consequences of aging). (7) Inflammatory phenotyping can also be classified into allergic or extrinsic (T2-high) and non-allergic or intrinsic (T2-low) asthma. (5)
Asthma endotypes can also be described as: eosinophilic, neutrophilic, mixed type (eosinophilic and neutrophilic) and paucigranulocytic, based on the molecular pathway of inflammation. Eosinophilic asthma is referred as T2-high endotype and is characterized by a high number of eosinophils in the airways which are involved in the inflammation pathway, whereas neutrophilic or non-eosinophilic asthma (higher number of neutrophils) and paucigranulocytic asthma (less eosinophils and neutrophils) are categorized into T2-low endotypes of asthma. (17)

Type 2 high (T2-high) asthma

Characteristic immune cells in this pathway include group 2 innate lymphoid cells (ILC2s), eosinophils, mast cells and CD4+ T2-helper cells (T2-cells). T2-cells produce specific cytokines like interleukins IL-4, IL-5, IL-9, IL-13, IL-25 which drive the inflammation. The release of those cytokines results in increased IgE triggered hypersensitivity to allergens as well as an increased infiltration of eosinophils and activation of airway epithelial cells. (3) Biomarkers which help to identify T2-high inflammation include among others, above mentioned interleukins, eosinophils in the airways, peripheral blood eosinophil counts, allergen-specific IgE, fractional exhaled nitric oxide (FeNo), prostaglandin D2 and TSLP. (14) Nevertheless, it is important to keep in mind that these biomarkers may vary independently due to different underlying pathways. Their presence does not guarantee a positive response to targeted treatments. (7) T2-high asthma can be further divided into early-onset allergic asthma and late-onset eosinophilic asthma.

Early-onset allergic asthma also refers to extrinsic asthma and can vary from a mild to severe form. (7) As the name suggests, this type of asthma often begins in childhood and in most cases is associated with atopy and other allergic conditions. This phenotype is characterized by elevated immunoglobulin E (IgE) levels and/or positive allergy skin test (2,7) Nevertheless, it is important to keep in mind that elevated total or specific IgE levels (as a biomarker for allergic asthma) are not entirely specific, as up to 50% of the general population may test positive in allergy tests. Furthermore, it remains unclear whether severe asthma develops progressively from a milder form or emerges directly as a severe condition during childhood. (7) When allergies to environmental allergens (e.g., infections) can neither be detected with a skin test nor with specific serum IgE levels, this type of asthma is referred to as intrinsic asthma or non-allergic asthma. This applies in almost half of adults with asthma. (2)

Late-onset eosinophilic asthma is another subset of T2-high asthma, mostly beginning in adulthood. This type is less responsive to corticosteroid treatments in around half of the affected patients, despite high sputum and eosinophil levels. Some patients also show increased sputum neutrophilia. This type of asthma is more severe and, in many cases, difficult to control. Therefore, recognizing this phenotype early might initiate to escalate asthma therapy earlier. (7)

A subset of this late-onset phenotype is aspirin-exacerbated respiratory disease (AERD) which is triggered by cyclooxygenase-inhibitors like aspirin. The underlying mechanisms of AERD are not fully understood, but it is assumed that certain deregulatory pathways and imbalances of inflammatory inhibition lead to increased bronchoconstriction. AERD is also a more severe type of asthma. (7)

Type 2 low (T2-low) asthma also refers to non T2-high asthma and in contrast tends to be associated less with eosinophils and instead includes asthma characteristic of neutrophilic and paucigranulocytic endotypes. This subtype of asthma is more commonly seen in adults than in children. Furthermore, it is also associated with (very) late-onset asthma, corticosteroid resistance and comorbidities such as obesity and gastroesophageal reflux disease. There is currently no agreed-upon definition or signature biomarker for T2-low asthma other than the absence of typical Th2 cells and eosinophilic inflammation and a limited number of biomarkers which are mediated by Th1 and Th17 cells, including among others IL-6, IL-8, IL-17A, and TNF- α. This lack of specific biomarkers for this subtype makes it challenging to develop effective treatments, leading to a more severe form of asthma. (14,18)

Severe asthma

Around 5-10% of asthmatics have severe asthma. Severe asthma can be defined as a condition that requires an add-on treatment such as high-dose ICS in combination with a second controller medication (and/or OSC) as prevention of becoming uncontrolled. Nevertheless, in some patients, severe asthma remains uncontrolled despite therapy. (19) Severe asthma phenotypes vary based on age and sex. Age distribution shows two peaks: one during childhood between ages 5 and 18, with more males being affected by severe asthma forms (mostly allergic asthma) and another peak in older adults over 60 years with female sex prevailing. In a prospective registry for severe asthma from the *German Asthma Net* with cases from more than 50 centers in Germany (also including data from patients in Austria), 57% of all registered patients were female. (19) Severe asthma is associated with a significantly lower lung function, resulting in overall increased mortality and higher costs for the health system. (20) Nevertheless, severe asthma exacerbations are seen very rarely in hospitals nowadays, and also the numbers of asthma deaths are significantly falling. (21)

4.6.1 Sex-specific types of asthma

Since sex differences are an important influential variable related to the characteristics of certain phenotypes, understanding and classifying clusters has become important to, among others, develop personalized treatment strategies.

A study by *Hsiao et al*. described and analyzed different asthma clusters with heterogenous characteristics, showing different predominant phenotypes between females and males. (22) The clusters which were more frequently observed in women, included an atopic, eosinophil-predominant and an obese, neutrophilic-predominant pattern. The eosinophil-dominant cluster was above all observed in younger females with an earlier onset of asthma, a normal BMI and normal lung function, but high total serum IgE levels and eosinophil counts. In addition, many of these women also had some kind of atopy, such as sneezing or allergic rhinitis. (22) Neutrophilic asthma associated with obesity is a distinct type of asthma which is seen more frequently in women than in men. Women generally have more subcutaneous than abdominal fat which secretes more leptin. Leptin attracts neutrophils to the airways, resulting in increased neutrophilic inflammation. Women with this late-onset type of asthma often have a lower lung function and a poorer response to corticosteroids, compared to non-obese women. This does not apply to men suffering from the same type. (23,24) Women with this neutrophil-predominant type show high blood neutrophil levels, but a lower total serum IgE and blood eosinophil count. (22) These two clusters described above have more than twice the risk of asthma exacerbations. A third cluster identified in females was a late-onset, non-atopy type with normal BMI, low neutrophil and eosinophil levels. This type was associated with lower inhaled (ICS) and oral corticosteroid (OCS) medication use and normal lung function compared to the other two types. (22) In men, two asthma phenotypes were identified which were associated with current and past smoking. In the group of current smokers, most patients showed an early asthma onset, a higher BMI, high blood neutrophils and total serum IgE levels. This type was also associated with allergic rhinitis and higher use of ICS and OCS. A later asthma onset, normal BMI and high blood eosinophil levels were observed in male ex-smokers. These patients had a significantly lower lung function. Males with a late-onset asthma type, normal BMI, lower IgE and blood eosinophil levels, most of them not smoking, had better lung function and required less medication. (22)

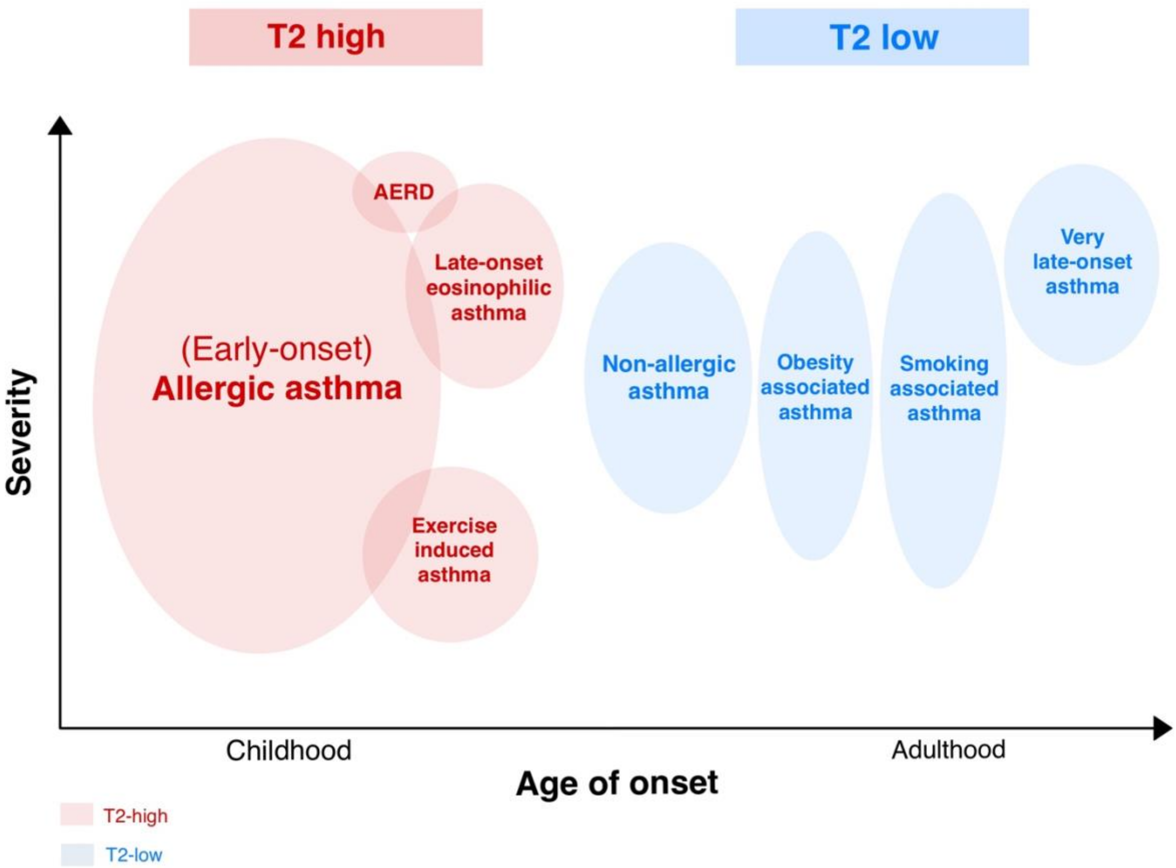

__Figure 2__ Asthma phenotypes and severity throughout the life span. The size of the circles indicates the relative population size, with red circles representing T2-high inflammation and blue circles T2-low inflammation. Individual subtypes can overlap and the onset of asthma can also vary with age. T2 high: Type 2 high inflammation, T2 low: Type 2 low inflammation, AERD: Aspirin exacerbated respiratory disease. Adapted from „Asthma phenotypes: the evolution from clinical to molecular approaches". (128)

4.7 Sex- and gender-specific risk factors

Genetics do play a role in asthma pathogenesis, although not all genes or specific gene-environment interactions, which might cause asthma, have been clearly identified yet.

Patients with asthma (especially T2-high asthma) often have a genetic predisposition for other atopic conditions such as allergic rhinitis or eczema. (2)

Regarding sex-specific differences, the X chromosome houses several regulatory response genes, which might play an important role in the development of immune-related diseases, such as asthma. The presence of two X chromosomes in women is a decisive factor for sex-specific differences regarding the role of enhancing innate and adaptive immune responses. (14,25) The X-inactive-specific transcript gene (XIST), located on the X chromosome, serves as a primary regulatory factor for X chromosome inactivation in mammals and is expressed higher in females. XIST can among others stimulate the proliferation and differentiation of certain immune cells, regulate obesity-related processes, and also seems to be involved in androgen and estrogen signaling pathways. Dysregulation of XIST could lead to dysregulation of immune function. This kind of dysregulation has among others been observed in association with autoimmune diseases and chronic inflammatory conditions. However, regarding sex-specific differences the relationship between XIST expression and asthma has not yet been researched sufficiently. (25)

Genetic polymorphisms, which are variations in DNA sequences that can affect how individuals respond to environmental exposures, also influence gender disparities. Researchers found that singe nucleotide polymorphisms (SNP) in certain genes have among others been linked to IgE levels and asthma risk. (26) A recent study from *Odimba et al.* identified sex-specific polymorphisms which might be involved in immunomodulatory mechanisms and airway remodeling associated with asthma. Five male-specific SNPs and three female-specific SNPs were significantly associated with asthma. Among these polymorphisms, some were associated with an increased and others with a decreased risk of asthma. (27) Another study investigating polymorphisms associated with asthma found two SNPs which were identified in the genomic region of TSLP. One of these SNPs has been associated with a reduced risk of asthma in women, the other one with a reduced risk in men. (28) These findings are examples that provide sex-specific genetic clues associated with asthma pathogenesis. However, more studies are needed to explore and find sex-specific expressions which are related to pathways of asthma pathogenesis. It remains unclear whether these differences are driven by gender or by sex-related hormonal differences and therefore further research on this topic is needed. (26)

Socioeconomic factors have an impact on the development and severity of asthma (*Figure 3*). Risk factors for early asthma development include maternal smoking, preterm birth, caesarean section, and significant use of antibiotics within the first two years of life. Studies like the long-term cohort study PIAMA (Prevention and Incidence of Asthma and Mite Allergy) tried to investigate risk and genetic factors for asthma and allergies in children. This study has shown that parental history of asthma or allergies, early life exposure to allergens and smoking during pregnancy can significantly influence the development of asthma and allergies. (29,30)

Smoking is a risk factor for an increased asthma prevalence, particularly in female smokers compared to female non-smokers. (31) Active or passive tobacco smoking, vaping, or smoking of marijuana impair lung function and often contribute to asthma exacerbation and poor asthma control. (2) Asthma patients who smoke also appear to be less sensitive to corticosteroids. (32) Regarding sex differences, results from a population-based survey found that adult male asthmatics with first- and secondhand smoke exposure were more likely to have asthma exacerbations than exposed females. The percentage of current smokers was higher in men than in women. (33) In terms of smoking during pregnancy *Murphy et al.* found that asthma exacerbations were more frequent and severe in female asthma patients who smoked than in female asthma patients who did not smoke. (31) In addition, the risk of low birth weight was increased in pregnant women with asthma who smoked compared to pregnant women who did not smoke, most likely due to the combined effect of asthma, smoking, and severe exacerbations. (31) Among transgender people, smoking rates are higher compared to non-transgender individuals, which negatively effects transgender health and contributes to the risk of worsening asthma symptoms in transgender asthma patients. (34,35)

Environmental factors (like air quality and pollution), demographics (education, ethnicity), and other lifestyle factors such as breastfeeding, physical activity and diet all seem to play important roles in the incidence and severity of asthma and allergic diseases. (30)
Women and men are often exposed to different occupational asthma triggers associated with allergic sensitization or deterioration of lung function. Several occupations and industries have a higher risk of causing occupational asthma (workplace-related exposure) and this risk seems to be related to sex. A retrospective study analyzed data over a timespan of more than 20 years to elucidate the relationship between sex differences and the onset and severity of occupational asthma. (36) This study showed that men were more likely to work in the automotive, construction, metal, forestry and wood industries, whereas females were more likely to work in health care related occupations. Men seem to be more often exposed to causative agents such as diisocyanates, whereas women reported to be more often exposed to allergens such as cleaning products, molds, yeast, and medications triggering asthma. Furthermore, it was observed that men compared to women had a longer time between occupational exposure and the onset of asthma symptoms (36 month for men and 18 months for women) and a longer time before being diagnosed with asthma (24 months compared to 14 months). Men with occupational asthma also showed an increased decline in lung function (measurements of FEV_1, FVC, and FEV_1/FVC-ratio) compared to women and that men had to leave their employment earlier due to occupational asthma. A follow-up analysis compared the development of symptoms, time to diagnosis, and lung function between men who never smoked and those who worked in "male-predominant" industries, but found no significant differences. However, it was found that these men whose asthma diagnosis took longer than 24 months had poorer lung function compared to those diagnosed within 24 months. (36)

Chemicals such as bisphenol-A (BPA), pesticides, and phthalates are associated with endocrine disruption and might also be involved in the pathology of asthma and allergies. These external chemicals are commonly contained in certain plastic materials and other consumer products such as cosmetics, toys, and medications, but are also found in food and the environment. (37) A population-based, case-control study investigating the association of early environmental exposures and

the risk of developing asthma in the first five years of life, found that the exposure of, among others, pesticides, herbicides, farm animals and crops were significantly associated with the development of early-onset persistent asthma in children. (38) *Glue et al.* found that when human cells were exposed to certain phthalates this was associated with an increased release of histamine and inflammatory mediators, suggesting that susceptible people might have an augmentation of the inflammatory response throughout exposure. (39) *Yan et al.* observed the effects of BPA in an animal study, where mice prenatally or in adulthood were exposed to different doses of BPA. A dose-dependent exposure induced a greater antigen-stimulated interleukin (e.g., IL-4, IL-13) and a reduced regulatory T cells production. This study highlights that especially an early exposure to BPA promotes an increased inflammatory reaction by reducing regulatory T cells. (40)
Future studies are needed to explore how these external chemicals contribute to the development of asthma.

A high **body mass index** (BMI) is recognized as another significant risk factor for asthma. Adipose tissue does not only impinge on the chest, which leads to a reduction in lung volumes, but can also produce pro-inflammatory cytokines which might contribute to and exacerbate systemic airway inflammation. Also, adipocytes produce estrogen and leptin (a hormone which among others is important for regulating appetite), both having pro-inflammatory effects. Obese patients have higher levels of estrogen and leptin, compared to those in non-obese individuals. (26) The relationship between obesity and asthma is multifaceted and seems to be more pronounced in women, particularly those aged 12 to 44 years. Women with higher BMI often experience more severe forms of asthma compared to men. (41) Among transgender people the rates for obesity were observed to be higher than in cisgender individuals (gender identity matching the biological sex). (35)
Nevertheless, the strength of the BMI effecting asthma remains unclear, and further research must be done to understand the relationship between asthma and BMI, to develop effective management strategies for women who are overweight.

To summarize, the most important risk factors include genetics, environmental factors, smoking or exposure to smoke, professions exposed to certain hazardous chemicals, as well as BMI, lifestyle, and diet. (2)

4.8 Comorbidities and quality of life in asthma patients

Quality of life and the overall well-being are vital endpoints of treatment, as they represent the disease's impact from the patient's perspective. (42) Nevertheless, routine assessment of psychological and emotional well-being is not currently a standard part of community-based asthma care, despite its association with poor asthma outcomes. (43,44) Diagnostic interviews or clinical questionnaires, such as an *Asthma Control Test* (ACT), *Asthma Control Questionnaire* (ACQ) or *mini Asthma Quality of Life Questionnaire* (AQLQ) can be used to assess factors that limit a patient's quality of life. These screening tools might include questions such as the frequency of exacerbations, influence of asthma on daily work or school performance, avoidance of daily life tasks or reduced social activities, due to asthma symptoms. (42) Other aspects which impact quality of life might include socioeconomic status (measured among others by marital status, education level, monthly income, or occupation), quality of sleep, access to healthcare services, and ageing. (42) However, these questionnaires do not address sex- and gender differences in assessment and are not tailored to sex- and gender-specific issues.

Asthma patients often suffer from additional comorbidities, which are associated with certain types of asthma. Some comorbidities seen in females, such as GERD or obesity, are in many cases associated with non-eosinophilic inflammation. (41) A study by *Dragon et al.* using medical records as data source also showed that transgender people are more likely to be affected by chronic conditions such as asthma, COPD, obesity, and depression than cisgender individuals. (34) Comorbidities can contribute to poorer asthma control and therefore are often associated with higher morbidity and lower quality of life. A retrospective cohort study concluded that certain chronic comorbidities occur with varying prevalence depending on gender. For example, chronic obstructive pulmonary disease (COPD) and coronary heart disease both seem to be more prevalent in men suffering from asthma, whereas osteoporosis, anxiety, or depression are more prevalent in asthmatic women. The study also observed that the presence of chronic diseases is generally more common in female asthma patients than in males. (45)

In adults, more women are affected from severe asthma forms than men. Especially women with a later onset of severe asthma have a more frequent use of relief medication, more frequent emergency department visits and higher rates of hospitalizations, which are to some extent associated with a lower quality of life and mental health issues. (46,47) Patients particularly with moderate or severe asthma seem to be more psychosocially affected than those with mild asthma. (46) Regarding mental health, there is a significant association between anxiety, nervousness, depression, and asthma. In general, asthma patients are up to six times more likely to suffer from anxiety or depression than the general population. (44,46) The relationship between asthma and psychological burdens appears to be bidirectional. Asthma can precede an individuals' anxiety and depression, while psychological and behavioral problems can also lead to worsening of asthma symptoms. (44) Mental health conditions can interfere with adherence to treatment plans, e.g., inappropriate or poor self-management behaviors or an overuse of rescue medication, often resulting in poor asthma control and thus lower quality of life. (12,44)

In summary, physical and psychological health significantly contributes to the burden of living with asthma. It is important to keep in mind that more women suffer from additional comorbidities, including mental health issues. (45)

To achieve good outcomes, not only screening for asthma symptoms but also treatment of mental health issues (evaluation of physical, emotional, and social health) must be an integral part of asthma management. A patient's personal perception of well-being as well as other factors such as gender, age or socioeconomic status should be considered and included in therapy plans. (42,44)

Potential factors that influence sex and gender differences in asthma patients:

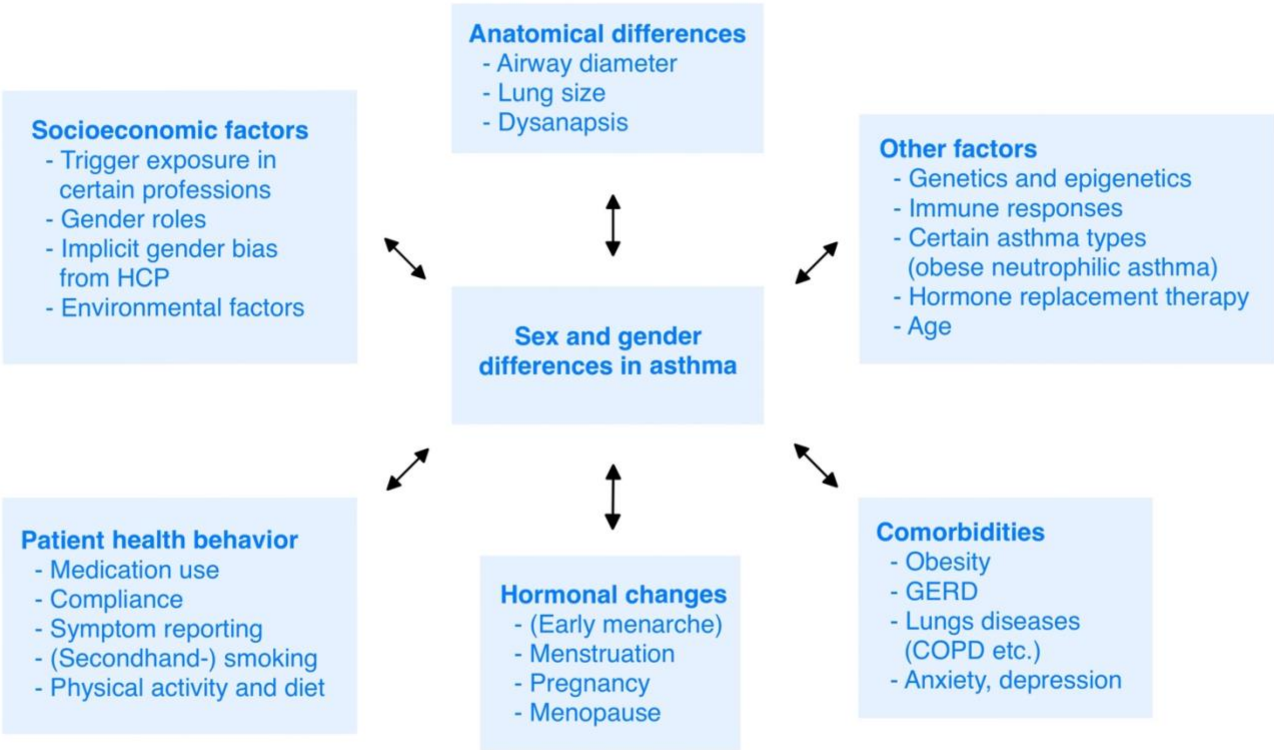

Figure 3 *Factors influencing sex and gender differences observed in asthma patients. The bi-directional arrows show these factors which potentially have impact on the disease and the sex differences. GERD: gastro-esophageal reflux disease, COPD: chronic obstructive pulmonary disease, HCP: health care provider. Adapted from "Sex and gender in asthma".* *(81)*

4.9 Diagnosis of asthma

Asthma is a clinical diagnosis which involves suggestive symptoms, airflow variability and airway hyperresponsiveness. It is important to exclude other diagnoses that may present with asthma-like symptoms. However, the absence of physical findings does not exclude asthma. Respiratory symptoms in asthma are often variable. Classical symptoms may include recurrent and episodic wheeze, shortness of breath, persistent cough, chest tightness and excessive mucus production. It is crucial to identify triggers, such as allergens (e.g., dust, pollen, animal dander) or non-specific triggers (e.g., cold air, exercise, perfumes, medications such as aspirin, NSAIDs or beta-blockers), and occupational exposures. Occupational asthma for instance improves during weekends or holidays. As asthma often runs in families, a precise family history of atopy (e.g., eczema, rhinitis, sinusitis, conjunctivitis, hay fever etc.) as well as a personal and birth history (preterm birth) are important questions in the anamnesis. Besides the patient's history, physical examination findings and specific tests, the evidence of variable and/ or reversible airway obstruction, and the response to asthma therapy are crucial to confirm asthma diagnosis. (2) Nevertheless, it is assumed that there are still many people, especially those with fewer symptoms, which are not doctor-diagnosed despite having asthma and/ or an allergy. (21)

4.9.1 Diagnostic tools

Diagnostic testing includes **pulmonary function tests** such as **spirometry**, which measures the patients respiratory flow rates and helps detecting variable and partially reversible airway obstruction. Spirometric measured values include the forced vital capacity (FVC), the one-second capacity (FEV_1) and the Tiffeneau index, the ratio of those two values (FEV_1/FVC). A reduced airflow can be seen in most asthmatics. The proof of variable airway obstruction requires serial lung function measurements. A normal lung function does not rule out asthma. (2)

Body plethysmography, another pulmonary function test, can be performed to determine the intrathoracic gas volume and the specific airway resistance. Together with spirometry, these two noninvasive tests enable an earlier diagnosis of asthma. These tests also help to differentiate between asthma and COPD. The results can be used to determine and grade the severity of obstruction. (2)

The reversibility test is used to check the reaction of the airways to bronchodilators such as a short-acting beta-agonist (SABA) or alternatively a short-acting muscarinic antagonist (SAMA). The reversibility can be shown as an increase in FEV_1 or FVC. Different guidelines define different values for positive testing based on the initial measurement. The test can also involve the use of inhaled corticosteroids (ICS) to confirm the diagnosis. This is often useful in cases where other diagnostic tests may not provide clear results, or to assess the effectiveness of a patient's anti-inflammatory treatment. (2) A positive reversibility test, combined with typical asthma symptoms, confirms the diagnosis. Even without reversibility, asthma can still be diagnosed if there are other additional indicators like elevated type 2 biomarkers or a positive response to ICS. (2,24)

The measurement of the **peak expiratory flow** (PEF) is commonly used in the diagnosis and management of asthma. The PEF provides insights into airway function and control by measuring how quickly a person can exhale air (as hard and as fast as possible, for more than one second). This diagnostic tool is a useful indicator of airflow obstruction. However, PEF should not be used as sole diagnostic tool since it may not capture all aspects of lung function. (2,24)

Biomarkers can provide valuable information for diagnostics, guide treatment decisions and monitor the effectiveness of therapies, especially in severe or uncontrolled asthma patients. Besides certain mediators and inflammatory cytokines, absolute and/or specific serum IgE is a good biomarker for atopy status. Serum IgE levels correlate positively with asthma severity in children and adults. (7) The peripheral blood eosinophil count (absolute eosinophils) is an important biomarker and helps to identify asthma pheno- and endotypes, and prognosis. Higher levels are associated with an increased risk of asthma exacerbations. (2) Another common way to assess eosinophils is through a patient's sputum. In 40-60% of patients with severe asthma eosinophilic airway inflammation is a key characteristic of asthma. (7) **Fractionated exhaled nitric oxide** (FeNO), another biological marker of airway inflammation, can be used as a noninvasive biomarker to assess bronchial inflammation and help with categorizing asthma into certain subtypes. Additionally, FeNO levels are used to monitor T2-high inflammation in the airways and help predict corticosteroid sensitivity in asthma. (2,48)

Specific allergy diagnostic tests are done if allergic asthma is suspected, since allergic sensitization is a very common trigger. The diagnostic includes an allergy history (exposure to allergens, trigger factors, family history of atopy and allergy), a skin prick test and/ or an intracutaneous test, measurement of specific IgE levels, provocation testing and/ or the exemption from exposure. A positive prick test for example is performed to identify allergens and makes the presence of (allergic) asthma more likely if the diagnosis is questionable. (2)

(This review only gives a short overview over the asthma diagnostic and refers to the S2k and GINA guidelines for more detailed information considering asthma diagnostics in different age groups.)

4.9.2 Sex and gender differences in diagnosis

Sex- and gender discrepancy, especially in adults, can lead to underutilization of objective testing methods when it comes to asthma diagnosis. For instance, spirometry is one of the most essential tools, providing objective measurements of lung function. Studies have shown that women, especially in higher age, are tested less frequently, leading to a delayed or even missed diagnosis. (49) A study from Italy showed that boys between the age of 6 and 17 years were twice more likely to receive spirometry testing during doctor visits than girls. (26) The age between females and males being diagnosed with asthma varies. A prospective registry for severe asthma from the *German Asthma Net* found that in Germany, there were differences in the age at first diagnosis between sexes, with 32.4% of men diagnosed before 12 years compared to 28.4% of women. (20) These are just some examples which show gender disparities in diagnoses, and that asthma might be underdiagnosed if there is a lack of consistent use of objective testing, especially in female patients. (49)

Regarding clinical parameters and (noninvasive) biomarkers for asthma diagnosis, several publications have examined some evidence of sex differences in biomarkers, including FeNO and certain cytokines. However, up to now, there are no sex-specific biomarkers for women and men as diagnostic tools.

A cross-sectional survey investigating the sex differences in FeNO levels and asthma symptoms among university students aged 18-24 years found that FeNO levels were significantly higher in male students compared to female students. Also, the overall prevalence of wheezing based on FeNO levels was greater in male students. (50) This observation was supported by a retrospective observational study, investigating the relationship of small airway function and FeNO in patients with mild asthma. This study found that FeNO levels differ between female and male patients, with higher mean FeNO levels in male patients. Additionally, they observed that FeNO values declined more rapidly with age among female patients, whereas in male patients FeNO levels were still high after the age of 40 years. (48) Other potential confounding factors such as smoking, allergies and BMI additionally influence FeNO levels. (48,50)

An observational study analyzing data from the *Severe Asthma Network* in Italy reported that in addition to mean FeNO values (which were likewise found to be higher in males in this study), serum IgE levels were also significantly higher in

men with severe asthma than in female patients. Regarding blood eosinophils, the study observed that blood eosinophil levels were similar in both sexes. (51)
These investigation and findings could potentially help to increase diagnostic accuracy in patients with (mild) asthma by considering age and sex-specific cutoff values for certain biomarkers and lung function parameters. Especially females might benefit from the use of female-specific cutoff values instead of the uniform standards for all genders. (48,51) Nevertheless, there is conflicting evidence on whether sex affects FeNO levels in asthma, and further research and studies are needed to investigate the clinical significance of using sex-specific cutoff values for asthma diagnosis. (48) The current *GINA* guidelines do not address sex-based differences regarding asthma diagnosis. (15,48)

In terms of symptom reporting, there is a noticeable difference in how asthma symptoms are experienced and reported by males and females, resulting in women often taking distinct actions regarding asthma control. (26) Results from a study investigating among others the efficiency and outcomes of therapy in asthma patient found that women and men often present with different symptom profiles which, when not interpreted correctly by healthcare providers, can lead to diagnostic errors. For instance, women might report a worse perception of their asthma and disease control or more bothersome symptoms during day- and nighttime, despite having a similar or even better pulmonary function compared to males. Some women might also have a greater hyperresponsiveness to asthma triggers and consequently report more activity limitations and a reduced general health status. Therefore, it is important to keep in mind, that the symptom reporting may not always correlate with objective measures of lung function. (52)
Implicit gender bias among healthcare providers is widespread and can unintentionally influence diagnosis and treatment decisions. (12) For example, when patients report having chronic pain, men may be seen as brave, while women are often perceived as “complaining” and therefore, might be recognized as “more emotional”. (12,45) When the symptoms presented by females are taken less serious and sometimes being attributed to psychological factors instead of serious physical health issues, this difference in symptom perception and reporting can lead to misdiagnosis, diagnostic delays, and inadequate treatment. On the other hand, women are more likely to have asthma with comorbidities such as

depression or anxiety (45) leading doctors to assign respiratory complaints to anxiety and focusing on psychological factors rather than recognizing the complaints as asthma symptoms. This often results in mismanagement of asthma and therefore is associated with poorer asthma outcomes. (49) In addition, many women report not being taken seriously by healthcare providers when discussing their symptoms. A review on this topic pointed out that the gender of the healthcare provider might influence how seriously a patient’s symptom reports are taken. (12)

Overall, those biases show how gender discrepancies potentially influence the diagnostic process and subsequent management of asthma, often resulting in women experiencing longer median times from symptom onset to diagnosis compared to men. (52)

4.10 Therapy

The goal of asthma therapy is to reduce the numbers of asthma attacks and emergency situations, achieve a good long-term symptom control (few/ no asthma symptoms, prevent exacerbations, no requirement for systemic corticosteroids, no sleep disturbance due to asthma and no unimpaired physical activity), maintain normal lung function, minimize long-term risk of asthma-related mortality and overall enhance the quality of life. Additionally, it is important to identify and enhance the patient's own goals. (15)

For asthma treatment there are drug and non-pharmacological approaches. The latter is intended as a supplement but should not replace pharmacological treatment. The therapy of asthma typically consists of long-term control and quick relief or rescue medications, combined with lifestyle management and patient education. (2) Early diagnosis, management of asthma-related symptoms, proper medical assistance, and suitable treatment strategies are important to stop the disease progression and ensure the patient's well-being and quality of life. (42) Every patient therefore should be given access to a structured individualized education program as soon as possible after diagnosis. (2)

4.10.1 Non-pharmacological approaches

Patient education is a crucial part of asthma treatment. Since asthma is a chronic condition, patients must utilize medications and adhere to treatment recommendations. (42) Every patient with indication for drug therapy should be recommended a structured, behavior-related training program and in case of children or adolescents their family members should also be involved. (2,15)

The introduction of disease management programs, which are special training and education programs for chronic conditions such as asthma, has more and more become established in the last few years. The goal of these programs is to enhance the quality and effectiveness of asthma therapy by focusing on the patient's needs, helping them manage their conditions independently and providing the necessary information to better understand their illness. (21,53) According to quality report published in Germany*,* only 22.5% of all patients who were offered a disease management program participated. The statistic showed that females were more likely to participate in such programs than males. (54) However, these plans are not tailored to women or to (trans-) gender differences.

Depending on the patient's self-management skills, regular follow-up appointments with healthcare providers should be scheduled to monitor symptoms, evaluate correct inhaler use, the effectiveness of and adherence to treatment plans, and if necessary, adapt the therapy. (15) A personalized (written) asthma action plan for coping with acute exacerbations, especially for women during certain phases such as menstruation or pregnancy, might be helpful to ensure the patient knows how to react during an asthma attack. It is also necessary to identify certain triggers that may worsen asthma and to make sure the patient avoids them. (2) In addition of providing information about proper use of medication it is also crucial to enlighten the patient about the risks of medication misuse and incompliance. (42)

Smoking cessation is a very important therapy approach in patients suffering from asthma. E-cigarettes are not less dangerous than conventional cigarettes and therefore should not be recommended as a substitute to quit smoking. (55) Healthcare providers should encourage asthmatics to quit any kind of smoking and provide access to evidence-based cessation programs. (2)

Respiratory physiotherapy helps to mobilize and strengthen the musculoskeletal parts of the respiratory system. Exercises such as yoga or systematic breathing retraining can contribute to effective self-management during asthma attacks, reduce the need for long-term medication, and enhance lung function in individuals with mild to moderate asthma. (2)

Physical exercise can lead to significant health benefits and improve symptoms and quality of life in adults with asthma. The type and intensity of physical exercise should be adjusted to the patient's individual fitness level (2) The use of reliver medications before exercising prevent exercise-induced bronchoconstriction. (15)

Allergen immunotherapy (AIT) is indicated for patients with allergic asthma, particularly those with a clear IgE-mediated response to specific allergens. The goal of this therapy is to achieve long-term control of asthma symptoms, reduce frequency of exacerbations and decrease the need for asthma medications. In some cases, remission of asthma symptoms can be achieved. Patients undergoing AIT should be monitored for any adverse reactions, especially during the initial phases of treatment, when the risk of systemic reactions is higher. (2)

4.10.2 Pharmacological approaches

Structured pharmacological approaches have been developed to assess and effectively manage asthma based on the patient's asthma severity and the treatment options available, providing guidance to clinicians on how to tailor treatment to the patient's needs. Basically, there are two main substance groups for long-term treatment of asthma: "*controller*" and "*reliever*" medications. Controller medications as maintenance therapy are prescribed to reduce inflammatory processes and therefore should be used on a regular basis. This approach provides a long-term control of asthma symptoms and aims to prevent exacerbations. (15) This group includes several classes of medications:

Inhaled Corticosteroids (ICS) are the most effective anti-inflammatory medications reducing the risk of severe exacerbations and improving symptom control. The current *GINA* guidelines emphasize using ICS as first-line treatment for persistent asthma from the time of asthma diagnosis, as it helps preventing the progression of inflammation and airway remodeling. (15)

Long-Acting Beta-Agonists (LABA) stimulate Beta-2 receptors in smooth airway muscles, leading to bronchodilation. LABAs are often combined with ICS. (15)

Leukotriene Receptor Antagonists (LTRAs) inhibit the binding of leukotrienes to their receptors. LTRAs may be used as add-on therapy in severe asthma. (15)

Long-Acting Muscarinic Antagonists (LAMA) block muscarinic receptors in airway smooth muscles leading to bronchodilation. LAMAs may also be used as add-on therapy in severe asthma. (15)

Biologics are targeted antibody therapy options for patients with severe asthma which cannot be controlled with standard treatments. These drugs target certain molecules such as IgE, IL-5, IL-4/IL-13, or TSLP and thus, inhibit the underlying inflammatory processes of asthma. (15)

Oral Corticosteroids (OCS) are prescribed as low-dose OCS in cases of severe asthma but are considered as a last resort due to potential long-term side effects such as osteoporosis and increased metabolic and cardiovascular risks. (15)

Reliever therapy aims to rapidly alleviate bronchoconstriction and therefore is used for quick relief of acute asthma symptoms, especially during asthma attacks. Relievers can also be used before exercise as short-term prevention of exercise-induced bronchoconstriction. Reliever medications include **Short-Acting Beta-Agonists (SABA)** which are primarily used for quick relief of symptoms as they provide rapid bronchodilation, **Short-Acting Muscarinic Antagonists (SAMA)** which lead to airway smooth muscle relaxation, and a combination of ICS and rapid-acting bronchodilators. All patients should be equipped with an inhaler. (15)

Depending on the patient's age and asthma severity two tracks guide the management of asthma based on the type of reliever (*Figure 4*). Within the tracks certain steps refer to the levels of treatment intensity based on the patient's asthma control, with the option to escalate or deescalate the treatment as necessary, with the same reliever. Before stepping up or down along one track, common problems such as incorrect inhaler technique, poor adherence, and environmental exposure should first be checked. (15)

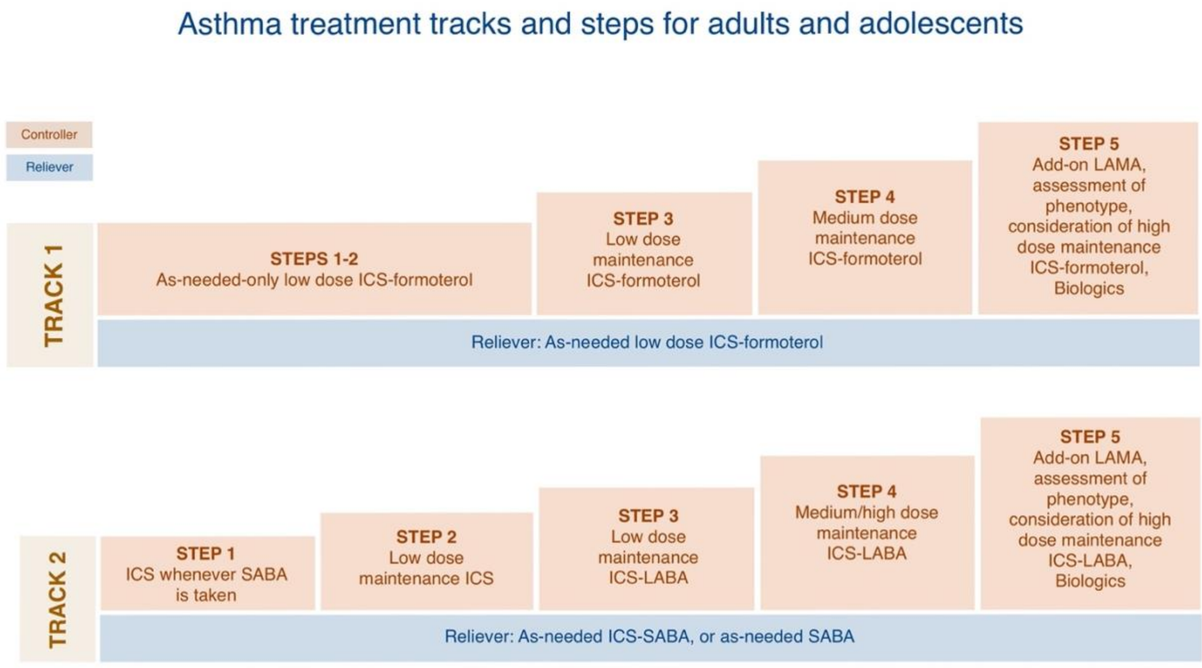

Figure 4 *Asthma treatment steps and tracks for personalized asthma management in adults and adolescents. ICS: inhaled corticosteroids, LABA: long-acting beta-agonist, LAMA: long-acting muscarinic antagonist, SABA: short-acting beta agonist. Adapted from the GINA guidelines 2024.* (15)

4.10.3 Sex and gender difference in asthma therapy

There are several (inhalation) medications currently available for the treatment of asthma. As described above, the *GINA* guidelines recommend a combination of ICS and LABA (such as formoterol) as a preferred treatment track for asthma patients. The guidelines do not suggest different preferences for women and men in clinical practice. (15) Nevertheless, it seems that there are significant differences in terms of prescription of inhaled pharmacotherapies among female and male asthma patients. A retrospective observation cohort study, focusing on these differences found that men compared to women were more likely to be prescribed a combination therapy (ICS/ LABA) as recommended in the *GINA* guidelines as first-line therapy. On the other hand, it was observed, that the prescription of ICS monotherapy was higher in female asthma patients than in male patients. (56) Another population-based cohort study found that women with asthma, especially older women, were less likely than men to be prescribed controller medications and instead had a higher rate of asthma reliever prescription. These differences might lead to poorer disease control and higher asthma severity. (57) The reasons for these observed sex disparities are unclear but could be partly explained by differences in disease characteristics, different healthcare-seeking behavior, and the way female and male patients perceive and report their symptoms. (56,57)

To achieve effective asthma treatment, it is important to use asthma medication correctly and adhere to treatment protocols. Inhalation medications, for example, have the advantage that they act rapid and local and have a low risk of systemic side effects. However, to ensure drug delivery, inhaler devices require a correct use. Incorrect inhalation technique can lead to poor disease control and might result in acute exacerbations and higher hospitalization rates. (24,58)

Regarding inhalation technique for certain inhaler devices, a systematic review focused on the impact sex might have on proper use. It was found that women may have a greater error rate than male patients when using certain inhalers. However, the evidence for these findings was limited and conflicting, with some studies observing a higher error rate in women, while other studies showed poorer performance in men or no real differences between the sexes. Whether or not sex is an important predictor of incorrect inhaler use remains controversial, and further research is needed to provide clear recommendations of adapting inhaler techniques and devices for females and males. In addition to close monitoring and assessment of correct medication use, clinicians might also consider sex when selecting inhaler devices for patients. (58)

Various publications indicate that the effectiveness of asthma treatment may be modulated by sex. Findings from a systematic review, examining sex-related differences in the pharmacological treatment of asthma, showed that men responded better to certain asthma medications than women. While combination therapies (ICS/ LABA/ LAMA) appeared to be equally effective in improving lung function, symptom and asthma control in both sexes, two studies showed that ICS were more effective in men than in women. (9) The first one, a cross-sectional observation study, found that men with ICS treatment had fewer symptoms and better asthma control than women. In contrast, women had a higher risk of uncontrolled asthma when treated with only ICS medications. (59) Another observational cohort study found that only men with moderate to severe asthma treated with dose-dependent ICS therapy showed a smaller decline in lung function (FEV_1) over a timespan of 23 years. This could not be observed in women. To understand this lacking effect of ICS on the decline of FEV_1 further research is needed. (60)

The *GINA* guidelines emphasize the careful use of OCS and only recommend it as an add-on therapy for patients (regardless of sex or gender) whose asthma remains uncontrolled despite receiving the highest possible dose of ICS. (15) In this context, a study focusing on the use of OCS in selected countries in Europe found that women are more frequently prescribed OCS for (severe) asthma control compared to men. However, the study does not go into detail about the reasons for the difference in prescribing. (61)

There is an urgent need for more research to understand these sex and gender differences in asthma therapy. Neither the *GINA* nor the *S2k*-guidelines provide sex- or gender-specific diagnostic protocols and treatment goals. These observations and findings could potentially contribute to sex- and gender-specific therapy recommendations and be adapted to the patient’s needs and response to therapy.

4.11 Overview of sex hormones

4.11.1 Estrogens

Estrogen is a steroid hormone, more precisely a cholesterol derivate produced by the ovaries, especially during reproductive years, but also in other tissues such as the adrenal glands, adipose tissue or during pregnancy in the placenta. (62,63)

Estrogen can be subdivided into three major forms, including estrone (E1), estradiol (E2), and estriol (E3). (64) Depending on the stage of life and physical needs of the body, E2 is the most potent and active form during reproductive years, whereas E1 is more predominant in postmenopausal women. E3 is the primary form of estrogen during pregnancy. (62)

In males, estrogen is mainly synthesized from circulating androgens. The aromatase enzyme converts androgens into estrogens, which takes place in certain tissues such as the testes, adipose and muscle tissue. (65)

The pulsatile release of gonadotropin-releasing hormone (GnRH) of the hypothalamus stimulates the pituitary gland to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH acts on the theca cells and FSH on the granulosa cells, both which are found in the ovaries. The theca cells mainly produce androgens, which are later converted to estrogens by the aromatase enzyme in the granulosa cells. (63)

When estrogen is not bound to proteins, such as albumin or the sex hormone-binding globulin, it acts as a free hormone in the bloodstream, able to enter different cells without regulation. Once inside the cell estrogen binds to either an alpha-estrogen receptor (ER-α) or beta-estrogen receptor (ER-β). (64) In humans ER-α and ER-β are among others expressed in tissues such as the breast, uterus, bones, and cardiovascular system (64) but also in bronchial epithelial cells, bronchial smooth muscle cells, vascular endothelial cells, and immune cells such as mast cells, macrophages, lymphocytes, eosinophils, and dendritic cells. (66–68) Throughout this intracellular receptor-binding a series of cellular responses and signaling pathways are activated, influencing a wide range of cellular processes such as gene expression, cell proliferation and differentiation. (64) Estrogens and ER activation seem to play an important regulatory role in the pathological process of airway inflammation. Nevertheless, their involvement is still poorly understood. (66,68)

4.11.2 Androgens

Androgens are essential sex hormones with wide-ranging effects on body development, fertility, and overall health in both, males and females. (69) Androgens are synthesized from cholesterol. In males, androgens are mainly produced from the Leydig cells in the testes, whereas in females, androgens are mainly produced in the ovaries and adrenal glands. Androgens can also be synthesized in peripheral tissues such as the fat tissue. Testosterone is one of the most common and most potential androgens. (63,69) Other major forms of androgens which are present in women and men are dehydroepiandrosterone (DHEA), its metabolite dehydroepiandrosterone sulphate (DHEAS), dihydrotestosterone (DHT) or androstenedione. (70) 98% of testosterone in the plasma is bound to albumin or the sex hormone-binding globulin. (63) The pulsatile release of GnRH into the bloodstream stimulates the pituitary gland to secrete among others the LH which stimulates the Leydig cells to produce testosterone. Through a negative feedback mechanism, higher testosterone levels inhibit the release of LH and GnRH. (63)

Androgens, especially testosterone and DHT, act by binding to intracellular androgen receptors (AR or NR3C4). Androgen receptors are present in tissues such as the testes, prostate, ovaries, bones, muscles, brain, skin, hair, lungs and airways. (63,71) Not only are androgens essential for sexual development and reproductive characteristics, (63) they also play an important role regarding immune function and respiratory health. (72,73)

4.11.3 Progesterone

Progesterone is a steroid hormone, mainly produced by the ovaries, the testes, and the adrenal cortex. During pregnancy it is also secreted by the ovarian corpus luteum and the placenta. Progesterone acts in various tissues in the body and is important to among others maintain pregnancy, regulate the menstrual cycle and the reproductive system, and in males the hormone promotes spermiogenesis and androgen synthesis. These effects are due to binding to intercellular progesterone receptors. (74)

4.12 Aim of the thesis

The current world population is estimated to be around 8 billion people worldwide, with more than the half being female. (75) Although in the last few years health research has focused more and more on sex and gender differences, certain (patho-) mechanisms of airway inflammation and chronic respiratory diseases in males and females remain unclear. Likewise, much of the research, development and dosage in medicine have often focused on the male sex, leading to a lack of understanding of how asthma affects women differently. A gender disparity in asthma prevalence exists with adult women having an increased prevalence compared to men. Poor understanding of sex and gender differences and the impact sex hormones have on the disease often result in less effective management and treatment of asthma.

The aim of this thesis is to provide an overview of the current literature and state of knowledge on sex and gender-specific differences, primarily the influence which sex hormones, in particular estrogen and testosterone have on asthma, especially during certain life phases and cycles in women. For this purpose, a closer look is taken on how these hormones contribute to the regulation of airway inflammation and how they might affect asthma symptoms, management, and outcomes especially for women, including quality of life. The effects of exogenous hormone therapy on the course of asthma are also discussed. Furthermore, this review examines current guidelines and analyzes recent publications to assess the recommendations provided for treatment and management of asthma in females, males and transgender people, as well as preventive strategies.

5 Methods

This narrative review was written based on original articles, reviews, studies, current guidelines, book content, case reports and clinical trials which were published in the last 20 years up to August 2024. Relevant material in English and German language was included. Series or letters were not included. No clinical data was collected. Online books were accessed via the library of the Medical University of Graz. The selection of sources does not follow a systematic approach and not all publications on this topic were included.

PubMed was the main online database used to collect and analyze literature, but other electronic databases such as *UpToDate, Science Direct, Google Scholar*, *Statistic Austria* and *Clinicaltrial.gov*. were also considered as source of information. The following key words and MeSH terms were used for the search throughout the online research: “asthma”, “gender”, “sex”, “hormones”, “estrogen”, “testosterone”, “diagnosis”, “menstruation”, “PMA”, “pregnancy”, “menopause”, “HRT”, “therapy” etc. The *Mendeley* citation program was used to collect and cite the literature. *Google* as a search engine was used to obtain relevant literature such as population data, current guideline recommendations and health-related information from official government websites and medical platforms.

A limiting factor for certain topics (such as “asthma in transgender people”) was the lack of well-designed prospective studies and the small number of available studies in general. Another limiting factor is, that many large studies and trials were conducted in different countries and regional differences might apply. Regarding environmental and socio-cultural differences around the world, some results may not be applicable one-to-one to the Austrian population.

6 Results

Sex and gender differences in asthma are influenced by several factors including among others, genes, age, sex, and sex hormones. One reason for different asthma prevalence and development between females and males is the role of hormonal changes throughout the lifetime. In certain life phases and cycles, females tend to have an increased prevalence and incidence of asthma compared to males. During childhood, asthma is more prevalent in boys, but this trend reverses in adulthood, with women having a higher prevalence of asthma. Around the fifth decade the prevalence of asthma rises again in males, when a decrease in especially testosterone levels, and in women a gradual decrease in sex hormones can be observed. (*Figure 1*). (72,76,77) These observations suggest a that sex hormones and their changing levels do have an important impact on asthma pathogenesis *(Table 1).*

6.1 Estrogen and asthma

Some women experience an alteration regarding asthma symptoms and severity, when estrogen levels change during menarche, menstruation, pregnancy, or menopause. Due to the rise of asthma prevalence in females, beginning around puberty, it is assumed that higher estrogen levels seem to correlate with an increased airway inflammation, resulting in bronchial hyperreactivity and asthma exacerbation. (72)

Estrogen concentrations might be higher in asthmatic patients than in patients without asthma. In a study *He et al.* found that the patients with asthma had higher serum concentrations of E2 and decreased serum levels of androgens, especially DHT, compared to healthy individuals. This applied to both, women and men. (78)

Estrogen receptors are expressed on immune cells such as T2 cells, which are involved in T2 high inflammation. Therefore, estrogen might directly interact with these immune cells by promoting differentiation into Th2 helper cells which produce inflammatory cytokines. (66–68,79). A study by *Cai et al.* with lymph node cells from allergic female mice showed that estrogen can induce the production of cytokines such as IL-5 and IL-13. When the mice were treated with an estrogen-receptor antagonist (tamoxifen), less IL-5 and IL-13 was produced. These finding underline the influence estrogen has on promoting cytokine production. (80)

Increased production of proinflammatory cytokines results in the recruitment of immune cells such as eosinophils and lymphocytes into the airways. These cytokines also promote differentiation of IgE-producing plasma cells. IgE binds to mast cells, leading to degranulation which results in airway hyperresponsiveness. (13,81) Estrogen itself might also directly influence certain inflammatory cells, such as mast cells. A study by *Jing et al.* found that in rats mast cells and histamine levels were increased in phases when estrogen levels were higher. The mast cell and histamine levels were significantly lower in ovariectomized rats. When these rats were administrated exogenous E2, these levels increased again. (82)
Estrogen also seems to be involved in T2-low inflammatory pathways. *Newcomb et al.* investigating the effect of E2 and progesterone on the production of IL-17A in ovariectomized mice. When these mice were administered E2 and progesterone, IL-17A production was increased. Additionally, the study observed that women with severe asthma IL-17A (produced from Th-17) cells was higher than in men. (83)
Estrogen might also have some positive effects upon modulating airway inflammation. *Van Anders et al.* found that there is a positive correlation between estradiol (E2) and the secretion of salivary immunoglobulin A (IgA), which acts as an immunological mucosal barrier, serving the purpose of a first line defense against the invasion of pathogenic microbes. The study's observation showed the association between low estrogen levels (for example in menopause) and the reduced ability of IgA secretion, suggesting that lower levels of estradiol may be linked to an increased susceptibility to respiratory infections. (84)
Estrogen does not act in isolation and its effect can also vary based on the presence of other hormones such as progesterone. Airway epithelial cells, which are important for mucociliary clearance, express estrogen and progesterone receptors. *Jain et al.* who used cultured human airway epithelial cells and exposed them to progesterone, found that the cilia beat frequency was significantly decreased. The administered E2 counteracted this effect. This could be observed in both, men and women. (85). These findings showed that the balance of sex hormones is important for epithelial cell function and that hormonal shifts influence respiratory health.
To summarize, estrogen seems to modulate the function of various inflammatory cells and immune responses in asthma. (68,79,81) Whether estrogen has only pro-inflammatory or also additional protective effects might also depend on factors

such as immune stimuli (foreign antigens or autoantigens), expression of estrogen receptors in certain cells and tissues, and the concentration levels and presence of other hormones, or immune cells which are involved in the inflammatory process. (68) The relationship between asthma and ovarian sex hormones, especially estrogen and progesterone, is still not fully explored. More research and individual studies are needed for a comprehensive understanding of how estrogen affects the mechanisms of inflammatory immune responses and contributes to the development of asthma.

Many studies, trying to investigate the impact estrogen has on the (molecular) inflammatory pathway of asthma, are performed on animals. The following chapters try to take a closer look on the gender disparity observed in asthma patients by looking at the potential impact estrogen might have during certain phases such as menstruation, pregnancy, and menopause in women with asthma.

6.2 Androgens and asthma

Testosterone levels in women and men vary physiologically by age. (77) Higher levels of androgens in boys (such as DHEA) are associated with fewer asthma symptoms, a better lung function and a lower risk of asthma in adolescents. (81,86) *Bulkhi et al.* found a positive correlation between serum testosterone and lung function. Testosterone seems to promote airway smooth muscle relaxation and reduce hyperreactivity, improving airflow and reducing asthma symptoms. Among patients with asthma, higher testosterone levels associate with better lung function (as measured by FEV_1) and a lower incidence of asthma symptoms. These results apply to both, women and men. Androgens also seem to have lung protective features by inhibiting airway hyperreactivity and therefore are associated with better lung function. (77,86)

It has been observed that asthma patients often have a lower airway androgen receptor expression compared to healthy individuals. Androgen signaling via intracellular androgen receptors seems to attenuate (allergic) airway inflammation suggesting a potential link between a reduced number of receptors and the presence of asthma. This applies to both sexes. (71,77) On the other hand, the decrease of testosterone levels in males, especially in their fifth decade, showed an increased asthma prevalence, a decrease in FEV_1 and an increased risk of asthma exacerbations. (81) These observations might help to explain gender differences observed in asthma prevalence throughout different age groups.

Also, the secretion of inflammatory cytokines, involved in (allergic) airway inflammation, is higher in the absence of androgens. Studies on mice whose testes were removed (consequently having lower testosterone levels) showed a higher inflammatory airway response, compared to intact male mice. (87) These findings imply a correlation between androgens and inflammatory responses in the airways. Nevertheless, more research must be done to understand the influence androgens have on asthma. (88)

In another animal study by *Ejima et al.* it was observed that androgens suppressed the cytokine production of Th2 cells. Modified mice with fewer T-cell specific androgen-receptors showed higher levels of cytokines which are involved in T2-high inflammation. Cells from mice with T-cell specific androgen-receptor deficiency and cells from control mice where exposure to DHT. The results showed that the production of IL-4 and IL-13 was significantly reduced in the control mice but not in the studied mice. (89)

To summarize, androgens, such as testosterone can suppress the production of pro-inflammatory cytokines which attract immune cells involved in asthma, and therefore reduce inflammatory responses in the airways.

Estrogen	Testosterone
↑ Airway hyperresponsiveness	↓ T2-high inflammation
↑ T2-high inflammation	- Eosinophils
- Eosinophils	- IL-33
- IL-13	↓ T2-low inflammation
- IL-5	- TSLP
↑ Allergic inflammation	- IL-17
- IgE	
↑ T2-low inflammation	
- Neutrophils	
- IL-17	

Table 1 *Potential asthma-modifying effects of estrogen and testosterone. The arrows pointing up indicate a pro-inflammatory effect, the arrows pointing down indicate an anti-inflammatory effect. T2: type 2, IL: interleukin, IgE: immunoglobulin E, TSLP: thymic stromal lymphopoietin. Adapted from "Personalized treatment of asthma: The importance of sex and gender differences". (12)*

6.3 Androgen based hormone therapy

Androgen therapy shows clear benefits in treating various symptoms and disorders in menopausal women. Currently androgen-based therapies (mostly testosterone) are primarily used for women with androgen deficiency syndrome (hypopituitarism, ovarian or primary adrenal insufficiency), sexual health issues (hypoactive sexual desire disorder) and genitourinary syndrome of menopause (vaginal dryness, urinary symptoms). (90)

While there is some research into androgens influencing respiratory function, the use of androgen hormone replacement is not typically indicated for the treatment of asthma. The role of testosterone in asthma management is not well established yet and current findings are not sufficient to recommend androgen therapy as a treatment option for asthma in (menopausal) women. However, studies with mice showed that a combination of androgen (especially DHT) and estrogens (especially E2) alleviate airway inflammation. DHT seems to modulate the inflammatory cascade and attenuates the immune cell differentiation, leading to airway inflammation. These findings suggest that androgens, especially in addition to estrogen therapy, might have beneficial effects on asthma symptoms. (78) Supplementing androgens to balance hormone levels could help to maintain testosterone levels during e.g., the premenstrual phase or in menopausal women when testosterone naturally decreases. This approach might stabilize asthma symptoms and improve overall disease control. (73)

Nevertheless, the potential side effects of androgen hormone therapy such as hormonal imbalances, increased cardiovascular risks, liver damage, skin changes, or body hair growth must be considered as well. (73) The approval for most preparations is rare and when prescribed, androgen hormone therapies are often prescribed off label. Therefore, the prescription requires a comprehensive patient education, regular monitoring, and careful observation of the woman's overall health, particularly with pre-existing health conditions. (90) However, given the protective effects of androgens on lung function and inflammation, there is great interest in exploring androgen replacement therapy as potential treatment option for managing asthma during certain phases such as menstruation or menopause. (66,90) Altogether, more research must be done to clarify the relationship between androgens and asthma prevalence, to among others develop potential therapeutic strategies and tailored treatment options. (77)

6.4 Menstruation and asthma

The hormonal changes in menstrual cycle during a woman's reproductive years can have significant effects on some patient's asthma disease. (72) Throughout the menstrual cycle, sex hormones, particularly estrogen and progesterone, underlie fluctuations. Whereas estrogen levels are especially high during the first half of the menstrual cycle (follicular phase), progesterone is the more dominant hormone in the second half (luteal phase). (91) The perimenstrual phase (around menstruation) is characterized by a decline of progesterone and estrogen to prepare the body for menstruation if pregnancy does not occur. (66)
A multicentric, population-based study examined the variation of certain respiratory symptoms in female asthmatics over the course of menstrual cycle. It was found that the highest incidence of shortness of breath occurred near ovulation, with a peak between days 14 and 16, and the highest wheezing incidence was observed on days 10 to 12 and 18 to 20. In both cases the incidence was lowest before and after menses. The cyclic patterns also varied depending on factors such as BMI or smoking status. These findings show variations in different asthma symptoms which change rhythmically during menstrual cycle. (92)
The interplay between estrogen, progesterone and androgens seems to have effects on inflammatory cell recruitment and cytokine production, all of which contribute to changes in asthma symptoms and control. Altering levels of these sex hormones impacts asthma symptoms and airway responsiveness during different phases of menstruation. (66,72) Sex hormones seem to regulate the function and distribution of certain immune cells such as mast cells. Mast cells are among others found in the layers of the uterus such as the endo- and myometrium. During menstruation when estrogen levels change, mast cells are upregulated and activated by this hormonal fluctuation. When activated, mast cells release inflammatory mediators that lead to a systemic inflammatory response, which as a result may worsen asthma symptoms. (93)

Additionally, the timing of menarche plays a significant role in asthma development and severity. Early menarche, defined as onset of menstruation before the age of 12 years, has been associated with up to twice the risk of new-onset asthma in females. (94,95)

6.4.1 Perimenstrual asthma

The worsening of the most common asthma symptoms around menses is also defined as perimenstrual asthma (PMA). More than one third of women in reproductive age experience PMA, most likely to the underlying inflammation caused by hormonal fluctuations. (66,96) The exact role of sex hormones during certain phases of the menstrual cycle is still unclear, as are the exact mechanisms driving these cyclic changes in asthma symptoms. The fact that some women experience these changes and others do not is also not yet fully understood. (72)

Many affected women also have a greater need for asthma medication and often require a more frequent use of corticosteroids. Women with PMA might also experience a greater likelihood of emergency visits, hospitalizations, and intensive care admissions. (86,96) The worsening of asthma-related symptoms can be seen in a deterioration of lung function tests. (94) A study by *Pereira-Vega et al.* also found that women with PMA had higher total IgE levels than women without PMA. However, the study did not find a direct link between total IgE levels and asthma severity. Further research is needed to establish this connection. (97)

Up to now there is no special treatment regime for women with PMA either the conventional asthma therapy (*described in the chapter "Therapy"*). However, some women with PMA who use oral contraceptives show reduced cyclical changes in asthma symptoms and airway reactivity. This might be due to a more stable hormonal profile throughout the suppression of estradiol and progesterone. (66,98,99) The use of hormonal contraceptives (HC) as a preventive strategy, might reduce the severity of asthma exacerbations and help managing PMA. (66) Especially the approach of oral contraceptives-use with a shorter hormone free interval has been shown to reduce (and in some cases even eliminate) symptoms, by suppressing ovarian activity. (94) The influence of HC on asthma is described more closely in the following chapter.

Overall, it is important that healthcare providers are aware of the potential influence menstruation has on asthma management. (66) Monitoring of symptoms, involving the patient tracking their symptom patterns during menstrual phases, helps to develop preventive strategies and personalized treatment approaches for women suffering from PMA. Nevertheless, more research and controlled studies are needed to understand the relationship between asthma and hormonal fluctuations during menstruation. (68,94)

6.5 Hormonal contraceptive use and asthma

Hormonal contraceptives (HC) are primarily used to prevent pregnancy by regulating the natural hormonal cycle involved in ovulation. Besides that, HC might also be prescribed to help women with irregular menstrual cycles and premenstrual syndrome, managing endometriosis and other conditions such as acne or heavy menstrual bleeding. (100) In the last few years the use of HC has also moved into focus of research in treating asthma exacerbations and severe symptoms. (101) The potential use of HC to treat for example PMA is to suppress the activity of endogenous sex hormones, which are considered to enhance inflammatory mechanisms of perimenstrual asthma. Especially women with PMA might benefit from the impact HC have on asthma symptoms, by stabilizing hormonal imbalances, and therefore reduce asthma exacerbations. This also applies to women with irregular menstrual cycles, experiencing a worsening of asthma symptoms. (66,98)

However, it is assumed that exogenous female sex hormones increase the incidence of asthma. A population-based cohort study investigating the association between asthma incidence and the use of HC found that women, especially younger than 18 years with a first-time use of HC showed an increased risk of asthma incidence. The same study also found that oral pills containing only progestin were significantly associated with an increased risk of developing asthma. It can therefore be assumed that the type of HC preparation also plays a role in the incidence of asthma. (102)

Another population-based cohort study found that the use of combined contraceptives (e.g., estrogen and progestogen) for longer than three years were associated with less asthma exacerbations, whereas progesterone only contraceptives did not necessarily provide the same protective benefits. These findings indicate that the type of HC as well as the duration of use influence asthma incidence and outcomes (98)

Matheson et al. investigated the relationship between asthma and HC use, and additionally the impact of the women's BMI might have in the incidence. It was observed that prolonged use of HC (longer than 11 years) was associated with a higher risk of developing asthma and experiencing exacerbation in obese, middle-aged women. This is most likely due to the interplay between body fat mass and the production of endogenous sex hormones. Heavier women typically have higher levels of estrogen due to increased fat tissue, whereas estrogen levels in lean women naturally tend to be lower. In contrast, normal weight women with long-term HC use showed a reduced risk. (99) However, another publication by *Nwaru et al.* refutes this claim and did not find a significant association between the use of HC among overweight and obese and asthma. (101) The difference in these observations could be explained by different cohort and study populations.

A population-based study from *Salam et al.* observed that women with a history of asthma using oral HC had a significant lower risk for asthma symptoms such as wheezing. In contrast among women with no history of asthma, the use of HC was associated with an increased occurrence of wheezing. (95)

The effects of HC impacting asthma are conflicting and have not yet been consistently established. While HC can be part of the management strategy for some women with asthma, further research must be done to evaluate potential benefits of exogenous sex steroids as additional use for individualized treatment plans. (98) According to the *S2k* and *GINA* guidelines the use of HC in general is considered safe for women in reproductive age with asthma. Nevertheless, neither the *GINA* nor the *S2k* guidelines provide a comprehensive management plan involving HC for the treatment of PMA. However, they emphasize a potential benefit of HC use in managing symptoms in women with PMA. (2,15)

Graziottin et al. proposed in a publication that a shortened hormone free interval (HFI) in the HC regimen (normally 21 days of HC use, 7 of HFI) could be a possible strategy for a better control of asthma-related symptoms in women with PMA. Reducing the HFI from 7 to 2 days showed the greatest improvement in perimenstrual symptoms. (94)

Overall, healthcare providers should be aware that conventional asthma therapies alone might not always be sufficient and effective in treating women with PMA and therefore asthma treatment should be adapted to the women's symptoms during the menstrual cycle. The use of HC should be tailored to each woman's needs, including the consideration of the patient's BMI. A close monitoring for any changes in asthma symptoms should be implemented when prescribing HC. (2,15)

6.6 Pregnancy and asthma

Bronchial asthma is considered the most common chronic disease in pregnancy. (103) During pregnancy a woman's body undergoes physical adjustments, such as metabolic, hormonal, cardiovascular, and respiratory changes. Increased levels of progesterone and estrogen can have effects on lung function and airway sensitivity. (88) Around one third of women find a worsening of symptoms during pregnancy, one third report improvement and the rest experiences no change. The explanation for this variability is still unexplained. (15) In females whose symptoms worsened during pregnancy, more than two thirds regained their pre-pregnancy lung function within three months after childbirth. (104)

In multiparous women, asthma prevalence increases progressively with the number of births. Pregnant women are exposed to higher levels of estrogen and greater cumulative exposures to sex hormones, which may worsen (already existing) asthma symptoms or increase the risk of developing asthma later. (105)

Not only do hormones effect bronchial asthma during pregnancy, other physiological changes, such as a higher oxygen consumption of around 20%, an enhanced tidal volume of the mother's lung by 30-40%, and a higher airway resistance due to increased blood volume influence lung function and mechanics. In the second and third trimester, when the fetus grows and the uterus size largens, the position of the diaphragm gets pushed upwards and as a result the functional residual capacity decreases, often leading to shortness of breath. (103)

Diagnosis and treatment of asthma in pregnant women differ from non-pregnant women to the extent that fetal safety must be ensured while maintaining asthma control. Diagnostic tests which might provoke acute bronchospasm are contraindicated in pregnant women, due to an increased risk of hypoxemia for the mother and child. In this case spirometry is a preferred diagnostic tool to diagnose bronchial asthma. Additionally, differential diagnoses such as gastroesophageal reflux disease (GERD), which is common in pregnant women, hyperventilation syndrome, or pulmonary embolism should be ruled out. (103)

The primary goals of managing asthma during pregnancy are to keep symptoms under control, maintain optimal lung function and prevent exacerbations, since exacerbations in pregnancy represent a major clinical problem. (103) *GINA* and *S2k* guidelines indicate that pregnant women should maintain their current regimen of asthma medications, if they are also effective in controlling asthma during pregnancy, especially the use of ICS, which are considered safe and effective and not associated with an increased incidence of fetal abnormalities. To ensure patient compliance, it is particularly important to inform the mother and clarify concerns of teratogenicity, because treatment cessation is a significant risk factor for exacerbations and fetal hypoxia. (15) All pregnant women with asthma (and those who are thinking of becoming pregnant) should receive comprehensive education on the importance of medication adherence, correct inhaler technique and management of exacerbations. (24) Especially women with high-risk asthma, should receive interprofessional treatment through collaboration between pulmonologists and obstetricians. Monthly revisions and regular monitoring of symptoms and lung function help to review, adjust, and optimize asthma treatment. (15) Well controlled asthma minimizes the risk of among others hypoxemia to the mother and baby. *Belanger et al.* found that the severity of asthma during pregnancy was similar to that in the year before pregnancy when the women continue to take their prescribed asthma medication, especially in women with mild and intermittent asthma. (106) Uncontrolled asthma in pregnancy has been linked to a higher incidence of low fetal birth weight, preterm birth, congenital anomalies, and an increased risk of the child developing asthma or pneumonia within the first five years of life. (107) Poorly controlled asthma can also lead to complications for the mother such as maternal hypoxia, preeclampsia, or pregnancy induced hypertension. (103,107)

An emergency asthma action plan should be established, including steps to take in case of an asthma attack or worsening of symptoms. (2) Furthermore, it is important to avoid certain triggers and smoking, particularly during pregnancy. (15,103) Additionally, changes in the asthmatic state which occur during pregnancy can last up to 3 months after delivery. Therefore, regular follow-up appointments with health care providers should be continued in the postpartum period (after pregnancy) as hormonal changes might still affect asthma control. (104)

6.7 Menopause and asthma

Menopause is defined as the absence of menstruation for consecutively 12 months, marking the end of a woman’s reproductive years. (108)

During menopause physiological hormonal, metabolic and anatomical changes occur, subsequently leading to a fluctuation of various symptoms associated with menopause and increasing the risk of metabolic syndrome and chronic conditions like diabetes and cardiovascular diseases. (109) Knowledge of how menopause affects the lungs and the immune system remains limited though, despite growing awareness of the role sex hormones together with ageing play in asthma and gender disparity. (110)

With age not only the immune function undergoes changes, also the lung function declines progressively due to structural anatomical modifications, such as rigidity of the ribcage and bone deformation (especially in the thoracic spine and chest wall). Furthermore, respiratory muscles such as intercostal muscles and the diaphragm weaken, leading to an increased work of breathing. The lung tissue loses elasticity, resulting in a decrease of lung volumes and a decline in lung function (reduced FEV1 and FVC). (111) Data analysis from the European Community Respiratory Health Survey (ECRHS) found that post-menopausal women and those in menopausal transition experienced a steeper decline in lung function compared to non-menopausal women. Especially the FVC was more reduced than FEV1, suggesting that the lung function was impaired more restrictively rather than obstructively. These findings were independent of smoking. The effect size of FEV1 decline was comparable to smoking 20 cigarettes (equals one pack) per day for 2 years and the decline in FVC. (111–113)

Additionally, various reviews reported that women with a higher BMI especially in menopause had an increased risk of new-onset asthma, which might be attributed to hormonal fluctuations and to the pro- or anti-inflammatory effects these hormones have. (12,110) New-onset asthma refers to any first-time diagnosis of asthma and regarding menopause, new-onset asthma is often set equal with late-onset asthma, which refers to asthma that begins later in life. (15) A high BMI and metabolic changes, especially in (peri-) menopausal women, therefore, additionally influence respiratory issues and might contribute to the development of new-onset asthma. (110) Not only do structural and metabolic changes have impact on the lung function, also hormonal changes around menopause influence respiratory health.

In perimenopause (often starting years before menopause) the ovaries gradually produce less estrogen and progesterone and therefore these hormone levels drop, which can lead to physical and emotional changes such as night sweats and hot flashes, mood swings, vaginal dryness, and irregular menstruation periods. (108)

Women with pre-existing asthma often report worsening of their symptoms during (peri-) menopause, potentially due to the loss of anti-inflammatory and protective effects certain sex hormones have on the lungs. (72) As already mentioned in the chapter "estrogen and asthma", estrogen plays a key role in modulating immune responses. Low levels, among others, can lead to a higher activity of certain pro-inflammatory cytokines and changes in the balance of immune cell types. A decline of estrogen and progesterone during menopause might be associated with a change in systemic inflammation reaction, often causing asthma exacerbation, and making it more challenging for affected women to manage their asthma symptoms. (68,110)

Not only does a fluctuation and a decline of estrogen impact asthma severity, but it also affects how women respond to asthma treatments. *Triebner et al.* overserved in a longitudinal population study that during menopause some women experience a poorer response to anti-inflammatory medications, leading to a less effective management of symptoms. (110)

In summary, the onset of asthma during menopause is likely related to hormonal and metabolic changes that occur during this life stage as well as other factors such as age, the use of menopausal hormone therapy (MHT), and lifestyle. (114) Therefore, understanding the impact of those changes in menopause is crucial for women's general health and disease management.

6.8 Menopausal hormone therapy and asthma

Menopausal hormone therapy (MHT) and hormone replacement therapy (HRT) both describe the replacement of hormones (primarily estrogen and progesterone). (115) In this review HRT and MHT refer to the same meaning, as a therapy in menopausal women. MHT is a very effective treatment for symptoms which occur around menopausal transition such as night sweats, hot flashes, vaginal dryness, mood swings, poor sleeping quality and to prevent effects of long-term estrogen deficiency such as osteoporosis or cardiovascular diseases. (109,116) Often a combination therapy (estrogen and progesterone) is established to manage the hormonal fluctuations. As estrogen monotherapy can cause a thickening of the endometrium, women with an intact uterus additionally need progesterone or progestin (a synthetic form of progesterone) to counteract the effects and prevent endometrial hyper- or neoplasia. (116)

MHT has been established for many years and provides significant benefits for managing menopausal symptoms, but also increases the risk for among others thromboembolic events, breast cancer, or endometrial carcinoma. (116,117) Whereas various studies focused on these risks, the relationship between MHT and respiratory health has received less attention.

The effects of MHT in association with respiratory health can vary depending on the start and the duration of the regimen, the type of hormones used (estrogen alone or combined therapy), the patient’s compliance, and the individual health profile of each patient. (118,119) MHT is not recommended for primary prevention or as a prophylactical therapy for (peri-)menopausal women with new-onset asthma (109). The *European Community Respiratory Health Survey* (ECRHS), an international prospective cohort study, has shown that women who took oral MHT for more than five years had a significantly reduced decline in lung function (measured by FVC and FEV_1) compared to women without MHT. The findings indicate that estrogen in particular seems to positively affect lung ageing and elevated levels appear to protect lung function in menopausal women. (118) Besides these positive effects estrogen might have on respiratory health, the influence of exogenous sex steroid hormones on the risk of developing new-onset asthma remains controversial among researchers. *Zhang et al.* analyzed existing and previous studies focusing on the association between MHT and new-onset asthma. The study reported mixed findings, highlighting the conflicting and inconsistent evidence and systematic biases in studies focusing on this context. (119) Also, the association between MHT and asthma depends on additional risk factors such as obesity and (cigarette) smoking, the age of menopausal onset and the patient's overall health profile. (120) Further research in form of e.g., longitudinal studies that take systemic biases into account will help to improve the evidence and make causal statements about the risks and benefits of MHT.

In summary, it is essential to weigh the benefits of MHT against the potential risks. To minimize harms and side effects that come with MHT, an individualized treatment plan must be tailored to each woman's needs. This might include a combined therapy with the lowest effective dose for the shortest duration necessary to effectively manage symptoms during menopause. (119) Patient education about the treatment with MHT and related side effects as well as regular follow up appointments with healthcare providers are crucial to optimize, adjust and assess the effectiveness of the therapy. (116) More research work is certainly needed to clarify the relationship between MHT and respiratory health to better understand the factors that might have an impact.

6.9 Transgender people with asthma

The terms “transgender“ or “gender diverse“ refer to people whose gender identity differs from the sex assigned to them at birth. Both terms emphasize the diversity of gender beyond the binary classification of “male” and “female” and are used as a summative term for a big group of diverse individuals. (121)

Estimates suggest that around 1-3% of the global population identifies as transgender (122,123). Studies on gender-diverse people with respiratory health issues are very limited. (34) In most literature the terms “sex” and “gender” are not always clearly defined. Whereas “sex” refers to the biological and physiological attributes such as chromosomes, hormones, and reproductive anatomy that distinguish females and males, “gender” is a sociocultural concept that refers to identities, characteristics, roles and behaviors of women, men, boys, girls, and gender-diverse individuals. Gender characteristics can also differ across cultures and evolve over time. (24)

Some people choose to express their identified gender by undergoing gender-affirming hormone therapy, which includes the intake of exogenous sex hormones. Circulating endogenous and exogenous sex hormones are associated with the incidence and prevalence of asthma and may influence asthma therapy, management, and outcomes. (121) Asthma prevalence, particularly in transgender patients who undergo gender-affirming hormone therapy changes compared to non-transgender individuals of the same birth sex. Individuals who undergo male-to-female gender affirming surgery might be at higher risk of developing or experiencing changes in their asthma symptoms when taking estrogen as replacement therapy. (12) Hormone replacement and sex reassignment therapy often have higher doses of external estrogens than oral contraceptives. (124)

In a case report a young transgender female with cystic fibrosis and a history of asthma and comorbid allergic conditions, who underwent male-to-female gender reassignment therapy showed a decline in lung function after starting estrogen therapy. However, the case report only highlights the risk of external estrogen use and a worsening of pulmonary function but does not provide further information about estrogen being the cause for this change. (124) Transgender people therefore might require unique considerations regarding asthma management, particularly in relation to the potential impact gender-affirming therapies might have on the patient’s respiratory health. For healthcare providers it is crucial to closely monitor these patients and adjust asthma management plans if necessary. Before starting sex reassignment therapy the patient should be offered comprehensive education about the potential risk of worsening symptoms and lung function decline. (124) Gender-affirming surgical interventions might have consequences regarding pulmonary function. The use of chest wall binders to reduce the appearance of breasts can cause additional problems such as dyspnea, pain, and even rib fractures which influence pulmonary function. (125) Clinicians should also consider that the rates of chronic conditions, including depression and anxiety, are significantly higher in transgender people with asthma. (12,34)

The diagnostic approach to asthma in transgender people is different than in cisgender individuals. Sex is one of the predictive criteria for pulmonary function tests. In order to interpret the spirometry results correctly, the values relating to the sex assigned at birth are the major determinant of predicted lung and chest size and should therefore be used as a reference. Using non-birth sex references might lead to misdiagnosis and inappropriate treatment. (126) It is important for healthcare providers to inform the patient about the need of a correct diagnostic procedure to avoid wrong test results leading to mistreatment of asthma conditions. A two-step method for determining the sex assigned at birth and gender identity could help transgender people to disclose their status. (121,126)

The current management and prevention guidelines for asthma do not provide any sex- or gender-related advice for the treatment of asthma. Continued research which focuses on respiratory conditions in transgender people is needed to create individualized treatment strategies and therapy recommendations.

Sadly, transgender people still face problems such as discrimination and disparities in the medical sector and therefore might seek healthcare services less frequently which often leads to delayed diagnostic and treatment. Mis- and underdiagnosis of asthma in transgender people is also due to the lack of training of healthcare providers. (127)

In general, among transgender people a good relationship between patient and doctor is crucial as well as tailored, gender-affirming in managing and ensuring effective asthma control, but also to improve overall health and quality of life. (121)

7 Discussion

This review examined some of the factors that contribute to the sex- and gender differences regarding asthma. In this part the main observations of this thesis will be summarized and discussed. Further, the main findings are shown as an overview in Table 2.

There are clear disparities in the prevalence, severity, and manifestation of asthma between women and men in different age groups, but also in terms of diagnosis, therapy, and overall asthma management. As far as the prevalence of asthma is concerned, in childhood it is much higher in boys than in girls, while around puberty prevalence and morbidity decrease in males and increase in females. (5,6) Various publications focus on the influence of sex hormones and their (physiological) changes in the course of life and consider them to be among the main factors for asthma development. Other factors might also contribute to this prevalence shift, such as dysanaptic (disproportionate) lung growth, which is observed more often in boys, while in girls the growth of bronchial airways and lung tissue is more proportional. (11) However, a change in severity and asthma symptoms in females can be observed during menstruation, pregnancy or (the onset of) menopause, indicating that fluctuating sex hormone levels impact the pathophysiology of asthma. Animal studies showed that estrogen signaling promotes T2-high (allergen mediated) and T2-low inflammation, as well as the upregulation of airway hyperresponsiveness. (80,82,83) This suggests that estrogen has a more pro-inflammatory role in modulating immune responses. (68,78,79) However, *Van Anders et al.* (84) also found that estrogen seems to have a positive effect on the immunological mucosal barrier. (84) Estrogen also acts together with other hormones such as progesterone, and therefore balanced levels appear to a crucial factor for respiratory health as well. (85) However more research is needed for a comprehensive understanding of how estrogen affects inflammatory pathways in asthma.

Androgens on the other hand seem to have more lung protective properties, with androgen signaling attenuating T2-high as well as T2-low airway inflammation. (71,77,87,89) Higher testosterone levels are associated with better lung function, in women and men. (77,86) The therapeutical approach to treat asthma symptoms with androgen-based hormone therapy has moved more into the focus of researchers. Currently this kind of therapy is not indicated for asthma management, given the potential side effects of androgen therapy. (73,78,90) Again, further research is needed to implement potential therapeutic strategies for asthma management and prove the safety of long-term androgen use.

A variety of observational studies *in vivo* have investigated the potential impact of exogenous estrogen and progesterone use in terms of treating asthma. In women with perimenstrual asthma, who experience an exacerbation of symptoms and worsening of lung function around the time of menstruation, the use of hormonal contraceptives could help to control asthma severity by reducing hormone free intervals and stabilizing imbalances. (66,94,96) However, involving hormonal contraceptives in asthma management requires close monitoring and symptom tracking, which helps to develop personalized treatment approaches for women with PMA, where conventional therapies alone may not always be effective. (99,101) Additionally, an emergency asthma action plan should be established, which includes self-management steps in case of an asthma attack. Although the guidelines emphasize that hormonal contraceptives might alleviate asthma symptoms, the use of external hormone therapies is not included in the treatment strategies. The evidence is still emerging, and further studies and clinical trials are needed to establish definitive guidelines for the use of external hormones.

There are many conflicting findings regarding the effects of menopausal hormone therapy and respiratory health, with some studies pointing out the risk of developing new-onset asthma, whereas other studies showing positive impacts of MHT on some women’s lung function and asthma symptoms. (110,120) The effects of MHT among others also depend on the types of hormones used, the start and duration of the regime. (118,119) More clinical studies are needed to find out when to start with which dose and how long to continue the therapy. However, this kind of therapy could be an important treatment option for (peri-) menopausal women, especially for those suffering from severe forms of late-onset asthma. It is essential to weigh up the benefits against the potential risks and also monitor these women closely, preferably in collaboration with pulmonologists and specialists in the field of hormone replacement therapy.

Up to now, hormonal therapies are not an integral part of asthma therapy and are also not officially recommended in any guideline. Studies should therefore focus on the effects of exogenous hormone therapies on asthma in order to implement effective management plans involving the use of HC or MHT. In general health care providers additionally need to inform women about possible aggravations caused by hormonal fluctuations which occur during certain life phases. Asthma is considered the most common chronic disease in pregnant women. The exposure to higher levels of estrogen during pregnancy might increase asthma exacerbations. Around one third of women experience a worsening of their symptoms. (15) The primary goal of keeping asthma symptoms under control and avoiding hypoxemia throughout exacerbations can only be achieved if pregnant women maintain the use of their asthma medications. To ensure patient compliance, health care providers need to do comprehensive educational work regarding the safety of ICS-use during pregnancy and the risks of non-adherence. Pregnant women with asthma need a particularly close monitoring of their symptoms, also after giving birth. In addition, gynecologists should be involved in asthma management. These women should furthermore be equipped with an asthma action plan for managing exacerbations during pregnancy.

Different endo- and phenotypes of asthma exist, with milder forms such as allergic asthma, which is more commonly in children, and more severe types with a later onset. Especially older women are more frequently affected from severe asthma forms, such as neutrophilic asthma with obesity compared to men, where certain asthma clusters are particularly linked to current and past smoking. (19,22) Severe asthma is associated with an increased risk of exacerbations, higher hospitalizations rates and a poorer response to corticosteroid therapy, requiring other asthma medications. (20)Phenotyping should be considered early in patients who do not respond properly to asthma therapy or in patients with late-onset and severe asthma before initiating treatment. Specialist review should be required as soon as the phenotype is diagnosed. An action plan with steps to take in case of asthma exacerbations is crucial for patients with severe asthma. Understanding the characteristics of certain asthma types and classifying clusters could help developing personalized treatment strategies and improve asthma control.

Diagnosis is still based on standardized guidelines, which do not adapt for sex or gender. Sex- and gender discrepancy however can lead to underutilization of objective testing methods. Several publications reported that women, especially in higher age, are tested less frequently compared to men, leading to delayed or even missed diagnosis of asthma and furthermore to inadequate asthma treatment. (20,26) As soon as asthma is suspected, this should be confirmed by using objective diagnostic tools and refer to sex- and gender-specific clinical parameters. Clinical biomarkers might additionally help in diagnosing and monitoring different asthma types. However, at present, there are no specific biomarkers for women or men as diagnostic tools. By considering sex- and gender-specific cutoff values instead of standardized parameters, higher accuracy in diagnosis could be achieved.
Around menstruation, when some women experience a worsening of their symptoms, a simultaneous deterioration of lung function tests and a change in biomarker levels can be observed. Here in particular, it is essential to adapt functional diagnostics and, if necessary, the therapy to female-specific reference ranges, as biomarker levels and parameters might vary among asthma patients in certain phases. (48,50,51) This also applies to adapting reference values in pregnancy, menopause, and for transgender individuals. However further research is needed to investigate how sex and gender affect certain biomarker levels, as these might not apply equally to all patients. Further studies could also contribute to the implementation of guideline recommendations for diagnosing and treating asthma. Current guidelines do not address sex- and gender- based differences in asthma diagnosis and therapy.

Women and men might also present with different symptom reporting and profiles, which sometimes do not correlate with objective measures of lung function. (12,26,52) It is important to take a patient’s complaints seriously and not assign asthma symptoms to other health conditions such as anxiety or depression. To raise awareness for sex- and gender bias regarding asthma diagnosis, comprehensive training, education, and self-assessment tools, which reflect and give feedback on treatment decisions, might help healthcare providers to improve management and asthma outcomes in female, male and transgender patients.

Asthma diagnosis can often be challenging due to confounding comorbidities, such as obesity, GERD and depression which are more often observed in female asthma patients, whereas COPD and coronary heart diseases seems to be more prevalent in male patients. (41,44–46) Also, transgender asthmatics are often affected by chronic conditions. Comorbidities often contribute to a poorer asthma control and limit a patient's quality of life. (34) In general, physical and psychological well-being is often only assessed throughout standardized questionaries which do not address sex and gender differences. (42) Adapting diagnostic interviews and clinical questionnaires to sex- and gender-specific issues might help clinicians to manage asthma more effectively including the treatment of other health conditions.

Patient education, especially but not only for women, should highlight the increased risks in females during certain phases in life. Also, all patients should be encouraged to stick to their treatment plans and follow a healthy lifestyle, including smoking cessation, physical activity and maintaining a normal BMI. Tailored disease management programs for women and transgender individuals could help these patients to better understand and manage their disease and should be offered as standard once the diagnosis is confirmed.

The exposure to certain occupational allergens in "traditionally" female or male occupations could trigger asthma and contribute to a worsening of asthma symptoms. The results from a study (36) showed that in men there was a longer time between occupational exposure and the onset of asthma symptoms and a longer time to diagnosis than in women. In addition, men showed a greater deterioration in lung function and had to leave their employment earlier due to occupational asthma. Future research should focus on identifying work-related factors that contribute to sex-differences regarding the severity of occupational asthma. Preventive measure plans and legal regulations in certain professions should be implemented to help reduce trigger exposure. (36)

Certain chemicals such as BPA, pesticides and phthalates seem to have estrogen-like effects and have been shown to promote allergen-driven inflammatory reactions in asthma. The effects of these external chemicals on the development of asthma may depend on the dose level. However, more studies are needed to establish safe levels in consumer products and the environment, and to further investigate how exactly these external chemicals contribute to asthma development, especially in early childhood. (37–40)

Finally, asthma also affects many transgender people. Studies on gender-diverse people with respiratory health issues are very underrepresented. The risk for exacerbating or developing asthma is significantly increased in transgender individuals undergoing gender-affirming hormone therapy. (121,124) Discrimination and disparities in the medical health care sector make it even more difficult for transgender people to receive appropriate asthma treatment. (127) For transgender patients undergoing hormone therapy it is important that they are informed about the potential risks which come along with gender-affirming hormone therapy or surgical interventions. Special monitoring is necessary for any changes of asthma symptoms which may be influenced by hormonal fluctuations. Evolving terminology helps transgender people to disclosure their status. Future research should include correct terminology to reduce errors and inconsistencies in asthma diagnosis, therapy, and overall management.

This review revealed that not only anatomical and biological differences, but also changing hormone levels, genetics, environmental exposures, cultural factors, as well as socially constructed “norms” contribute to sex- and gender differences in asthma. However, the current (inter-) national guidelines do not provide specific recommendations for treating perimenstrual asthma or menopausal women with new-onset asthma. Furthermore, these guidelines also do not adapt to the unique needs for transgender people with asthma, nor do they provide specific treatment protocols, indicating a significant sex and gender gap.

By developing treatment strategies that take these sex and gender differences into account, healthcare providers could improve their understanding of how certain factors affect asthma. This increased awareness could lead to effective treatment and close sex and gender gaps in healthcare. Therefore, to improve overall asthma management and provide individualized treatment strategies, future guidelines must consider these disparities and adapt to the diverse needs of all asthma patients.

Table 2: Overview of insights of this review on sex- and gender-specific differences

Differences	Insights of this review	References
Asthma prevalence	During childhood, asthma is more prevalent in boys than in girls. With the start of puberty, asthma prevalence rises in girls. In adulthood the prevalence is higher in females. Around the fifth decade asthma prevalence rises again in males, but is still higher in females.	(4,5)
Dysanapsis	Dysanaptic (disproportionate) lung growth in early childhood is observed more often in boys than in girls. Lung growth in girl is more proportional.	(2,10)
Anatomy	Men tend to have a larger lung size with larger airway diameter and greater absolute lung volumes. Relative lung volumes and capacities are similar between males and females.	(7,9,11)
Severe Asthma	In childhood more boys are affected from severe asthma forms (mostly allergic asthma) than girls. In adulthood more women are affected by severe asthma than men.	(18,19,45,50,127)
Asthma phenotypes	Atopic-eosinophilic phenotype, obese-neutrophilic phenotype, and late-onset non-atopy phenotype are more frequently observed in female asthma patients. Atopic-neutrophilic phenotype associated with smoking, late-onset-eosinophilic phenotype associated with past smoking, and late-onset phenotype are more frequently observed in male asthma patients.	(4,6,21,128)
Genetics	The X chromosome houses several regulatory response genes, which might be involved in asthma. The XIST gene (higher expression in females) is among others involved in immune cell responses, estrogen and testosterone signaling. Various genetic polymorphisms which are associated with a higher risk of asthma have been identified in women and men.	(13,24-27)
Risk factors	Male asthmatics exposed to first- or secondhand smoking have a higher risk of asthma exacerbation compared to females. Smoking during pregnancy in women with asthma increases the risk for exacerbations, delayed fetal development and birth complications. Smoking rates are higher in transgender compared to non-transgender individuals. Women with higher BMI experience more severe forms of asthma compared to men. Rates for obesity are higher in transgender compared to non-transgender individuals.	(29-34)

Table 2: Overview of insights of this review on sex- and gender-specific differences (continued)

Differences	Insights of this review	References
Occupational asthma	Women and men are exposed to different asthma triggers in certain occupations. For men the time between occupational exposure and onset of asthma symptoms as well as the time to diagnosis is longer than for women. In addition, men have a poorer lung function in this regard, especially when diagnosis takes longer than 24 months. Men leave their employment earlier due to asthma.	(37,38)
Comorbidities	The presence of chronic diseases is more common in female than in male asthma patients. Obesity, GERD, anxiety and depression is more common in female asthma patients. COPD and coronary heart disease is more common in male asthmatics. Transgender people are more often affected by COPD, obesity, asthma and depression than cis-transgender people.	(33,40,41-43)
Diagnosis	Females, especially in higher age, are tested less likely for asthma leading to delayed or missed diagnosis. Asthma is often diagnosed earlier in boys than in girls. Mean FeNO levels are higher in male than in female asthmatics. Female and male asthmatics present with different symptom reporting, which do not always correlate with lung function tests. Symptoms are more frequently attributed to depression or anxiety in female than in male asthma patients.	(11,13,19,25,47,49-51)
Therapy	Combined ICS/LABA therapy is prescribed more frequently to male than female patients. Women are less likely than men to be prescribed a controller medication. Female asthmatics might have a poorer performance regarding inhalation techniques. Men might better respond to ICS therapy than women. OCS is prescribed more often to female than to male patients.	(8,55-60)
Hormones	Estrogen signaling promotes airway hyperresponsiveness, T2-high and T2-low inflammation, and can directly influence inflammatory cells such as mast cells. Estrogen positively affects IgA secretion.	(67,77,78,81-83)
	Androgen signaling attenuates T2-high and T2-low inflammation and suppresses cytokine production. Among asthma patients, higher testosterone levels are associated with better lung function. Asthma patients often have a lower androgen receptors expression. Lower testosterone levels go along with an increased inflammatory response.	(70,72,76,85,86,88)

Table 2 *Overview of insights of this review on sex- and gender-specific differences. XIST: X-inactive specific transcript gene, BMI: body mass index, GERD: gastro-esophageal reflux disease, COPD: chronic obstructive pulmonary disease, FeNO: fractionated exhaled nitric oxide, ICS: inhaled corticosteroids, LABA: long-acting beta-agonist, OCS: oral corticosteroids.*

8 Conclusio

Life expectancy is increasing, and the world's population is getting older, half of whom are women. Much of the research, drug development and dosing in medicine has been based on the male sex. In recent years and decades, research has focused more and more on sex- and gender-associated disparities and a lot has happened in the field of gender medicine. However, when it comes to sex- and gender-specific differences in relation to (chronic) lung diseases, research has not yet focused as much on these differences as it has in the case of other diseases. This review is primarily intended to draw attention to the fact that there are many factors and causes that lead to sex- and gender-specific disparities in diagnosis and treatment, but also regarding the course of the disease, morbidity, and quality of life. Likewise, many (patho-) mechanisms and causes are still not understood, which is why many more studies and research in this field are needed. It is high time to personalize medicine to sex and gender.

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