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Review

Sex-Based Differences in Bronchial Asthma: What Are the Mechanisms behind Them?

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Abstract: Sex-based differences in bronchial asthma can already be observed in childhood, at which time allergic atopic asthma is more frequently found in boys than in girls. In adulthood, higher prevalence of asthma is reported in women, especially for the more severe neutrophilic subtype associated with obesity, which responds poorly to corticosteroids. Sex-based differences seem to be attributable to changing levels of estrogens, progesterone, and testosterone, which may exert mainly pro-inflammatory (estrogens, progesterone) or anti-inflammatory effects (testosterone). Sex steroids differentially influence lung immune responses, airway reactivity, and pulmonary circulation and may thereby contribute to the higher susceptibility of females to more serious complications resulting from inflammatory lung diseases compared to males. However, other factors, such as anatomical and physiological differences in the lungs, differences in genetically conditioned factors, obesity and lifestyle, smoking, exposure to environmental and occupational factors, chronic stress, etc., may also contribute to the sex-based differences in asthma. Elucidation of the mechanisms behind these differences may contribute to more appropriate personalized therapy for asthma. For the review, articles in the English language from the PubMed database were used.

Keywords: bronchial asthma; asthma endotypes; asthma phenotypes; sex hormones; sex-based differences; obesity; smoking; chronic stress; genetically determined factors

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1. Introduction

Bronchial asthma (or asthma) is one of the most frequently occurring chronic respiratory diseases. Worldwide, asthma affects more than 330 million people of all age groups, and its prevalence is generally higher in high-income countries [1]. Asthma has been recognized as an extremely heterogenic respiratory disorder that presents in the form of several endotypes with distinct underlying pathophysiological mechanisms and various phenotypes with observable clinical characteristics potentially responsible for varying responses to treatment [2–4]. The main features of asthma include chronic airway inflammation leading to remodeling of the airways and epithelial fibrosis, hypersecretion of mucus, metaplasia and hyperplasia of goblet cells, and hypertrophy and hyperplasia of airway smooth muscle. Clinical symptoms of asthma include episodes of airway narrowing associated with wheezing, shortness of breath, chest tightness, and as a non-specific symptom, cough, while the intensity of the respiratory signs may be variable. Careful investigation of personal history pointing to relations between the occurrence of respiratory symptoms and exposure to environmental factors, viral infection, allergies, obesity, etc. is very important for making diagnoses [1,3]. In addition to the heterogenic pathophysiological and clinical characteristics of the various subtypes of asthma, sex-based differences have been also described.

Thus, the purpose of this article was to summarize current knowledge on the sex-based differences found in male versus female patients with bronchial asthma, as well as

differences demonstrated in various animal models of airway inflammation and hyperreactivity resembling human asthma. For the review, articles in the English language from the PubMed database were used. The collected material highlighted the potential mechanisms responsible for the differences between males and females and gave rise to many questions about how these differences may influence the therapy given, how different the treatments given to women and men with asthma should be, and which preventive measures can be employed to improve the status of asthma patients.

2. Sex- or Gender-Based Differences in Asthma?

For decades, women and female laboratory animals were under-estimated in studies because of greater variability in the physiological parameters. Male subjects dominated in clinical studies, as well in experimental measurements, which could have resulted in misinterpretations and detrimental consequences for females [5,6]. On the other hand, the opposite bias exists for some models of diseases with female predominance (e.g., osteoporosis) where the data collected from females does not completely fit men. Currently, modern trends in biomedical research recommend the recruitment of patients and laboratory animals of both sexes to reliably reproduce the standard situation in populations [5,6].

The terms "sex" and "gender" are often used interchangeably; however, they bear different meanings. While "sex" refers to genetically determined anatomical, physiological, and biological differences between males and females, including the production of hormones, "gender" is more complex and refers to social and cultural differences, including the self-identification of the individual [7].

3. Endotypes and Phenotypes of Bronchial Asthma

In accordance with the dominant type of granulocytic inflammation and the contributions of specific subtypes of T-lymphocytes, three main endotypes of asthma may be distinguished: eosinophilic, non-eosinophilic, and mixed granulocytic asthma [1]. However, the different asthma endotypes and phenotypes are not fully understood, and additional research is needed to adequately define the different asthma endotypes and phenotypes and describe their characteristics.

The eosinophilic (or T2-high) endotype of asthma, which is present in about 50% of adult asthma patients, is divided into allergic and non-allergic subendotypes. The allergic subendotype is characterized by sensitization to allergens (pollen, house-dust mites, etc.). Contact between allergens and alarmins—epithelial barrier-derived mediators such as thymic stromal lymphopoietin (TSLP), interleukin (IL)-25, and IL-33—activate dendritic cells and group 2 innate lymphoid cells (ILC2s) and induce the type 2 signaling pathway through the mediation of T-helper (Th)2 lymphocytes. Activated dendritic cells and ILC2s are potent producers of IL-4, IL-5, and IL-13, which recruit eosinophils into the lungs, promote goblet cell overexpression, stimulate the secretion of mucus, increase airway hyperresponsiveness, and increase expression of extracellular matrix proteins (e.g., periostin), contributing to airway fibrotic remodeling [3]. IL-4 drives the switching of the B-cell isotype and synthesis of immunoglobulin (Ig)E, which binds to mast cell high-affinity IgE receptors. Subsequent activation of mast cells leads to allergen-mediated IgE cross-linking [1]. In the non-allergic subendotype of eosinophilic asthma, ILC2s produce IL-5 and IL-13 in response to prostaglandin (PG)D2 and the alarmins IL-33, IL-25, and TSLP released from the epithelium due to deterioration resulting from pollutants and microbes [1–3].

T2-high asthma clinically presents in three phenotypes that have been identified up to now. Atopic asthma, one subtype of early-onset asthma, is corticosteroid-sensitive and typically appears during childhood because of allergic sensitization. Late-onset asthma is a steroid-resistant phenotype of eosinophilic asthma that develops in older patients as more severe asthma with fixed airflow obstruction. Aspirin-exacerbated respiratory disease (AERD) is a subset of late-onset asthma that originates due to dysregulated arachidonic acid metabolism [3].

The non-eosinophilic (or non-T2 or T2-low) endotype of asthma is characterized by the absence of eosinophilia and the presence of neutrophilic inflammation with neutrophil sputum levels greater than 40% (i.e., neutrophilic asthma) or may manifest as the paucigranulocytic type of asthma with normal sputum levels of eosinophils and neutrophils [3]. Although the mechanisms of neutrophilic asthma are not yet fully understood, chronic infection with atypical bacteria, obesity, and smoking likely contribute to the activation of Th1 and/or Th17 lymphocytes or type 3 ILCs [1–3]. Paucigranulocytic asthma is a special endotype of asthma in which both eosinophils and neutrophils are below the thresholds for the diagnosis of the previously mentioned types of asthma. Paucigranulocytic asthma is poorly understood and, instead of inflammation, airway smooth muscle dysfunction and bronchial hyperresponsiveness appear as the main pathophysiological features [2,8].

Several T2-low phenotypes have also been identified. Obesity-associated asthma is a non-atopic and corticosteroid-refractory form of asthma occurring in middle-aged women with obesity. Smoking-associated asthma originates due to smoking exposure-induced oxidative stress. Very late-onset asthma develops in older patients because of decreased lung function due to reduced elastic recoil and immunosenescence [3]. However, non-eosinophilic asthma may also present in children and adolescents as one form of early-onset asthma [9].

In the mixed granulocytic endotype of asthma, both allergic-dependent and allergic-independent mechanisms may occur hand in hand, leading to mixed granulocytic inflammation [1]. The pathophysiological characteristics of the main endotypes of asthma are summarized in Table 1.

Table 1. Features of major asthma endotypes (modified from [1–3,8]).

	Eosinophilic Asthma		**Non-Eosinophilic Asthma**		**Mixed Granulocytic Asthma**
	Allergic	**Non-allergic**	**Paucigranulocytic**	**Neutrophilic**	
Triggering agents	Allergens	Pollutants, microbes	Pollutants, oxidative stress	Pollutants, oxidative stress, microbes, obesity	
Involvement of eosinophils	++	++	−	−	+
Sputum eosinophils	>3%	>3%	<3%	<3%	>3%
Blood eosinophils	+	+	−	−	−
Atopy	+	−	−	−	−
Involvement of neutrophils	−	−	−	++	+
Sputum neutrophils	<61%	<61%	<61%	≥61%	≥61%
Epithelial damage	++	++	+	++	++
Mucus	+	+	+/−	++	++
Reticular membrane basement thickening	++	++	+/−	+	+
Airway smooth muscle mass	++	++	+	+	+

Notes: ++: high increase, +: moderate increase, +/−: inconsistent changes, −: no increase.

Differences in the pathophysiological backgrounds of the major asthma endotypes not only result in different diagnostic criteria for individual types of asthma but may also be responsible for variations in the appropriate treatment [2,10–13]. For instance, eosinophilic subtypes of asthma usually respond well to corticosteroids [12,14], while both non-eosinophilic subtypes of asthma are insensitive to corticosteroids and, therefore, novel treatments have been intensively studied [13].

A review of clinical and biochemical biomarkers for eosinophilic, neutrophilic, and paucigranulocytic asthma is provided in Table 2, and currently available and promising treatments are listed in Table 3.

Table 2. Potential clinical and biochemical biomarkers for the eosinophilic, neutrophilic, and paucigranulocytic endotypes of bronchial asthma (modified from [1–3,8]).

	Eosinophilic Asthma	Neutrophilic Asthma	Paucigranulocytic Asthma
FeNO	++	+/−	+
AHR	++	+/−	+
Endotype-specific changes in biochemical biomarkers	↑ serum periostin ↑ serum IgE (in atopy) ↑ sputum supernatant ECP, EDN, EPO, eotaxin-2, IL-5, IL-13, GM-CSF, osteopontin, angiopoietin-I, Grx1; ↑ MMP-9	↑ serum CRP and IL-6 ↑ sputum supernatant IL-8, IL-17, MPO, NE, TNFα, CXCR1, and CXCR2 ↓ sputum gal-3 ↑ gal-3BP and IL-1β ↓ gal-3/gal-3BP and IL-1Ra/IL-1β	↑ Grx1

Abbreviations: AHR: airway hyperresponsiveness, CRP: C-reactive protein, CXCR: chemokine (C-X-C motif) receptor, ECP: eosinophil cationic protein, EDN: eosinophil-derived neurotoxin, EPO: eosinophil peroxidase, FeNO: fractional exhaled nitric oxide, gal-3: galectin-3, gal-3BP: galectin-3 binding protein, GM-CSF: granulocyte-macrophage colony-stimulating factor, Grx1: glutaredoxin 1, IgE: immunoglobulin E, IL: interleukin, IL-1Ra: interleukin-1 receptor antagonist, MMP: matrix metalloproteinase, MPO: myeloperoxidase, NE: neutrophil elastase, TNFα: tumor necrosis factor alpha, ++: high increase, +: moderate increase, +/−: low values, ↑: increase, ↓: decrease.

Table 3. Currently available and prospective treatments for eosinophilic, neutrophilic, and paucigranulocytic endotypes of bronchial asthma.

Classified Drugs	Examples of Drugs Used	References
Eosinophilic asthma		
Currently available treatments:		
Inhaled corticosteroids (ICSs)	Budesonide, fluticasone	[12,14,15]
Oral corticosteroids (OCSs)	Prednisolone	[12,14]
Bronchodilators (SABA, LABA, SAMA, LAMA)	Salbutamol, formoterol, ipratropium, tiotropium	[12,15]
Xanthine derivatives	Theophylline	[16,17]
Anti-IgE	Omalizumab	[18,19]
Anti-IL-5/IL-5R	Mepolizumab, benralizumab	[20,21]
Anti-IL-4R	Dupilumab	[22,23]
Anti-TSLP	Tezepelumab	[23,24]
Anti-leukotrienes	Montelukast	[25,26]
Prospective treatments:		
Anti-IL-13	Tralokinumab	[27]
Tyrosine kinase inhibitors	Dasatinib	[28,29]
Statins	Simvastatin, atorvastatin	[30,31]
Macrolide antibiotics	Azithromycin	[32]
PGD2 receptor 2 antagonist	Fevipiprant	[33]
Neutrophilic asthma		
Currently available treatments:		
Macrolide antibiotics	Azithromycin	[32,34]
Bronchodilators (LAMA)	Tiotropium	[35,36]
Xanthine derivatives	Theophylline	[16,17]
Prospective treatments:		
PDE4 inhibitors	Roflumilast	[37,38]
Statins	Simvastatin, atorvastatin	[30,31]
Tyrosine kinase inhibitors	Dasatinib	[28,29]
CXCR2 antagonists	AZD5069	[39,40]
Anti-TNFα	Etanercept	[41,42]
Anti-IL-17	Brodalumab	[43,44]

Table 3. *Cont.*

Classified Drugs	Examples of Drugs Used	References
Paucigranulocytic asthma		
Prospective treatments:		
Bronchial thermoplasty		[45,46]
Bronchodilators (LAMA)	Tiotropium	[35,36]
Mast-cell directed therapy		[47,48]

Abbreviations: CXCR: chemokine (C-X-C motif) receptor, ICSs: inhaled corticosteroids, IgE: immunoglobulin E, IL: interleukin, IL-4R: interleukin-4 receptor, IL-5R: interleukin-5 receptor, LABA: long-acting β2-agonist, LAMA: long-acting muscarinic antagonist, OCSs: oral corticosteroids, PDE: phosphodiesterase, PGD2: prostaglandin D2, SABA: short-acting β2-agonist, SAMA: short-acting muscarinic antagonist, TNFα: tumor necrosis factor alpha, TSLP: thymic stromal lymphopoietin.

4. Sex-Based Differences in Different Life Periods

Sex-based differences in the incidence and severity of asthma occur in all periods of life, as recently demonstrated by Shah and Newcomb [49] and Chowdhury et al. [50] in their excellent reviews. Therefore, only fundamental information necessary for understanding the other parts of this article is provided in the following section.

4.1. Childhood

Sex-based differences in the development of asthma or wheeze in childhood are probably linked to several contributing factors, including prenatal stress, preterm birth, low birth weight, maternal smoking, maternal obesity during pregnancy, no or shorter period of breastfeeding, repetitive respiratory tract infections, use of antibiotics or corticosteroids, and/or genetic susceptibility [51].

Prematurity, low birth weight, and/or prenatal maternal stress have been confirmed as factors increasing the risk of asthma and impaired lung function in early childhood, which may persist up to adulthood [52,53], while reduced expiratory flow and higher vulnerability are more strongly associated with male sex [54]. Greater occurrences of preterm births with worse response to prenatal corticosteroids and worse prognosis in boys than girls [55–57] are likely caused by sex hormones. Female neonates exhibit decreased susceptibility to infection and accelerated lung maturation under the stimulatory action of estrogen on the transition from the terminal saccular stage to the alveolar stage and the production of pulmonary surfactant, while testosterone has the opposite effects [58]. Dysanaptic lung development, characterized by retarded growth in the large airways in comparison to the lung parenchyma in boys, leading to narrower airways, is an additional factor resulting in sexual disparity in children [59]. A relation between low birth weight and decreased lung function or risk of asthma later in childhood and/or in adulthood has been demonstrated in several studies [60,61], with some of them finding a higher risk of asthma in males [62,63].

Higher risk of asthma or wheeze during childhood is also associated with other factors [64], such as maternal smoking during pregnancy [65–67], maternal obesity in pregnancy [68], maternal use of antibiotics during pregnancy [69], exposure to allergens and endotoxins [70], and low vitamin D status during pregnancy [71]. However, while the lung functions of male fetuses exposed to smoking in utero may be more adversely affected than those of females [72], no convincing sex-specific associations between the other mentioned risk factors and the development of wheeze in children have been found [65,73].

The higher prevalence of asthma—mainly allergic asthma—in boys of prepubertal age is linked to two times more frequent admissions to hospital due to asthma exacerbation [74–77]. In addition, boys have increased serum immunoglobulin (Ig)E levels and interferon (IFN)-γ levels, and positive skin prick tests for allergens are more frequent [78,79]. In both sexes, higher incidences of asthma were found in overweight or obese children; however, respiratory symptoms of asthma (wheezing, shortness of breath) were more frequently reported in obese boys than in obese girls [80].

4.2. Adolescence

During adolescence, the occurrence of asthma gradually decreases in boys and simultaneously increases in girls. In addition, there is a positive correlation between body mass index (BMI) and the risk of asthma in adolescent girls [81]. The likelihood of the development of asthma symptoms particularly increases in girls who were already overweight or obese between 6 and 11 years of age, but this association was not observed in boys [82].

The BAMSE (Swedish abbreviation for Children, Allergy, Milieu, Stockholm, Epidemiology) study evaluating body mass index (BMI) from birth to adolescence among children with and without asthma found the highest BMIs in girls with persistent asthma, while there were no clear associations between asthma and BMI in boys [83]. The abovementioned studies indicate a more obvious association between pediatric obesity and asthma in boys. In the puberty period, the association between obesity and asthma in girls increases.

4.3. Adulthood

In adulthood, the higher prevalence of asthma in women in comparison to men continues, and the course of the disease in women is more severe and associated with three times more frequent admissions to hospital with asthma complications [84,85]. This sex-related difference remains until menopause [76,77,86,87].

Worsening scores in the pulmonary function tests, more frequent asthmatic symptoms, and higher requirements for medication are observed in about one third of women before and during menstruation [88–90]. Pauli et al. [91] found that, in women with asthma, the morning values for peak flows and asthma symptoms deteriorated from the follicular to the luteal phase of the menstruation cycle. These findings were confirmed by other authors, who found the best airflow values at the end of the luteal phase through to the beginning of menstruation, followed by a decline over the subsequent two weeks [92]. However, in healthy controls, no changes in airway functions were observed in relation to fluctuations in estrogen and progesterone during the menstruation cycle [91,92], suggesting more complex mechanisms may be responsible for perimenstrual worsening of asthma status in women [76]. In this context, the recent finding by Eid et al. [93] that 24% of women with AERD also show perimenstrual worsening of asthma could be interesting.

Several studies have investigated the effects of contraceptive pill use in premenopausal women on the changes in lung functions and the occurrence of asthma symptoms. However, the results of these studies were often contradictory. While Macsali et al. [94] demonstrated that normal and overweight women taking hormonal oral contraceptives reported higher occurrences of wheezing and other asthma symptoms in comparison to lean women, other authors found no differences in lung functions or asthma medication use in women taking contraceptives compared to those with a natural menstrual cycle [95] or even found decreased airway responsiveness in women taking contraceptives [96]. This discrepancy indicates that further studies should be performed to evaluate the effects of contraceptives containing gestagen only or combined hormones (gestagen + estrogen) with different doses or ratios of gestagen and estrogen in relation to current asthma status, as well as new onsets of asthma.

Asthma control may change during pregnancy. In an older study by Schatz et al. [97], asthma symptoms increased in about one third of pregnant women while the status reverted within the first three months *post-partum* in about 73% of them. However, other studies found no change or even improvements in asthma symptoms [98,99]. A more recent analysis by Schatz et al. showed that asthma exacerbations during pregnancy occurred in 12.6% of patients with asthma initially classified as mild, 25.7% of patients with asthma initially classified as moderate, and 51.9% of patients with asthma initially classified as severe, while in 30% of mild asthma patients, the course of the disease worsened to moderate and, vice versa, 23% of patients with moderate–severe asthma showed improvements in their status to mild asthma [100].

The contradictory results of the studies performed with women undergoing menopause may be attributable to fluctuating levels of hormones, the use of hormone replacement

therapy (HRT), and the influence of other factors, such as smoking or concomitant diseases [101–107].

Nevertheless, similarly to the puberty period, a clear relation between asthma prevalence and obesity can be observed in women but not in men, and a higher risk of asthma was reported in obese women than in women with normal body weight [108,109]. Late-onset asthma in obese women, which represents a special phenotype of asthma, is characterized by more severe symptoms, increased counts of neutrophils in sputum, and higher requirements for treatment [110,111].

5. Factors Contributing to Gender-Based Differences in Asthma

5.1. Sex Hormones

Sex hormones seem to be primarily responsible for the differences between females and males in the prevalence and severity of asthma. Nevertheless, the mechanisms responsible for the sex-based differences in asthma may be more complex.

Sex steroids, such as estrogens, progesterone, and testosterone, have been mainly defined through their association with the normal functioning of the reproductive system. However, via their signaling mechanisms, they influence many processes in the body [112] and contribute to varying incidences of several diseases in females and males [113]; e.g., cardiovascular [114–116], neurological [117–119], metabolic [120–122], and respiratory diseases, including asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, lung cancer, and respiratory infections [113]. While androgens mainly exert anti-inflammatory effects, estrogens promote inflammation and may even induce tumorigenesis [123]. Interestingly, women complain more frequently of cough, including dry cough, which is known as an adverse effect associated with the use of angiotensin-converting enzyme (ACE) inhibitors due to the increased excitability of peripheral and central cough pathways in women [124].

Sex steroids are produced in hormone-secreting organs (ovaria, testes, placenta), as well as in other tissues; e.g., adrenal glands and adipose tissue. All sex steroids are synthesized from common precursor dietary cholesterol in the process of steroidogenesis [125] (Figure 1).

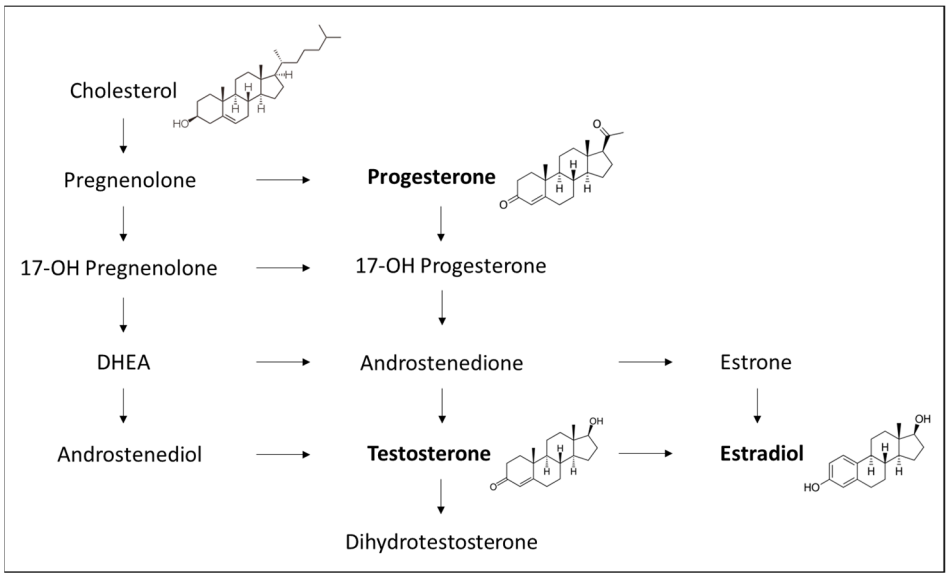

Figure 1. Outline of sex hormone synthesis (modified from [112,126–129]).

Production of sex steroids from other tissues—e.g., adipose tissue, skin fibroblasts, bones, or brain—can contribute significantly to the circulating pool of estrogens [130,131].

However, in addition to signaling intermediates, the action of steroid receptors can be modified by various coregulators, which act as coactivators or corepressors of steroid-

responsive gene expression [132]. The coregulators not only regulate hormonal events in pregnancy, sex differentiation, development, reproduction, and sexual behavior but also influence the functions of non-reproductive tissues, such as the heart, kidneys, pancreas, bone, and brain. Mutation and/or aberrant expression of the coregulators affecting the normal function of steroid hormones may result in the development of obesity, diabetes mellitus, atherosclerosis, osteoporosis, cancer, neurodegenerative disorders, or breast cancer [132].

5.1.1. Estrogens

A group of endogenous estrogens containing 18 carbons are known as C18 steroids. While estradiol (or 17-β estradiol) is produced in ovarian follicles and *corpora lutea* and represents the predominant circulating estrogen during the reproductive period, estriol and estretol are synthesized during pregnancy in the placenta or fetal liver, while estrone is generated by extraglandular tissues during menopause [133].

In cells, estrogens act by binding to specific nuclear estrogen receptors (ERs), ER-α and ER-β. They activate transcriptional processes and/or signaling events that result in the control of gene expression. The actions of estrogens can be mediated through direct binding of ER complexes to specific sequences in gene promoters (genomic effects) or through mechanisms that do not comprise direct binding to DNA (non-genomic effects) [134].

In genomic signaling, after binding of estrogen to ER-α or ER-β, the complex translocates to the nucleus, inducing transcriptional changes in estrogen-responsive genes with or without DNA estrogen-response elements [135]. In indirect genomic signaling, estrogen receptor complexes exert their actions via protein–protein interactions with other transcription factors and response elements [136]. Non-genomic effects are mediated via membrane-associated estrogen receptors and contribute to modulation of intracellular Ca^{2+} and activation of signal-transduction mechanisms, with subsequent production of intracellular second messengers, regulation of cyclic adenosine monophosphate (cAMP), and protein-kinase activation of signaling cascades, leading to rapid biological effects [137]. In addition, as an ER-independent action, estrogen may exert antioxidant effects, and as estrogen-independent actions, ligand-independent genomic events may occur [134]. Nevertheless, the actions of estrogens in the various cells are likely mediated by a combination of processes comprising genomic and non-genomic pathways, as well as additional convergent pathways enhancing transcriptional activity in specific tissues and physiological processes [138,139].

Estrogens exert a broad spectrum of effects, including induction of primary and secondary sexual characteristics, regulation of the menstrual cycle and reproduction, effects on bone density, effects on brain function (including cognitive processes and memory), and cholesterol mobilization [140]. Moreover, estrogens have many direct biological effects in the lungs, where significant distributions of ER-α and ER-β—with more abundant ER-β—have been demonstrated [141]. ER-β acts as an inhibitor of ER-α-mediated activity and may reduce the cell response to estrogens [142].

In the lungs, twice as much ER-β as ER-α is expressed in human bronchial epithelial cells, regulating epithelial Ca^{2+} signaling [143,144]. Estradiol stimulates the production of nitric oxide (NO) from bronchial epithelial cells and increases the activation of endothelial NO synthase (eNOS), contributing to bronchodilation, largely via ER-α [145]. In addition, estradiol may modulate epithelial-to-mesenchymal transition and barrier function in bronchial epithelial cells [144,146]. Estrogens also increase the number of goblet cells and the production of mucus, mainly via ER-β [147]. Although data from animal studies are not consistent, they suggest that estrogens may have a protective effect on airways, modulating airway responsiveness via activation of the NO-cyclic guanosine monophosphate (cGMP) pathway or by decreasing Ca^{2+} influx [148–151]. However, estrogens stimulate airway inflammation, as confirmed in animal studies [152–154]. Estrogens enhance the differentiation of dendritic cells [155] and elevate counts of ILC2s [156], eosinophils [152,154,157], and IFN-γ-producing Th1 cells [158] more obviously in females.

5.1.2. Progesterone

Progesterone action is mediated via two isoforms of the progesterone receptor (PR), PR-A and PR-B [159], leading to interaction with progesterone-response elements and ensuing regulation of target genes [160]. However, PRs can also interact with regulatory proteins and exert actions via non-genomic mechanisms [161].

PRs are distributed in many tissues, including the lungs. In addition to reproductive functions, progesterone participates in the regulation of neurosteroid activity in the central nervous system, inhibition of smooth muscle contractile activity in the gastrointestinal tract, vasodilation, and regulation of the development and maturation of the lungs [162].

Although there are fewer studies evaluating the effects of progesterone in asthma or its models, the available results indicate a mild pro-inflammatory effect as a consequence of increased IL-4 and IL-5 levels, eosinophil counts, and airway hyperreactivity [163,164]. In human bronchial epithelial cells, progesterone was found to decrease ciliary beat frequency, leading to inhibition of the mucociliary apparatus; however, this effect was prevented by co-administration of estradiol and progesterone [165].

5.1.3. Testosterone

The effects of testosterone and its highly active metabolite 5α-dihydrotestosterone (DHT) are mediated via androgen receptors (ARs), leading to binding to androgen-responsive elements and downstream upregulation or downregulation of the target genes [166]. Similarly to ERs, ARs are distributed in many tissues, including the lungs, in which high concentrations of ARs have been detected in the alveolar type II cells and bronchial epithelium [167]. Androgens show potent anti-inflammatory action. They reduced populations of Th2 and ILC2 cells, which subsequently led to reduced eosinophilic inflammation, but also decreased Th17-mediated production of IL-17A and reduced neutrophilic inflammation [156,168]. Via suppression of IL-17A, testosterone may reduce Ca^{2+} sensitization and airway smooth muscle contractions [169]. However, in a murine model, it was demonstrated that male sex hormones may promote airway responsiveness to cholinergic stimulation via vagal nerve-mediated reflex mechanisms [170].

Lower levels of testosterone may be associated with higher risk of asthma not only in women but also in men older than 50 years [86]. Bulkhi et al. found that serum testosterone was inversely associated with current asthma prevalence regardless of sex, and this value correlated with better lung function [171]. In accordance with these results, higher expression of bronchial ARs and higher androgen levels were associated with better lung function, fewer symptoms, and a lower FeNO in human asthma [172], while lower expression of ARs in the airways was linked to more frequent occurrence of asthma in both sexes [173]. Decreased values for the testosterone precursors dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS) were also found in postmenopausal asthmatic women compared to non-asthmatic subjects [174].

The therapeutic effect of testosterone on neutrophilic inflammation may be partially related to testosterone-induced decreases in IL-17A. IL-17A induces expression of glucocorticoid receptor (GR)-β, which inhibits GR-α and is primarily responsible for anti-inflammatory action via the suppression of the expression of genes relating to inflammatory cytokines. Thus, testosterone-induced declines in IL-17A may decrease expression of GR-β, resulting in enhanced corticoid action [175]. Potent therapeutic action was also demonstrated for precursors of testosterone produced by adrenal glands. For instance, DHEA inhibited the epithelial–mesenchymal transition, an important mechanism involved in airway remodeling, via the inhibition of the PI3K/Akt-dependent signaling pathway stimulated by transforming growth factor (TGF)-β1 [176]. The anti-inflammatory action of DHEAS was confirmed in an in vitro study where DHEAS dose-dependently inhibited chemotaxis of human peripheral blood neutrophils and airway smooth muscle cells [177]. Supplementation with DHEAS improved lung function in asthma patients; in particular, those women who had low DHEAS levels [178]. These and other studies suggest a potential future role for testosterone supplementation in the treatment of asthma [175,179–181].

However, further research is needed to identify an appropriate androgen derivative and establish appropriate dosing, delivery methods, etc.

An outline of the actions of the abovementioned sex hormones is provided in Figure 2.

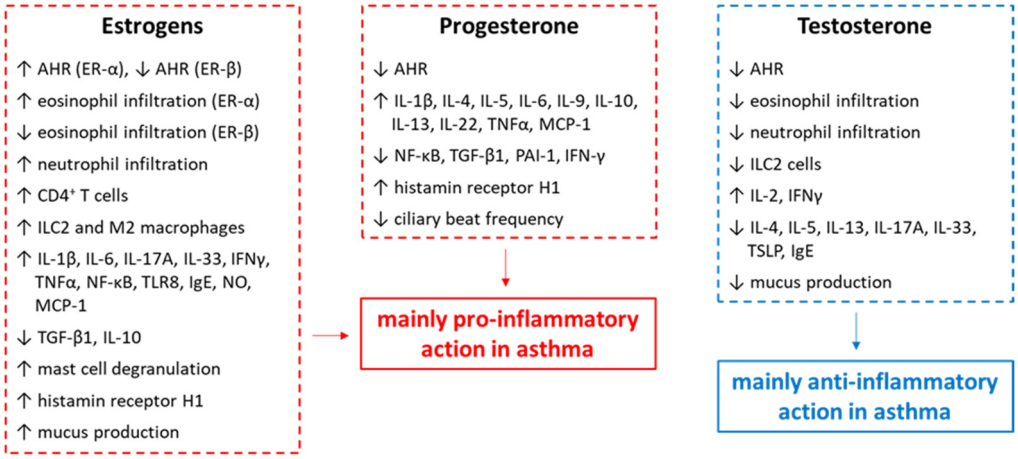

Figure 2. Outline of the actions of estrogens, progesterone, and testosterone in bronchial asthma. Abbreviations: AHR: airway hyperreactivity, ER-α and -β: estrogen receptors, IgE: immunoglobulin E, IL: interleukin, IFN-γ: interferon gamma, ILC2: group 2 innate lymphoid cell, MCP-1: monocyte chemoattractant protein-1, NF-κB: nuclear factor kappa B, NO: nitric oxide, PAI: plasminogen activator inhibitor, TGF-β1: transforming growth factor beta 1, TLR: Toll-like receptor, TNFα: tumor necrosis factor alpha, TSLP: thymic stromal lymphopoietin, ↑: increased, ↓: decreased.

5.2. Anatomical and Physiological Differences in the Lungs

Differences in lung architecture may be considered additional factors contributing to sex-related differences in asthma [6]. Due to the action of sex hormones, differences between females and males may be found in the development of the lung, the production of pulmonary surfactant, and the local production and functions of various bioactive substances [179]. Estrogens enhance the development of the lung and the maturation of surfactant-producing type II cells, while androgens have the opposite effect [182], resulting in "male disadvantage" involving a higher risk of respiratory distress syndrome (RDS) and a more severe course in male preterm neonates. Although female neonates have smaller lungs with fewer respiratory bronchioles at birth, they are more mature than the lungs of male neonates [183].

In the prepubertal stage, the higher prevalence of asthma in boys is partially attributable to dysanaptic lung growth expressed as retarded airway growth compared to parenchymal growth [6]. In adulthood, a disproportional relationship between lung and airways sizes has been found in women, who had smaller airways in relation to the lung size, and women's smaller lung volumes and lower maximum expiratory flow compared to men may also contribute to sex differences in asthma [6]. In addition, the lower capacity of the airways in women may be partially responsible for the lower efficacy of inhaled corticosteroids because of the presumably lower airway deposition of the delivered drug [184].

5.3. Obesity and Lifestyle

As mentioned above, obesity is an important risk factor for asthma. Chen et al. demonstrated that obesity is associated with higher risk of asthma and increased asthma severity in women but not in men [108]. This was later confirmed by other studies, including a cluster analysis, which demonstrated female predominance in the less atopic—but corticosteroid-unresponsive—asthma associated with obesity [185]. More recently, several authors have suggested that obesity-associated phenotyping should differentiate between two phenotypes: (1) obese asthmatics with an age of onset < 12 years, more atopic features, poor control, significant airway hyperreactivity (AHR), and increased type 2 biomarkers,

who do not demonstrate sex predominance; and (2) obese asthmatics with an age of onset > 12 years, fewer atopic features, lower AHR, better control, and normal values for type 2 biomarkers, who do show female predominance [186–188].

The mechanisms proposed for how obesity can interact with asthma have still not been fully elucidated [188,189]. Obesity is associated with increased macrophages and ILC2s producing IL-5 and IL-13. Obesity-associated inflammation is also linked with elevated levels of pro-inflammatory cytokines, such as IL-1β, IL-6, TNFα, and IFN-γ, and increased oxidative stress. In addition, adipose tissue produces estrogens, leptin, and adiponectin. Adiponectin predominantly exerts anti-inflammatory effects via the inhibition of pro-inflammatory NF-κB, IL-6, and TNFα [190,191]. On the other hand, potentially increased levels of leptin due to estrogens and progesterone treatment affect both immune and adaptive immune responses [192]. They enhance production of Th1 cytokines (IL-2, IFN-γ, and TNFα) and decrease production of Th2 cytokines (IL-4, IL-5, and IL-10) [191]. In analyses of estrogens and leptin concentrations in serum, no differences between obese and non-obese women were found for estrogens [111], but increased leptin levels were detected in women compared to men at any given BMI [193]. High obesity-induced concentrations of pro-inflammatory cytokines may also be responsible for poor response to corticosteroids, as the cytokines reduce the induction of mitogen-activated kinase phosphatase 1 by glucocorticoids [194,195].

Furthermore, increases in chest wall loading in severe obesity may reduce lung volume and thereby worsen dyspnea [196]. Weight loss may improve the situation, as demonstrated in the study by Dixon et al., where reducing BMI improved asthma symptoms and pulmonary function tests [197]. However, the response to the weight loss may depend on the asthma subtype. Chapman et al. found that weight loss in obese patients could enhance lung function only in T2-high but not in T2-low asthmatics, suggesting a complex interplay between asthma and obesity [198].

In relation to obesity, adults with asthma usually show lower physical activity [199], and women are generally less engaged in regular physical activity than men [200], which may contribute to the association between obesity and asthma in women [181].

5.4. Environmental Factors and Smoking

The occurrence of occupational exposure-associated asthma depends on the individual occupations predominantly performed by men and women. Among women, inorganic dust, hair products, and ozone cause asthma more frequently than among men, while among men, organic dust, diesel, flour/bakery products, and wood or wood-component dust deteriorate lung function more frequently than among women [50,201].

Although men are generally more likely to smoke, smoking among women has dramatically increased during the last 50 years. In addition, women who smoke have an increased risk of asthma [202]. Greater lung vulnerability in women to tobacco smoke may be explained by, for example, estrogen-induced upregulation of the expression of cytochrome P450 (CYP) enzymes involved in the metabolism of the constituents of cigarette smoke, which may lead to production of intermediates potentially toxic for the lungs [203]. Moreover, cigarette smoke exposure may alter estrogen signaling in the airway smooth muscle, which may increase airway contractility in women [204].

Smoking also affects responses to treatment. In the study by Lazarus et al., inhaled corticosteroid beclomethasone decreased sputum eosinophils and ECP in both smokers and non-smokers but only increased forced expiratory volume in 1 s (FEV1) in non-smokers [205]. Similar declines in therapeutic responses were found for oral corticosteroids in smokers with asthma [206]. Reduced effectiveness of corticosteroids in smokers may be attributable to smoking-induced oxidative and nitrosative stress and the related reduction in histone deacetylase activity or to neutrophilic inflammation and overproduction of pro-inflammatory cytokines. However, other factors, such as reduced numbers of glucocorticoid receptors (GRs) or altered affinity of the ligand for GRs, should be also taken into account [207–209], suggesting that smoking may be considered a predictor of weak

response to corticosteroids [205]. On the other hand, oral administration of the leukotriene receptor antagonist montelukast enhanced peak flow in smokers but not in non-smokers, which may be explained by enhanced leukotriene synthesis or sensitivity in smokers [205].

However, little is known about differing sensitivity to treatment among smoking men and women. The 23 year follow-up study by Dijkstra et al. showed that both male and female adult patients with moderate to severe asthma demonstrated comparable declines in lung function before therapy with inhaled corticosteroids [208]. The beneficial effects of inhaled corticosteroids were dose-dependent and present in men with <5 pack years but not in men with >5 pack years or in women [210]. This may have been related to the fact that smoking contributes predominantly to neutrophilic inflammation, which is more frequent in women and against which inhaled corticosteroids are less effective.

5.5. Chronic Stress

In chronic respiratory disorders, the influence of other hormonal systems—primarily, activation of the hypothalamic–pituitary–adrenal (HPA) axis—should be considered. Chronic stress-induced elevation in the production of glucocorticoids may limit certain actions of synthetic corticosteroids, contributing to corticosteroid resistance [211]. There is a very close relationship between stress, activation of immune responses, and disorders of the respiratory system, including asthma [212–214]. As reviewed in the article by Miyasaka et al., stress response facilitates events in the central nervous and endocrine systems. Secretion of stress hormones, including glucocorticoids, epinephrine, and norepinephrine, into the blood enhances Th2 and Th17 immune responses and attenuates regulatory T (Treg) cell responses in humans and rodents, thus exacerbating asthma [215]. For instance, psychosocial stress in mice increased airway reactivity to allergens, elevated counts of inflammatory cells infiltrating the lungs, and increased concentrations of cytokines in serum and bronchoalveolar lavage fluid in comparison to an ovalbumin-sensitized group without exposure to psychosocial stress [216]. Similar results were also observed in humans, among whom chronic psychosocial stress was associated with more frequent asthma exacerbations [217]. However, it is not clear whether any sex-related differences exist in the relationship between stress and asthma. While no such differences were found in the study by Eng et al. [218], in the study by Runeson-Broberg and Norbäck, work-related psychosocial stress was reported as a risk factor for asthma only in men [219]. In contrast, associations between a higher degree of work-related stress and the onset of asthma [220] and between both work stress and family stress and asthma [221] have been clearly demonstrated in women. Moreover, women perceive asthma more sensitively and report more respiratory discomfort than men, even if the symptoms and objective clinical measures are similar [222].

5.6. Genetically Conditioned Factors

5.6.1. Sex-Specific Genes, Epigenetic Changes, and miRNA

The influences of the genetic framework, epigenetic changes, and miRNA on gender differences in asthma have been thoroughly described in the excellent review by Ekpruke and Silveyra [179]. Recently, researchers have identified male- and female-specific genes, as well as male-and-female specific genes, that are mainly expressed in the airway epithelium, among which several are involved in the pathogenesis of asthma. Gautam et al. found that the male-specific genes *FBXL7*, *ITPR3*, and *ALOX15* are increased and *RAD51B* decreased in asthma, while a female-specific gene *HLA_DQA1* is decreased. Additional differences were observed for more male-specific hypoxia-inducible factor 1 signaling pathways and for more female-specific IL-17 and chemokine signaling pathways [223]. In a genome analysis of Latin American and African American populations, the *17q12-21* asthma locus was identified as a significant contributor to asthma susceptibility in women [224]. In addition, several asthma-risk sex-specific alleles have been identified for women (*2q23.3*, *2q34*, *6q27*, *17213.3*) and men (*5q31.1*, *10q26.1*) [225], as well as sex-specific single nucleotide polymorphisms (SNPs) in β2-adrenergic receptors [226] and TSLP [227,228]. Determination of gene alleles or SNPs in asthma patients may indicate which polymorphisms are more

or less sensitive for a given therapy, as was demonstrated in the differential response to β2-agonists [229,230].

Gene expression is regulated by small non-coding microRNAs (miRNA). Recent studies have demonstrated that there are sex-specific miRNAs associated with lung function, regulation of immune responses, and asthma [231–233]. Circulating miRNA correlate well with clinical parameters and the response to therapy [234,235], suggesting their potential for precise diagnostics and personalized medicine in the future.

5.6.2. Susceptibility to Several Diseases in Relation to Bronchial Asthma

Sex-related differences in asthma prevalence and severity can also be considered from a more global perspective. As recently shown, susceptibilities toward many diseases differ between males and females. In general, the female immune system responds more efficiently to common viral and bacterial infections [236,237], which may result in overreactive immune responses; e.g., as observed in the higher prevalence of autoimmune diseases [238] and the greater adverse effects of vaccination [239]. Sex-related differences have been also demonstrated for COVID-19, with males exhibiting greater disease severity and mortality than females, likely due to differences in the innate immune system and renin–angiotensin–aldosterone (R-A-A) system [240]. Estrogens were found to interact with the R-A-A system, which is considered one of the most critical pathways affecting COVID-19 infectivity, and modulate vasomotor homeostasis. In contrast, testosterone was found to enhance the expressions of ACE2 receptor and transmembrane protease serine-type 2 (TMPRSS2), thereby increasing viral load and delaying viral clearance in men compared to women [241]. In the study by Wark et al., elevated ACE2 gene expression was associated with older age and male sex but not with smoking pack years. However, ACE2 expression was lower in asthma patients and reduced ACE2 protein expression was also found in endobronchial biopsies of asthma patients [242]. Additional studies indicated that having a T2-high asthma phenotype might be associated with reduced COVID-19 morbidity and mortality because of the anti-viral action of eosinophils [243,244], while non-T2 asthma accompanied by high IFN-γ levels, eosinopenia, lymphopenia, a higher neutrophil-to-lymphocyte ratio in peripheral blood, and increased lymphocytes in the bronchoalveolar lavage fluid could be associated with a higher risk of more severe COVID-19 [245].

6. Sex-Related Differences in Responses to Therapies Given for Asthma

Generally, more currently available treatment options target the T2-high type of asthma, which is less common in women. This may partially explain the worse control of asthma and more severe clinical manifestations among women [50,246]. The sex-related differences in responses to therapy may be caused by several factors, including the actions of male/female sex hormones, airway geometry, the deposition and particle size of inhaled corticosteroids, and differences in lung compliance [50,210].

In both male and female mice with a T2-high model of asthma, intranasally delivered corticosteroid budesonide dose-dependently diminished pulmonary inflammation and airway hyperreactivity; however, female mice were slightly less sensitive to the inhibitory effects of budesonide on IL-5 synthesis and the generation of airway hyperreactivity [153]. Similarly, in human adults, inhaled steroids are more effective in men compared to women [210].

In contrast, anti-leukotrienes are more effective in women compared to men, presumably due to androgen-induced attenuation of 5-lipoxygenase protein (FLAP), a protein necessary for activation of 5-lipoxygenase and production of leukotrienes [247]. In women, a stronger bronchodilator response [248] and a tendency for a more sensitive response to bronchodilator [249] have also been found, as well as a better response to anti-IL-5 mepozulimab [250]. Nevertheless, no gender- or sex-related differences were observed for the combination of ICS/LABA/LAMA [251]. The treatment effect of omalizumab, an anti-IgE antibody, was greatest in patients with more severe asthma, while no gender- or

sex-related differences were found [252]. In a more recent study, males reported fewer asthma symptoms after omalizumab treatment than women [222].

Major sex-based differences in lung-related features and asthma are presented in Table 4.

Table 4. Sex-based differences in lung-related features and asthma. For more details, see the text above.

	Males	**Females**
Lung maturation in neonates	Delayed compared to female neonates	
Lung dysanapsis	Retarded AW growth in boys	Smaller AWs vs. lungs in adult women
Excitability for cough	↓	↑
Clinical course of asthma		↑ severity and hospital admissions
Type 2 inflammation	↓	↑
Non-type 2 inflammation	↓	↑
General immune response	↓	↑
Effectiveness of response to viral infections, including COVID-19	↓	↑
Effectiveness of response to bacterial infections	↓	↑
Relation to smoking	↑ exposure to smoke	↑ vulnerability to smoke
Occupation-associated asthma	↑ exposure to organic dust, diesel, flour/bakery products, wood/wood-component dust	↑ exposure to inorganic dust, hair products, ozone
Obesity-associated asthma	↑ risk in boys	↑ risk in adolescent and adult women
Stress-associated asthma	↑ risk	↑ risk
Sex-specific genes associated with asthma	↑ *FBXL7*, *ITPR3*, *ALOX15*; ↓ *RAD51B*	↓ *HLA_DQA1*
Sex-specific alleles associated with asthma risk	*5q31.1*, *10q26.1*	*2q23.3*, *2q34*, *6q27*, *17213.3*
Response to corticosteroids	↑	↓
Response to bronchodilators	↓	↑
Response to anti-leukotrienes	↓	↑
Response to anti-IgE	↑	↓
Response to anti-IL-5	↓	↑

Abbreviations: AW: airway, IgE: immunoglobulin E, IL: interleukin, ↑: increase, ↓: decrease.

7. Future Directions

The differences between the sexes may be primarily caused by the different actions of female and male sex hormones in the lungs. The influence of changing levels of sex hormones on the production of pro- and anti-inflammatory cytokines, airway reactivity, and the production of mucus in the airways represents an important factor in the pathogenesis of asthma. This should be considered in the diagnostics, especially in complex therapy for asthma. However, there are additional factors that may contribute to the sex-related differences in asthma, such as anatomical and physiological differences in the lungs of males and females; differences in genetically conditioned factors; obesity and lifestyle; and exposure to environmental factors, including smoking, chronic stress, etc. Although experimental and clinical research in recent decades has gathered the principal information necessary for differentiation of asthma into several endotypes and phenotypes, resulting in the introduction of more appropriate treatment, there are many questions that should be answered in the future. In particular, large clinical studies should be carried out on the

evaluation of sex-related differences in the response to the asthma therapy given. In female patients with asthma, the effects of hormonal contraceptive pills in pre-menopausal women, as well as the effects of HRT in menopause/post-menopause, should also be thoroughly investigated in relation to asthma endotypes/phenotypes. Searches for novel biomarkers should continue in order to find more sensitive and specific indicators for precise diagnoses of asthma endotypes/phenotypes. Further analysis of genetic, epigenetic, and other factors may reveal higher susceptibilities for asthma in selected groups of patients, which may be of importance for early screening of asthma. In addition, with increasing numbers of transgender individuals, clinical studies showing the impact of hormonal substitution are warranted to estimate the effects of exogenously administered hormones on asthma incidence and changes in the severity of asthma in these individuals.

8. Conclusions

Sex-related differences seem to be primarily attributable to the complex actions of sex hormones. However, differences in lung architecture and airway geometry, genetically conditioned factors, obesity and lifestyle, smoking, exposure to environmental and occupational factors, chronic stress, etc. may also contribute to the differences between females and males suffering from asthma. Our article demonstrates that many of these mechanisms and interactions have already been elucidated. Nevertheless, further research is needed to reveal the effects and clinical importance of the mentioned contributing factors. In addition, many additional questions need to be answered; e.g., how sex-based differences may influence the asthma therapy given and what preventive measures could be undertaken to improve the status of asthma patients.

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