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REVIEW

An interdisciplinary analysis of sex and gender in relation to the pathogenesis of bronchial asthma

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Sex/gender;
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Complex interactions

Summary

Background: An increasing number of studies confirm that pathogenesis and prevalence of bronchial asthma are age and sex dependent. Detailed physiological mechanisms of the changing sex ratios with age are not fully known, however, the gender (socio-cultural) factors are also imperative. Although multiple factors definitely influence the pathogenesis of asthma, only individual or few combinations of these have been investigated.

Methods: The terms 'sex', 'gender' and plausible combinations of both were systematically researched in selected databases (Medline, Scopus) or other sources, including publications from January 2000 to June 2007. Generated articles were categorized, either as endogenous or exogenous factors influencing the pathogenesis of asthma, and divided into the following subgroups: genetic, immunological, hormonal, gynaecological, nutritional, and environmental parameters.

Results: An increasing number of studies investigate the influence of sex and gender in the aetiology, therapy and prevention of asthma. While their results are still debatable, others regarding its initiation, perpetuation and cessation have been clarified. Recent insights into interactions at biomolecular and immunological levels greatly contribute to clarifying sex-specific influences. Despite occasional oversimplifications, a trend for explanations considering the complex interplay of different factors can be observed. This work is in line with this trend and offers explanation models from our point of view.

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Conclusions: Some disagreements regarding the patho-physiology, diagnosis, treatment and prevention of asthma still prevail. Nevertheless, in order to better appreciate its complexity, openness to and persistent consideration for interdisciplinary as well as sex- and gender-related factors is required of the medical-research community in future investigations.

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Introduction

A number of recent studies have found that the prevalence of bronchial asthma varies with age and sex. In addition to the examination of asthma in the total population¹ or sex- and gender-non-specific subgroups,² an increasing number of studies observed asthma in children, adolescents, and adults of both sexes, in the last few years. These findings confirm that there are differences in the prevalence of asthma among both sexes from childhood through adulthood. While during childhood asthma is more common among boys than among girls,^{3–5} adult women are more frequently affected than adult men. Studies further show that the gravity of asthma not only reduces from childhood to adulthood, but also that after adolescence, the condition continues to improve in males, but not in females.^{6,7} However, the exact time and the detailed mechanisms of these changes in sex ratios are not yet known. Biological (sex-related) and socio-cultural (gender-related) factors have been proposed to explain the differences between male and female asthma progression, and their possible role in biased diagnostic and therapeutic practices.⁸

As far back as the Greek antiquity, medical literature made references to associations between gender and bronchial asthma. For instance, Aretaeus of Cappadocia (130–200 AD) considered women to be more susceptible to asthma than men.⁹ In the first half of the 20th century, some clinical studies

on the differences in the prevalence of asthma among the sexes were published. Other examples of gender-related asthma prevalence include studies by Jaeger, 1925, who proposed that women are more likely to suffer asthma than men in the ratio 3:1¹⁰ and Baagöe, 1928, 1931, who found that boys between the ages 0 and 15 years were more often affected by asthma than girls of the same age,¹¹ especially when the disease had its onset somewhere in the first five years of life or after the age of 40 years.¹² Other studies on the influence of sex on asthma include Hunt, 1939, which suggest that neither age nor sex seem to exert any definite influence upon the blood eosinophil count in asthmatics.¹³ In 1945, Zondek et al. described the clinical observation that asthma “take a particularly severe form during the premenstrual phase in which production of the follicle and corpus luteum hormones reaches maximal levels”.¹⁴

Some of the first articles which used the term ‘gender’ in the context of asthma were “The influence of gender on theophylline dosage requirements in children with chronic asthma” by Hendeles et al. in 1981¹⁵ and “The sensations of pulmonary dyspnea” by Janson-Bjerkie et al. in 1985.¹⁶ In the latter, a relationship between personal variables such as age, gender, fatigue, moods and parameters like the intensity and frequency of asthma symptoms were found.

Today, most investigations focus on specific aspects of asthma’s development as a result of the increasing specialization in medical sciences.

The main objective of this report is to paint a picture of the disease process of asthma in relation to sex and gender as precisely as possible. Interactions between different physiological parameters and the influence of external components on disease processes will also be reviewed.

Methods

A systematic literature research in the databases Medline and Scopus from January 2000 to June 2007 with the key words/phrases 'asthma', 'sex' or 'gender' or 'sex and gender' were targeted as basis for this report. When the terms 'asthma' and 'sex' were combined 1478 articles were generated from Medline and 202 from Scopus. The terms 'asthma' and 'gender' jointly brought about 655 articles from Medline and 143 from Scopus. When jointly searched for, 'asthma' and 'sex and gender' resulted in 194 articles from Medline and 11 from Scopus. For background information on medical—historical aspects, two publisher-specific databases, SpringerLink and ScienceDirect were used. In addition to the above English terminologies, the German word 'Geschlecht' was also included in the search. 'Geschlecht' means both sex and gender but these terms could not be differentiated during the research. In the English language, 'sex' and 'gender' are also often used synonymously. Three articles were found in SpringerLink and two in ScienceDirect.

After generating articles, endogenous (genetic, immunological, hormonal) and exogenous (gynaecological, nutritional, environmental) as well as sex- and gender-related factors, influencing the development of asthma, were defined. Using these definitions as criteria for including or excluding articles, a total of 99 articles were found in relation to 'genetics', 75 relating to 'immunology', 42 relating to 'endocrinology', 100 relating to 'pregnancy', 151 relating to 'obesity' and 658 in relation to 'smoking'. Additionally, a 'sex'- and 'gender'-unspecified literature search was carried out with respect to endogenous and exogenous parameters.

Results

During the research on sex- and gender-specific literature, six different major areas relating to the initiation, perpetuation and termination of asthma were identified. While endogenous asthma pathogenesis included sub-areas like genetics, immunology, and endocrinology exogenous asthma pathogenesis encompassed sub-areas like gynaecology, nutrition and environmental medicine. Consequently, sex- and gender-dependent and independent aspects of asthma's pathogenesis influence prevention and therapeutic strategies.

The literature search resulted in 62 articles, which described interactions between two different aspects. Seven articles dealt with the gene—gene interaction, five with the gene—immune system interaction, three with the gene—hormone interaction, three with the hormone—immune system interaction, 17 with the hormone—pregnancy interaction, three with the gene—obesity interaction, three with the obesity—immune system interaction, 16 with the gene—environment and five with the environment—immune system interaction.

Both the endogenous and exogenous factors as well as their relationship, which influence asthma will be analysed in this work.

Pathogenesis

Genetic influences on the pathogenesis of asthma

Genetic disposition, determined by family history of asthma, seems to be the primary determinant of asthmatic disease, defined by clinical symptoms and functional tests. Family history is thus associated with acute or perpetual asthma.¹⁷ The influence of parental allergy and male sex on the development of wheezing and sensitization during childhood may possibly be determined by sex-specific hereditary components consistent with X-linked genes.¹⁸ Certain studies reveal the possibility that separate genetic mechanisms play a role in asthma at different ages for both males and females. In males, wheezing usually begins during childhood while the onset of wheezing in females frequently started during adolescence. Although both maternal and paternal asthma influenced the onset of childhood wheeze, paternal atopy contributed identically and significantly only for males. For the onset of adolescent wheeze, maternal history was a significant risk factor in females only. When both childhood and adolescence asthma were examined together, paternal history was a strong risk factor for wheezing in females only.¹⁹

Sex, genetically determined, has also been shown to influence the development of asthma. Interleukin-1 beta (IL-1 β), a major pro-inflammatory cytokine produced in a variety of cells including blood monocytes or tissue macrophages, induces effects due to its locus, probably important in the pathogenesis of asthma. These effects are relevant for men, but not for women.²⁰

The interleukin-9 receptor (IL-9R) gene, located on the pseudo-autosomal region (homologous sequence of nucleotides) of the X and Y chromosomes, possibly also plays a role in the patho-physiology of allergic diseases, which may be sex dependent. Children suffering from wheezing and controls were analysed for IL-9R single nucleotide polymorphisms (SNPs), occurring when single nucleotides which build blocks of DNA is replaced with others. The study revealed that a specific haplotype, which is a combination of marker alleles on a single chromosome (haploid genotype), had significant protective effects against wheezing upon exposure to inhaled allergens in boys, but not in girls.²¹

Furthermore, the role of prostaglandins in the aetiology of asthma was also analysed. Prostaglandins are generated via the cyclooxygenase (COX) pathway and are essential mediators of inflammation in bronchial asthma. A variation in the positive activator of COX-2 transcription, the promoter polymorphism of COX-2 gene G-765C, has been identified. The G-765C polymorph was found both in asthmatic patients and healthy controls in a Polish study. Compared to healthy females, CC homozygotes for this gene were over-represented in the subgroup of female asthmatics but were much less among healthy males of the same subgroup i.e., CC homozygosity was less abundant in male asthmatics.²²

Chemokines also play a role in the pathogenesis of asthmatic diseases. They belong to the family of cytokines involved in the trafficking of leukocytes to inflammation sights in the body and can be divided into four genetic groups (C, CC, CXC, and CX3C). The chemokine CXC receptor 3 (CXCR3) gene, which is important for both inflammatory and immune responses, was investigated in a study, as well as genetic polymorphisms of this gene. The results indicated that one of the SNPs of the CXCR3 gene was associated with the development of asthma, especially in males.²³

Similarly, SNPs in the estrogen receptor α (ESR1) gene have been shown to be associated with inflammatory disease. The function of the ESR1 is mediated by the ESR1 protein and was analyzed in asthma probands and their families. These probands were genetically screened for SNPs in the ESR1 gene in another study. The results indicated that ESR1 gene variants may affect the development of bronchial hyper-responsiveness and may lead to a more rapid loss of lung function, especially in female asthmatics.²⁴

The results of yet another study on childhood and adulthood asthma further supported the hypothesis that genetic factors influence asthma sub-phenotypes depending on both sex and age. Furthermore, failure to address such complexities will hinder the unravelment of processes involved in the cause of asthma.²⁵

Gene–gene interactions

A systematic genome-wide search for asthma-susceptibility genes was conducted, in two stages, including families from three U.S. populations (African American, European American, and Hispanic), and allele sharing among affected relatives was investigated using multipoint linkage analyses. Multipoint linkage analyses are used to localize disease-predisposing genes in related genotypes, which lie at multiple or closely positioned distinct regions on a given chromosome. According to Xu et al., 2001, there exists a likelihood that several genes, each of a different strength, act together to determine the overall risk of asthma development in an individual. This indicates that there is an imbalance in the genetic complexity of these interactions and portrays the rather simplified genetic analyses usually carried out in primary linkage studies.²⁶

In a Dutch asthmatic population, the interaction between an SNP in the interleukin-4 receptor (IL4R) gene and a variation in the promoter (a regulatory region of the DNA located upstream of a gene) of interleukin-13 (IL-13), was investigated. An interaction was observed for individuals with risk-associated genotypes, for both interleukin-4 receptor- α (IL4RA) and IL-13.²⁷ This significant gene–gene interaction between IL4RA and IL-13 was also confirmed in a study on Chinese children aged 5–18 years, diagnosed with asthma.²⁸ Moreover, an animal study on the direct effects of sex steroids on gene expression in the vasculature demonstrated a significant expression of the IL4R in the mesenteric arteries of rats in response to estrogen, but not to testosterone.²⁹

Apart from polymorphisms in the IL-13 gene, the IL4RA gene interacts with polymorphisms of the interleukin-4 (IL-4) gene promoter. This gene–gene interaction increases an individual's susceptibility to asthma and modulates the severity of the disease. This was observed in Korean

children³⁰ and in a Caucasian population.³¹ Genes coding for IL-4 and genes of toll-like receptor 4 (TLR4), which is the principal receptor for bacterial endotoxin, show an epistatic effect on the risk of asthma in females.³²

Other gene–gene interactions in the asthmatic disease process include the interaction between genes of interleukin-5 (IL-5) and the thromboxane A2 receptor (TBXA2R). IL-5 is important in allergic inflammation, while TBXA2R is a member of the prostanoïd receptor subfamily; and plays an essential role during blood clotting, by reacting with thromboxane A2 to induce platelet aggregation. This gene–gene interaction was observed in children suffering atopic asthma.³³ The density of the human platelet TBXA2R is regulated by endogenous testosterone, and low blood testosterone is associated with a significant reduction in platelet TBXA2R density.³⁴

Immunological influences on the pathogenesis of asthma

T helper (Th) cells are cells of the immune system, which produce cytokines and are essential in the initiation, maintenance and regulation of immune responses. Th cells are mainly divided into two subgroups, Th1 and Th2 cells. Pro-inflammatory cytokines like IL-5 and IL-13, already mentioned above, are produced by Th2 cells and both contribute to the initiation and perpetuation of asthma. Contrary to Th2 cells, the products of Th1 cells exhibit anti-inflammatory and asthma-protective properties. The hygiene hypothesis proposes that infections during early childhood stimulate Th1 production within the otherwise Th2 skewed immune response. Instead of an increase in child mortality due to acute respiratory infections, children born with a Th1 maturation defect may survive today due to better medical care and availability of new medicines, at the cost of exhibiting higher asthma rates.³⁵

In mouse-models, female mice were more susceptible to allergic respiratory inflammation than males. This was generally accompanied by a reduction in the percentage of pulmonary CD4⁺CD25⁺ regulatory T cells (Tregs).³⁶ Despite evidence for sex-related differences in the susceptibility to asthma, most animal experiments on immunological processes do not take them into consideration.^{37,38}

In a prospective study, designed to evaluate the interactions between age, sex, immune responses and virus infections on the development of asthma and allergic diseases, cytokine response profiles were analyzed at birth and at the ages of 1 and 3 years. When results were stratified based on sex, boys aged 3 years, who wheezed, had significantly higher interferon-gamma (IFN- γ) responses than wheezing girls. Moreover, in relation to history of wheezing during the third year of life, phyto-haemagglutinin (PHA), which is a sugar-binding protein found in plants, induced a significant increase in the secretion of both IL-5 and IL-13 in wheezing boys but not in wheezing girls.³⁹

Gene–immune system interactions in the pathogenesis of asthma

Apart from pathogenic aspects, the interactions between genetic and immunological factors could be used

therapeutically. For example, there are indications that gene transfer of interleukin-12 (IL-12), a Th1-cytokine, inhibits allergic respiratory disease by suppressing Th2 inflammatory responses.^{40,41} The interleukin-12 p40 (IL12B) gene encodes the p40 chain of IL-12, a pro-inflammatory cytokine that antagonizes Th2 expression. In adult men, immunoglobulin E (IgE) levels were found to be dependent on IL12B genotypes, and in girls, pulmonary function may also possibly be associated with IL12B promoter polymorphism.⁴²

Hormonal influences in the pathogenesis of asthma

The influence of sex and age on the incidence, period of occurrence, severity, and advancement of asthma, suggests the possibility of manipulating pathogenetic mechanisms modulated by sex hormones.⁴³ Past experimental models do not provide conclusive evidence for the role of hormones, like sex hormones. Inflammatory changes in the bronchial tissues of pre-pubertal mice have been associated with non-specific environmental conditions as a result of high sex hormone dose.⁴⁴

Recent animal studies indicate that sex hormones play a dual role in regulating allergic lung inflammation. Experimental observations in female mice, ovariectomized before sensitization, support the conclusion that estrogen plays a role in the process of antigen sensitization. When female mice are ovariectomized after sensitization, the results of treating with estradiol benzoate support an anti-inflammatory role of sex hormones during the effector phase of the response to inhaled antigen.⁴⁵ Moreover, estrogen receptor-alpha knockout mice have spontaneously enhanced airway responsiveness without increased inflammation after allergen sensitization and challenge.⁴⁶ Another animal study confirms the suspicion that estrogen could inhibit bronchoconstriction and prevent airway hyperresponsiveness in asthma.⁴⁷ The dual effect of sex hormones on the inflammatory response in the asthmatic lung may explain the conflicting epidemiological and clinical data reported in the literature.

An epidemiological study on asthmatic children aged 16 years or more and adults from the age of 18 years indicated that peri-menstrual asthma was significantly associated with higher eosinophil counts. According to the authors, a stronger pattern of eosinophilia can be observed in adult peri-menstrual asthmatic women due to the hormonal changes that take place during the menstrual cycle. This is consistent with the hypothesis that eosinophils play an important role in the persistence and severity of asthma.⁴⁸

The role of sex hormones was also shown in another study which revealed that both endogenous and exogenous sex steroids influence asthma in young women. Marked associations between the use of oral contraceptives and both forms of wheezing, current and exercise-induced, in asthmatic and non-asthmatic women were observed. In women with a history of asthma, the use of oral contraceptives was inversely associated with both forms of wheezing, while in those with no history of asthma, oral contraceptive use was positively associated with both forms of wheezing. The significance of these results increased with the duration of oral contraceptive use.⁴⁹ Contrary to these results, a large Danish study did not report any relationship between the use

of oral hormone-based contraceptives and asthma. Nevertheless, in subjects who had never smoked, there was a higher prevalence of self-reported asthma and asthma medication use than in those who received postmenopausal hormone replacement therapy.⁵⁰

The role of hormones in the aetiology of asthma was further investigated in a follow-up study which included women aged 46–54 years using hormone replacement therapy, amongst others, at the time of the study. The results indicated that asthma and asthma symptoms were significantly more common among women using hormone replacement therapy. Stratifying by BMI, hormone replacement therapy was significantly associated with a higher risk of asthma only in lean women.⁵¹

Hormone–gene and hormone–immune system interactions in the pathogenesis of asthma

Hormone–gene interactions in the asthma disease process have been observed. The transcription factor T-bet (T box expressed in T cells) initiates the development of naive T helper precursor (Thp) cells from Th1 cell lines. The gene TBX21 encodes for the transcription factor T-bet, and has been implicated in the pathogenesis of asthma. Genetic variations in TBX21 may alter asthma phenotypes with regard to specificity of treatment. This assumption is supported by the results of a clinical trial, which demonstrated that a non-synonymous variation in TBX21 substantially enhances the effects of inhaled corticosteroid on respiratory pathway sensitivity in asthmatic children.⁵²

In the case of hormone–immune system interactions, the hypothalamic–pituitary axis, a neuro-endocrine system, which interchanges signals between the hypothalamus, the pituitary and the adrenal glands, was shown to regulate inflammations using the general anti-inflammatory effects of glucocorticoid hormones. These glucocorticoids are produced in the adrenal cortices after hypothalamic–pituitary–adrenal (HPA) axis stimulation. Their effect indicates that associations between a blunted HPA axis, autoimmune reactions and inflammatory diseases are relevant in the development of allergic asthma.⁵³ In one study, significantly reduced cortisol responses in children aged 7–12 years suffering from allergic asthma were reported.⁵⁴

Similarly, the cervical sympathetic trunk–submandibular gland (CST–SMG) axis is a part of the neuro-endocrine axis that modulates pulmonary inflammatory response. Cervical sympathetic nerves control the synthesis and release of polypeptide factors, which originate from the submandibular glands and control immunological and inflammatory reactions in the lungs, such as allergic asthma.^{55,56} However, sex differences exist in the proposed HPA axis activity⁵⁷ and are influenced by the levels of reproductive hormones. An increase in progesterone stimulates axis activity in women,⁵⁸ while a decrease in testosterone stimulates cortisol production in men.⁵⁹ Additionally, a significant and positive relationship between the activity of the HPA axis and testosterone has been observed in obese women.⁶⁰

Direct links have also been found between sex hormones and the immune system,⁶¹ such that in some cases, genetic variations and sex hormones show similar effects. The *IL4R* gene encodes the alpha chain of the interleukin-4 receptor,

a type I transmembrane protein that binds IL-4 and IL-13 and regulates the production of IgE. A meta-analysis of case-control studies, testing the association between IL4R variants and asthma, showed that the R551 poses a modest but significant risk for the development of atopic asthma.⁶² Both estrogen and progesterone function similarly, since they both have been shown to increase IL-4 and IL-13 levels in mononuclear cells of peripheral blood.⁶³

The influence of pregnancy on the pathogenesis of asthma

During pregnancy both foetus and mother are involved in asthma-linked processes. Female foetuses are more sensitive to alterations in cortisol exposure, through the inhalation of glucocorticoids by pregnant woman, than males. This leads to reduced foetal adrenal function and reduced growth.⁶⁴ Probably an influence on the foetal HPA axis growth and development predisposes the affected female neonates to an increased risk of developing diseases later in life, as a result of altered foetal programming.⁶⁵

Secondly, in pregnant women suffering asthma, an association between foetal sex and asthma severity during pregnancy is evident. In the case where the foetus was male, respiratory deficiencies continued to improve in pregnant women.⁶⁶

Pregnancy-hormone interactions in the pathogenesis of asthma

There are indications that during pregnancy, the treatment of asthma using inhaled glucocorticoids is associated with better placental function and foetal development.⁶⁷ While pregnancy complications due to untreated asthma are linked to a decrease in birth weight of neonates, the use of inhaled steroids does not result in reduced intrauterine growth.⁶⁸ A reduction in the activity of placental 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2) increased foetal cortisol and decreased foetal estradiol, contrary to the results of Murphy et al., 2003 mentioned above. Furthermore, inhaled corticosteroids do not seem to impair foetal growth, regardless of foetal sex, but systemic corticosteroids may have minimal effects on birth weight and length.⁶⁹

A maternity cohort study, however, did not show any association between the concentration of sex hormones during early pregnancy and the risk of asthma or other allergic diseases in children, at 5–6 years of age.⁷⁰ Nevertheless, the hormonal changes which take place during pregnancy may influence underlying respiratory pathway inflammations.⁷¹ Higher maternal testosterone levels are strongly and negatively associated with lower total IgE levels in boys, but not in girls aged 7 years.⁷²

The role of body mass index (BMI) in the pathogenesis of asthma

The relationship between obesity and asthma is complex; involves biological and non-biological factors and is probably causal. Biological factors influencing asthma are immune-, inflammation-, genetic-, hormone-, sex-,

nutrition-, 'physical activity'-related and are linked to foetal development mechanisms,⁷³ while non-biological parameters like socioeconomic and educational status, are associated with obesity.⁷⁴

There is increasing evidence with regard to the association between BMI and asthma, even though this is most consistent only for adolescent girls.⁷⁵ In a survey among children aged 4–17 years, the prevalence of asthma rose significantly with increasing quartiles of BMI. After adjustment for confounders, a significant positive association still existed, but no effect modification due to sex was seen.⁷⁶ Other studies have shown that overweight in boys was associated with an increased risk of asthma.⁷⁷

In a children's study overweight girls aged 6 and 11 years, were 5.5 and 7 times more likely to develop new asthma symptoms, when they reach the age of 11 and 13 years, respectively, than lean girls. There was no significant increased risk of asthma symptoms in overweight boys of the same ages.⁷⁸ Similarly, a study on asthma in children, born in 1972 or 1973, with follow-up assessments at ages 3, 5, 7, 9, 11, 13, 15, 18, 21, and 26 years, indicated that BMI was positively associated with asthma in females, but not in males. No evidence was found for girls aged 9 years in cross-sectional analyses, but at 26 years of age, the association between BMI and asthma was statistically significant. The association in females between 9 and 26 years of age seems to have emerged during the late teens⁷⁹ and was stronger after puberty.^{80,81} In another study with 25 years of follow-up, females free of asthma in the first 7 years of life, revealed a correlation between adiposity and asthma at the age of 32 years.⁸² However, the relationship between asthma and obesity in childhood has not been fully clarified.

Adult studies^{83,84} suggest a stronger association between obesity and asthma in females than in males.⁸⁵ Both overweight and obesity, defined by BMI, have also been associated with an increased risk of acute asthma, while obesity alone has been significantly associated with increased risk of persistent asthma in women.⁸⁶ The relationship between asthma diagnosis, weight gain and physical activity was analysed in another study. Here, asthma was also associated with BMI and reduced with increase in physical activity. However, this association was independent of physical activity in females.⁸⁷ Other studies also conclude that obesity was related to development of asthma in women only⁸⁸ and that a significant association between BMI and asthma prevalence only existed in the lowest weight category. Women showed a monotonic asthma-obesity link, while in men an increase in the prevalence of asthma existed both in underweight and obese categories.⁸⁹

There exist both general and specific obesity-asthma associations, e.g. associations between obesity and the severity of asthma. Studies show that for both allergic and non-allergic men and women, a higher prevalence of asthma existed in the obese groups than in the normal-weight groups. Differences were more conspicuous in non-allergic women and obesity-allergy history interactions were statistically significant for women, only.⁹⁰ Furthermore, the association between BMI and asthma severity was stronger in women who experienced early menarche than others.⁹¹

Obesity—gene and obesity—immune system interactions in the pathogenesis of asthma

Both asthma and obesity are said to be hereditary, indicating that there are similarities in specific genetic components of related phenotypes. In twins, this association has already been confirmed. It is very likely that the relationship between respiratory inflammatory disorders and excessive body fat is predominantly influenced by shared genetic risk factors for both conditions.⁹²

A genetic influence on asthma can be seen in the polymorphism of the β_2 -adrenergic receptor (β_2 AR), i.e. 'glycine at position 16' (Gly16 polymorphism). This receptor is involved in down-regulation mechanisms and is over-expressed in nocturnal symptoms of asthma. It may be an essential genetic factor influencing the occurrence of asthma in phenotypes.⁹³ The Gly16 allele predicted the onset of asthma in sedentary women, but genetically comparable women who were physically active showed no increased risk for asthma. Moreover, the association between BMI and asthma was most obvious among women who lived an inactive lifestyle.⁹⁴

In the case of the immune system, leptin, a protein mainly synthesized by adipose tissues, which regulates immune functions,⁹⁵ plays a role in the aetiology of asthma. The secondary structure of leptin resembles that of cytokines and its receptor is homologous to the signal-transducing subunit of the interleukin-6 (IL-6) receptor family.⁹⁶ A Swedish study found considerably increased levels of serum leptin in overweight children compared with normal-weight children at the age of 12 years. Furthermore, despite similarities in BMI, overweight children suffering from asthma had twice as much serum leptin as asthma-free children. These results were however not statistically significant.⁹⁷

In another study, leptin was predictive of asthma, but neither sex or age, nor BMI were, except for the fact that healthy boys had significantly lower serum leptin levels than healthy girls. These findings support the hypothesis that leptin may play a role in atopic asthma and may explain the higher prevalence of childhood asthma among males.⁹⁸

In adults, higher serum leptin concentrations have been associated with prevalent asthma and this association was stronger in women, especially in pre-menopausal women, than in men.⁹⁹

Environmental components in relation to the pathogenesis of asthma

In a 10-year longitudinal study on the respiratory health of school-aged children suffering from asthma, insufficiencies in lung function or respiratory deficiencies, were linked to intrauterine exposure to tobacco smoke due to maternal smoking. However, this was exclusively true for asthmatic boys only. Contrarily, past exposure to tobacco smoke was associated with reduced lung function among girls without asthma, but not in asthmatic girls.¹⁰⁰

Another factor which influences asthma is the function of the soluble cluster of differentiation 14 (sCD14). This is an endotoxin receptor that has been implicated in the

hygiene hypothesis which suggests that exposure to bacteria results in reduced sensitivity towards allergens. A study, which investigated the associations between possible risk factors for allergic diseases and sCD14 levels at the age of 2 years, showed that girls had higher mean sCD14 levels than boys. Furthermore, in the case of exposure to environmental tobacco smoke, negative effects, especially of antenatal and parental asthma were found in girls only.¹⁰¹

In another study on students aged 13–18 years, girls reported more symptoms than boys despite comparable smoke exposure burden. A dose–response relation between smoking and reduced lung function was found only in girls. Therefore, girls are more vulnerable to the impact of smoking than boys.¹⁰²

In asthmatic adults, the influence of sex differences and active smoking was analyzed in a Japanese survey in 2000. Male current-smokers were more likely to suffer asthma-related symptoms like morning sputum, cough, and severe sleep disturbance than non-smokers. However, in females, these symptoms were significantly uncommon in current-smokers. According to the authors, sex differences in the susceptibility to asthma and in smoking habits, suggest the necessity for gender-specific strategies to encourage smoking cessation.¹⁰³

In mouse-models, exogenously administered progesterone aggravates allergic respiratory pathway inflammation, and was observed in increased bronchial hyperresponsiveness and respiratory eosinophilia.¹⁰⁴ Furthermore, exposure to environmental tobacco smoke has a synergistic effect with progesterone in the mouse model.¹⁰⁵

The role of home environment in relation to asthma has also been investigated, but the results are inconsistent. Results of a study including adults aged 21–63 years were consistent with the hypothesis that both the keeping furry pets and parental atopy increase the risk of developing asthma in adulthood.¹⁰⁶ Owning pets notably modified the influence of smoking on asthma incidence in females. Contrary to little variations in asthma incidence among female smokers, ex-smokers and non-smokers who did not own pets, a significant effect due to smoking was observed among females living with pets.¹⁰⁷

With regard to factors influencing work-related asthma, sex differences have not been largely explored.¹⁰⁸ Work-related asthma or respiratory deficiency symptoms were significantly higher in men than in women.¹⁰⁹

Environment—gene and environment—immune system interactions in the pathogenesis of asthma

A genetic study on asthma which intended to identify gene loci that contribute to the development of asthma and asthma-related phenotypes, showed that environmental tobacco smoke exposure modified genetic influences on asthma, i.e. the presence of specific genes increased susceptibility to asthma when subjects were exposed to tobacco smoke.¹¹⁰

At the genetic level, variants of the interleukin-1 receptor antagonist (IL1RN) gene may contribute to the pathogenesis of asthma.¹¹¹ This gene encodes interleukin-1 receptor antagonist (IL1RA) and binds to the interleukin-1 (IL-1) receptor, blocking IL-1-mediated inflammation.

Smoking during pregnancy modifies the role of the IL1RN gene and increases the risk of developing asthma during childhood.¹¹²

Other studies show that CD14, a lipopolysaccharide receptor on monocytes and other inflammatory cells, which is also a key component of the innate immune system, exhibits increased plasma levels of sCD14 in subjects suffering from acute asthma.¹¹³ Interactions between CD14 genotypes, asthma severity and levels of IgE, an immunoglobulin class important for allergic reactions, have also been observed. These interactions were relevant in asthmatics on exposure to environmental tobacco smoke¹¹⁴ and portray gene–environment interactions in the pathogenesis of asthma.

Therapy

The relation between sex hormones and immune responses plays a role in the progression of asthma, and insights into the anti-inflammatory effects of testosterone and the pro-inflammatory effects of female sex steroids can be used as strategies for drug development. This should take gender and organ-specific therapy into consideration, e.g. modifying immune-modulating sex steroids. This can be successful, provided the effects on the female reproductive system, such as the virilising effects of androgens, can be excluded.¹¹⁵ Furthermore, the link between inhaled corticosteroids, a class of steroid hormones, and an increase in the percentage of CD4⁺CD25^{hi} Tregs, which are said to prevent allergic disease through the suppression of T_H2 responses, may present a future therapeutic target of asthma in children. In this case, the role of pulmonary Tregs can be exploited.¹¹⁶

There are sex and gender differences in the use of metered-dose inhalers in asthmatics. In a study where maximal inspiratory mouth pressure was significantly lower in females and the experience of dyspnea as well as mean daily beta₂-agonist consumption were significantly higher at baseline, inspiratory muscle training resulted in females attaining the same muscle strength as in their male counterparts, who were originally stronger and experienced less symptoms. This indicates that the sex difference in maximal inspiratory muscle strength is probably responsible for the observation that women are more symptomatic than men.¹¹⁷ Therefore, eliminating sex differences in inspiratory muscle strength could reduce asthma in females.

Prevention

The literature research for this work revealed the fact that only a few studies on the prevention of asthma exist and even fewer studies deal with sex- and gender-specific prevention. Nevertheless, a good number of strategies have proved reliable in reducing wheezing and early onset of childhood asthma. These include the promotion of breast-feeding, the discouragement of parental tobacco consumption and encouragement of proper housing conditions.¹¹⁸ More recent findings stress the importance of prolonged breast-feeding for the prevention of asthma.¹¹⁹ However, the influence of breast-feeding on asthma is dependent on child sex. In comparison with non-breast-fed girls with maternal atopy, breast-feeding increases the risk

for developing atopy in girls with maternal atopy, but does not in girls with paternal atopy. Breast-feeding also increases the risk for atopy among boys with paternal atopy compared with non-breast-fed boys with paternal atopy. Similar effect does not exist in boys with maternal atopy.¹²⁰ Despite the benefits of breast-feeding for children's health, it could be an important clinical aspect in assessing risk factors of asthma and allergy.

Secondly, while the low intake of antioxidant vitamins may have adverse effects on pulmonary function in school-age children, especially in asthmatic boys,¹²¹ the consumption of leafy vegetables, tomatoes and carrots leads to a reduced frequency of asthma in females, with significant dose responses.¹²² This indicates that the adequate intake of these dietary components is relevant for the prevention of asthma.

Contrary to the few studies which deal with sex- and gender-specific asthma prophylaxis, with emphasis on behavioural influences, an increasing number of prevention-oriented studies deal with the role of genetic polymorphisms, genetic predisposition and genetic susceptibility. In some cases sex-specific asthma relevant genes or gene variations such as polymorphisms in the multiple vitamin D receptor (VDR), combined with changes in immunoglobulin E levels have been described.¹²³

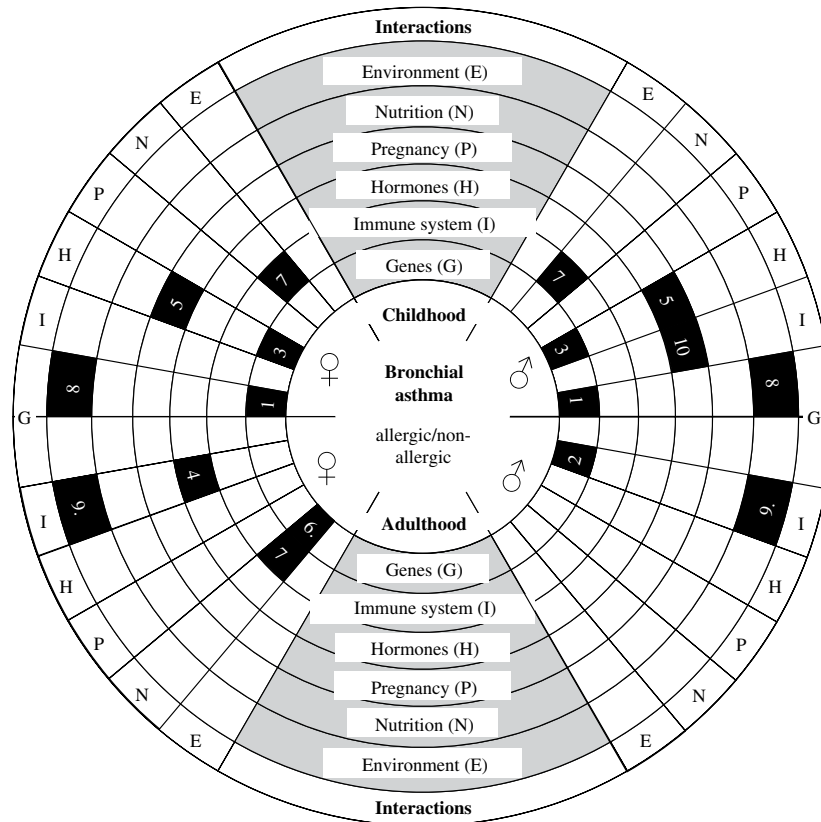
Finally, scanning the genome and its potential to point out risk profiles and risk constellations, will hopefully be integrated into improved prevention strategies for bronchial asthma.^{124–127}

Discussion

Eighty years after Dehner, 1927,¹²⁸ described the frequency, possible origin and role of eosinophils in the pathology of bronchial asthma, Rosenberg et al. (2007) analyse the role of new sex- and gender-oriented therapies such as antiselectin (adhesion inhibiting molecules) and antichemokine (cytokines inhibiting chemoattractants) receptor modifications, designed to block the development and trafficking of eosinophils.¹²⁹ In 1901, Osler declared in "The principles and practice of medicine" that blood eosinophil levels are largely elevated during asthmatic disease, especially in men.¹³⁰

The fact that there are sex differences in the incidence, prevalence and severity of asthma in children, adolescents and adults is generally accepted,¹³¹ as well as the hypothesis that sex hormones influence differences in the susceptibility to asthma. Environmental factors like the exposure to tobacco smoke add to asthma influencing parameters.¹³² Trends can be observed in recurring discussions on secondary influential aspects such as the association between asthma and pregnancy.¹³³ A tendency to oversimplify the determinants of asthma can also be observed, especially with regard to endogenous mechanisms such as immunological processes^{134–136} and exogenous factors such as environmental conditions.^{137–139} Contrarily, the model in Fig. 1 reflects the complexity of the asthma pathogenesis.

Despite an increase in the number of studies which take sex and gender aspects into consideration, disagreements with regard to patho-physiology,¹⁴⁰ diagnosis,¹⁴¹ treatment and prevention of asthma still prevail. However, the future



No.	Type of Interaction(s)	Nature of interaction	Relevance with regard to sex and age groups of asthmatics
1	Gene-gene interaction between IL4R(receptor)A and IL-4 promotor ²⁹ and the IL-13 promotor respectively ²⁸	Risk factor	Children = Relevant, no sex differences Adolescents = Irrelevant Adults = Irrelevant
+	Gene-gene interaction between TBX(thromboxane)A2R and IL-5 ³¹	Risk factor	Children = Relevant, no sex differences Adolescent = Irrelevant Adults = Irrelevant
2	Gene-immune system interaction between IL12B genotypes and IgE levels ⁴⁰	Risk factor	Children = Irrelevant Adolescents = Irrelevant Adults = Relevant, harmful for men only
3	Gene-hormone interaction between the TBX(T-box)21 variant and exogenous corticosteroids ⁴⁷	Therapeutic adjuvant	Children = Relevant, no sex differences Adolescents = Irrelevant Adults = Irrelevant
4	Hormone-immune system interaction between oestrogen, progesterone, and IL-4 and IL-13 ⁵⁸	Risk factor	Children = Irrelevant Adolescent = Irrelevant Adults = Relevant in women only
5	Pregnancy-hormone interaction involving 11 β -HSD(hydroxysteroid dehydrogenase)2, foetal cortisol and estriol ⁶⁴	Risk factor when untreated	Relevant, no sex differentiation among foetuses
6	Gene-obesity interaction between Gly16 β 2A(adrenergic)R and BMI ⁸⁹	Risk factor	Children = Irrelevant Adolescents = Irrelevant Adults = Relevant in adult females only
7	Immune system-obesity interaction between (cytokine-like) leptin and BMI ⁹⁴	Risk factor	Children = Irrelevant Adolescents = Irrelevant Adults = More relevant in females than males
8	Environment-gene interaction between ETS(tobacco smoke) and IL1R(receptor)N ¹⁰⁷	Risk factor	Children = Relevant, no sex differences Adolescents = Irrelevant Adults = Irrelevant
9	Environment-immune system interaction ETS + CD14 ¹⁰⁸ and IgE ¹⁰⁹	Risk factor	Children = Irrelevant Adolescents = Irrelevant Adults = Relevant, no sex differentiation
10	Hormone-immune system interaction between maternal testosterone during pregnancy and IgE production in children ⁶⁷	Protective factor	In male offspring s only

Figure 1 Model of interactions in the pathogenesis of asthma in relation to age and sex (for explanation of numbers see legend).

of asthma research lies in studies which aim at clarifying sex- and gender-related factors which play a role in its development and therapy.¹⁴²

Conflict of interest statement

The authors Richard Lux, Wendy Awa, and Ulla Walter have no conflicts of interest.

References

- Breton CV, Zhang Z, Hunt PR, Pechter E, Davis L. Characteristics of work related asthma: results from a population based survey. *Occup Environ Med* 2006;**63**(6):411–5.
- Toelle BG, Ng K, Belousova E, Salome CM, Peat JK, Marks GB. Prevalence of asthma and allergy in schoolchildren in Belmont, Australia: three cross sectional surveys over 20 years. *BMJ* 2004;**328**(7436):386–7.
- Irvin CG. Interaction between the growing lung and asthma: role of early intervention. *J Allergy Clin Immunol* 2000;**105**(2 Pt 2):S540–6.
- PausJenssen ES, Cockcroft DW. Sex differences in asthma, atopy, and airway hyperresponsiveness in a university population. *Ann Allergy Asthma Immunol* 2003;**91**(1):34–7.
- Kurukulaaratchy RJ, Fenn M, Twiselton R, Matthews S, Arshad SH. The prevalence of asthma and wheezing illnesses amongst 10-year-old schoolchildren. *Respir Med* 2002;**96**(3):163–9.
- Kjellman B, Gustafsson PM. Asthma from childhood to adulthood: asthma severity, allergies, sensitization, living conditions, gender influence and social consequences. *Respir Med* 2000;**94**(5):454–65.
- Watson L, Turk F, James P, Holgate ST. Factors associated with mortality after an asthma admission: a national United Kingdom database analysis. *Respir Med* 2007;**101**(8):1659–64.
- Ensom MHH. Gender-based differences and menstrual cycle-related changes in specific diseases: implications for pharmacotherapy. *Pharmacotherapy* 2000;**20**(5):523–39.
- Marketos SG, Ballas CN. Bronchial asthma in the medical literature of Greek antiquity. *J Asthma* 1982;**19**(4):263–9.
- Jaeger A. Über Asthma bronchiale. *J Mol Med* 1925;**4**(34):1652–6.
- Baagöe KH. Untersuchungen über Asthma, besonders bei Kindern. *J Mol Med* 1928;**7**(11):507–10.
- Baagöe KH. Asthma im Verhältnis zu Alter und Geschlecht. *J Mol Med* 1931;**10**(29):1352–4.
- Hunt HB. Some observations on the blood eosinophil count in asthmatics. *J Allergy* 1939;**10**(2):146–55.
- Zondek B, Bromberg YM. Endocrine allergy. I. Allergic sensitivity to endogenous hormones. *J Allergy* 1945;**16**(1):1–16.
- Hendeles L, Vaughan L, Weinberger M, Smith G. Influence of gender on theophylline dosage requirements in children with chronic asthma. *Drug Intell Clin Pharm* 1981;**15**(5):338–40.
- Janson-Bjerkklie S, Kohlman Carrieri V, Hudes M. The sensations of pulmonary dyspnea. *Nurs Res* 1986;**35**(3):154–9.
- Grassi M, Bugiani M, de Marco R. Investigating indicators and determinants of asthma in young adults. *Eur J Epidemiol* 2006;**21**(11):831–2.
- Melén E, Kere J, Pershagen G, Svartengren M, Wickman M. Influence of male sex and parental allergic disease on childhood wheezing: role of interactions. *Clin Exp Allergy* 2004;**34**(6):839–44.
- Mandhane PJ, Greene JM, Cowan JO, Taylor DR, Sears MR. Sex differences in factors associated with childhood- and adolescent-onset wheeze. *Am J Respir Crit Care Med* 2005;**172**(1):45–54.
- Karjalainen J, Nieminen MM, Aromaa A, Klaukka T, Hurme M. The IL-1 β genotype carries asthma susceptibility only in men. *J Allergy Clin Immunol* 2002;**109**(3):514–6.
- Melén E, Gullstén H, Zucchelli M, Lindstedt A, Nyberg F, Wickman M, Pershagen G, Kere J. Sex specific protective effects of interleukin-9 receptor haplotypes on childhood wheezing and sensitisation. *J Med Genet* 2004;**41**(12):e123.
- Szczeklik W, Sanak M, Szczeklik A. Functional effects and gender association of COX-2 gene polymorphism G₇₆₅C in bronchial asthma. *J Allergy Clin Immunol* 2004;**114**(2):248–53.
- Cheong HS, Park CS, Kim LH, Park BL, Uh ST, Kim YH, Lym GI, Lee JY, Lee JK, Kim HT, Ryu HJ, Han BG, Kim JW, Park C, Kimm K, Shin HD, Oh B. CXCR3 polymorphisms associated with risk of asthma. *Biochem Biophys Res Commun* 2005;**334**(4):1219–25.
- Dijkstra A, Howard TD, Vonk JM, Ampleford EJ, Lange LA, Bleecker ER, Meyers DA, Postma DS. Estrogen receptor 1 polymorphisms are associated with airway hyper-responsiveness and lung function decline, particularly in female subjects with asthma. *J Allergy Clin Immunol* 2006;**117**(3):604–11.
- Oryszczyn MP, Bouzigon E, Maccario J, Siroux V, Nadif R, Wright A, Kauffmann F. Interrelationships of quantitative asthma-related phenotypes in the epidemiological study on the genetics and environment of asthma, bronchial hyper-responsiveness, and atopy. *J Allergy Clin Immunol* 2007;**119**(1):57–63.
- Xu J, Meyers DA, Ober C, Blumenthal MN, Mellen B, Barnes KC, King RA, Lester LA, Howard TD, Solway J, Langefeld CD, Beaty TH, Rich SS, Bleecker ER, Cox NJ Collaborative Study on the Genetics of Asthma. Genomewide screen and identification of gene-gene interactions for asthma-susceptibility loci in three U.S. populations: Collaborative Study on the Genetics of Asthma. *Am J Hum Genet* 2001;**68**(6):1437–46.
- Howard TD, Koppelman GH, Xu J, Zheng SL, Postma DS, Meyers DA, Bleecker ER. Gene-gene interaction in asthma: IL4RA and IL13 in a Dutch population with asthma. *Am J Hum Genet* 2002;**70**(1):230–6.
- Chan IHS, Leung TF, Tang NLS, Li CY, Sung YM, Wong GWK, Wong CK, Lam CWK. Gene-gene interactions for asthma and plasma total IgE concentration in Chinese children. *J Allergy Clin Immunol* 2006;**117**(1):127–33.
- Eyster KM, Mark CJ, Gayle R, Martin DS. The effects of estrogen and testosterone on gene expression in the rat mesenteric arteries. *Vascul Pharmacol* 2007;**47**(4):238–47.
- Lee SG, Kim BS, Kim JH, Lee SY, Choi SO, Shim JY, Hong TJ, Hong SJ. Gene-gene interaction between interleukin-4 and interleukin-4 receptor α in Korean children with asthma. *Clin Exp Allergy* 2004;**34**(8):1202–8.
- Beghé B, Barton S, Rorke S, Peng Q, Sayers I, Gaunt T, Keith TP, Clough JB, Holgate ST, Holloway JW. Polymorphisms in the interleukin-4 and interleukin-4 receptor α chain genes confer susceptibility to asthma and atopy in a Caucasian population. *Clin Exp Allergy* 2003;**33**(8):1111–7.
- Adjers K, Karjalainen J, Pessi T, Eklund C, Hurme M. Epistatic effect of TLR4 and IL4 genes on the risk of asthma in females. *Int Arch Allergy Immunol* 2005;**138**(3):251–6.
- Hong SJ, Lee SY, Kim HB, Kim JH, Kim BS, Choi SO, Lee SG, Shin ES, Hong TJ. IL-5 and thromboxane A₂ receptor gene polymorphisms are associated with decreased pulmonary function in Korean children with atopic asthma. *J Allergy Clin Immunol* 2005;**115**(4):758–63.
- Ajayi AAL, Halushka PV. Castration reduces platelet thromboxane A₂ receptor density and aggregability. *QJM* 2005;**98**(5):349–56.
- Wjst M. Is the increase in allergic asthma associated with an inborn Th1 maturation or with an environmental Th1 trigger defect? *Allergy* 2004;**59**(2):148–50.

36. Melgert BN, Postma DS, Kuipers I, Geerlings M, Luinge MA, van der Strate BWA, Kerstjens HAM, Timens W, Hylkema MN. Female mice are more susceptible to the development of allergic airway inflammation than male mice. *Clin Exp Allergy* 2005;**35**(11):1496–503.
37. Silverman ES, Breault DT, Vallone J, Subramanian S, Yilmaz AD, Mathew S, Subramaniam V, Tantisira K, Pacák K, Weiss ST, Majzoub JA. Corticotropin-releasing hormone deficiency increases allergen-induced airway inflammation in a mouse model of asthma. *J Allergy Clin Immunol* 2004;**114**(4):747–54.
38. Nakae S, Ho LH, Yu M, Monteforte R, Iikura M, Suto H, Galli SJ. Mast cell-derived TNF contributes to airway hyperreactivity, inflammation, and T_H2 cytokine production in an asthma model in mice. *J Allergy Clin Immunol* 2007;**120**(1):48–55.
39. Uekert SJ, Akan G, Evans MD, Li Z, Roberg K, Tisler C, DaSilva D, Anderson E, Gangnon R, Allen DB, Gern JE, Lemanske Jr RF. Sex-related differences in immune development and the expression of atopy in early childhood. *J Allergy Clin Immunol* 2006;**118**(6):1375–81.
40. Kolb M, Martin G, Medina M, Ask K, Gaudie J. Gene therapy for pulmonary diseases. *Chest* 2006;**130**(3):879–84.
41. Kim TS, Kang BY, Cho D, Kim SH. Induction of interleukin-12 production in mouse macrophages by berberine, a benzodioxololizine alkaloid, deviates CD4⁺ T cells from a Th2 to a Th1 response. *Immunology* 2003;**109**(3):407–14.
42. Khoo SK, Hayden CM, Roberts M, Horak E, de Klerk N, Zhang G, Robertson CF, Goldblatt J, Le Souëf P. Associations of the IL12B promoter polymorphism in longitudinal data from asthmatic patients 7 to 42 years of age. *J Allergy Clin Immunol* 2004;**113**(3):475–81.
43. Balzano G, Fuschillo S, Melillo G, Bonini S. Asthma and sex hormones. *Allergy* 2001;**56**(1):13–20.
44. Erden S, Buyukozturk S, Ozdaş B, Sennazlı G. Do sex hormones influence airway mucosa? *Allergy* 2002;**57**(8):755–6.
45. Riffo-Vasquez Y, Ligeiro de Oliveira AP, Page CP, Spina D, Tavares-de-Lima W. Role of sex hormones in allergic inflammation in mice. *Clin Exp Allergy* 2007;**37**(3):459–70.
46. Carey MA, Card JW, Bradbury JA, Moorman MP, Haykal-Coates N, Gavett SH, Graves JP, Walker VR, Flake GP, Voltz JW, Zhu D, Jacobs ER, Dakhama A, Larsen GL, Loader JE, Gelfand EW, Germolec DR, Korach KS, Zeldin DC. Spontaneous airway hyperresponsiveness in estrogen receptor- α -deficient mice. *Am J Respir Crit Care Med* 2007;**175**(2):126–35.
47. Dimitropoulou C, White RE, Ownby DR, Catravas JD. Estrogen reduces carbachol-induced constriction of asthmatic airways by stimulating large-conductance voltage and calcium-dependent potassium channels. *Am J Respir Cell Mol Biol* 2005;**32**(3):239–47.
48. Siroux V, Curt F, Oryszczyn MP, Maccario J, Kauffmann F. Role of gender and hormone-related events on IgE, atopy, and eosinophils in the Epidemiological Study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy. *J Allergy Clin Immunol* 2004;**114**(3):491–8.
49. Salam MT, Wenten M, Gilliland FD. Endogenous and exogenous sex steroid hormones and asthma and wheeze in young women. *J Allergy Clin Immunol* 2006;**117**(5):1001–7.
50. Lange P, Parner J, Prescott E, Suppli Ulrik C, Vestbo J. Exogenous female sex steroid hormones and risk of asthma and asthma-like symptoms: a cross sectional study of the general population. *Thorax* 2001;**56**(8):613–6.
51. Gómez Real F, Svanes C, Björnsson EH, Franklin KA, Gislason D, Gislason T, Gulsvik A, Janson C, Jögi R, Kiserud T, Norbäck D, Nyström L, Torén K, Wentzel-Larsen T, Omenaas E. Hormone replacement therapy, body mass index and asthma in perimenopausal women: a cross sectional survey. *Thorax* 2006;**61**(1):34–40.
52. Tantisira KG, Hwang ES, Raby BA, Silverman ES, Lake SL, Richter BG, Peng SL, Drazen JM, Glimcher LH, Weiss ST. TBX21: a functional variant predicts improvement in asthma with the use of inhaled corticosteroids. *Proc Natl Acad Sci U S A* 2004;**101**(52):18099–104.
53. Sternberg EM. Neuroendocrine regulation of autoimmune/inflammatory disease. *J Endocrinol* 2001;**169**(3):429–35.
54. Buske-Kirschbaum A, von Auer K, Krieger S, Weis S, Rauh W, Hellhammer D. Blunted cortisol responses to psychosocial stress in asthmatic children: a general feature of atopic disease? *Psychosom Med* 2003;**65**(5):806–10.
55. Dery RE, Mathison R, Davison J, Befus AD. Inhibition of allergic inflammation by C-terminal peptides of the prohormone submandibular rat 1 (SMR-1). *Int Arch Allergy Immunol* 2001;**124**(1–3):201–4.
56. Dery RE, Ulanova M, Puttagunta L, Stenton GR, James D, Merani S, Mathison R, Davison J, Befus AD. Frontline: Inhibition of allergen-induced pulmonary inflammation by the tripeptide feG: a mimetic of a neuro-endocrine pathway. *Eur J Immunol* 2004;**34**(12):3315–25.
57. Putnam K, Chrousos GP, Nieman LK, Rubinow DR. Sex-related differences in stimulated hypothalamic–pituitary–adrenal axis during induced gonadal suppression. *J Clin Endocrinol Metab* 2005;**90**(7):4224–31.
58. Rubinow DR. Reproductive steroids in context. *Arch Womens Ment Health* 2005;**8**(1):1–5.
59. Rubinow DR, Roca CA, Schmidt PJ, Danaceau MA, Putnam K, Cizza G, Chrousos G, Nieman L. Testosterone suppression of CRH-stimulated cortisol in men. *Neuropsychopharmacology* 2005;**30**(10):1906–12.
60. Vicennati V, Ceroni L, Genghini S, Patton L, Pagotto U, Pasquali R. Sex difference in the relationship between the hypothalamic–pituitary–adrenal axis and sex hormones in obesity. *Obesity* 2006;**14**(2):235–43.
61. Bouman A, Heineman MJ, Faas MM. Sex hormones and the immune response in humans. *Hum Reprod Update* 2005;**11**(4):411–23.
62. Loza MJ, Chang BL. Association between Q551R IL4R genetic variants and atopic asthma risk demonstrated by meta-analysis. *J Allergy Clin Immunol* 2007;**120**(3):578–85.
63. Guerra S, Wright AL, Morgan WJ, Sherrill DL, Holberg CJ, Martinez FD. Persistence of asthma symptoms during adolescence: role of obesity and age at the onset of puberty. *Am J Respir Crit Care Med* 2004;**170**(1):78–85.
64. Clifton VL. Sexually dimorphic effects of maternal asthma during pregnancy on placental glucocorticoid metabolism and fetal growth. *Cell Tissue Res* 2005;**322**(1):63–71.
65. Murphy VE, Gibson PG, Giles WB, Zakar T, Smith R, Bisits AM, Kessell CG, Clifton VL. Maternal asthma is associated with reduced female fetal growth. *Am J Respir Crit Care Med* 2003;**168**(11):1317–23.
66. Kwon HL, Belanger K, Holford TR, Bracken MB. Effect of fetal sex on airway lability in pregnant women with asthma. *Am J Epidemiol* 2006;**163**(3):217–21.
67. Murphy VE, Zakar T, Smith R, Giles WB, Gibson PG, Clifton VL. Reduced 11 β -hydroxysteroid dehydrogenase type 2 activity is associated with decreased birth weight centile in pregnancies complicated by asthma. *J Clin Endocrinol Metab* 2002;**87**(4):1660–8.
68. Namazy J, Schatz M, Long L, Lipkowitz M, Lillie MA, Voss M, Deitz RJ, Petitti D. Use of inhaled steroids by pregnant asthmatic women does not reduce intrauterine growth. *J Allergy Clin Immunol* 2004;**113**(3):427–32.
69. Bakhireva LN, Jones KL, Schatz M, Johnson D, Chambers CD, Organization of Teratology Information Services Research Group. Asthma medication use in pregnancy and fetal growth. *J Allergy Clin Immunol* 2005;**116**(3):503–9.

70. u B, Pekkanen J, Husman T, Keski-Nisula L, Koskela P. Maternal sex hormones in early pregnancy and asthma among offspring: a case-control study. *J Allergy Clin Immunol* 2003; **112**(6):1101–4.
71. Tan KS, Thomson NC. Asthma in pregnancy. *Am J Med* 2000; **109**(9):727–33.
72. Shaheen SO, Hines M, Newson RB, Wheeler M, Herrick DRM, Strachan DP, Jones RW, Burney PGJ, Henderson AJ. Maternal testosterone in pregnancy and atopic outcomes in childhood. *Allergy* 2007; **62**(1):25–32.
73. Castro-Rodríguez JA. Relationship between obesity and asthma. *Arch Bronconeumol* 2007; **43**(3):171–5.
74. Paeratakul S, Lovejoy JC, Ryan DH, Bray GA. The relation of gender, race and socioeconomic status to obesity and obesity comorbidities in a sample of US adults. *Int J Obes* 2002; **26**(9):1205–10.
75. Eder W, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med* 2006; **355**(21):2226–35.
76. von Mutius E, Schwartz J, Neas LM, Dockery D, Weiss ST. Relation of body mass index to asthma and atopy in children: the National Health and Nutrition Examination Study III. *Thorax* 2001; **56**(11):835–8.
77. Gilliland FD, Berhane K, Islam T, McConnell R, Gauderman WJ, Gilliland SS, Avol E, Peters JM. Obesity and the risk of newly diagnosed asthma in school-age children. *Am J Epidemiol* 2003; **158**(5):406–15.
78. Castro-Rodríguez JA, Holberg CJ, Morgan WJ, Wright AL, Martinez FD. Increased incidence of asthmalike symptoms in girls who become overweight or obese during the school years. *Am J Respir Crit Care Med* 2001; **163**(6):1344–9.
79. Hancox RJ, Milne BJ, Poulton R, Taylor DR, Greene JM, McLachlan CR, Cowan JO, Flannery EM, Herbison GP, Sears MR. Sex differences in the relation between body mass index and asthma and atopy in a birth cohort. *Am J Respir Crit Care Med* 2005; **171**(5):440–5.
80. Matricardi PM, Grüber C, Wahn U, Lau S. The asthma–obesity link in childhood: open questions, complex evidence, a few answers only. *Clin Exp Allergy* 2007; **37**(4):476–84.
81. Tollefsen E, Bjermer L, Langhammer A, Johnsen R, Holmen TL. Adolescent respiratory symptoms – girls are at risk: the Young-HUNT study. Norway. *Respir Med* 2006; **100**(3):471–6.
82. Burgess JA, Walters EH, Byrnes GB, Giles GG, Jenkins MA, Abramson MJ, Hopper JL, Dharmage SC. Childhood adiposity predicts adult-onset current asthma in females: a 25-yr prospective study. *Eur Respir J* 2007; **29**(4):668–75.
83. Guerra S, Sherrill DL, Bobadilla A, Martinez FD, Barbee RA. The relation of body mass index to asthma, chronic bronchitis, and emphysema. *Chest* 2002; **122**(4):1256–63.
84. Kim S, Camargo Jr CA. Sex-race differences in the relationship between obesity and asthma: the Behavioral Risk Factor Surveillance System, 2000. *Ann Epidemiol* 2003; **13**(10):666–73.
85. Weiss ST. Obesity: insight into the origins of asthma. *Nat Immunol* 2005; **6**(6):537–9.
86. Chen Y, Rennie D, Cormier Y, Dosman J. Sex specificity of asthma associated with objectively measured body mass index and waist circumference: the Humboldt study. *Chest* 2005; **128**(4):3048–54.
87. Beckett WS, Jacobs Jr DR, Yu X, Iribarren C, Williams OD. Asthma is associated with weight gain in females but not males, independent of physical activity. *Am J Respir Crit Care Med* 2001; **164**(11):2045–50.
88. Chen Y, Dales R, Tang M, Krewski D. Obesity may increase the incidence of asthma in women but not in men: longitudinal observations from the Canadian National Population Health Surveys. *Am J Epidemiol* 2002; **155**(3):191–7.
89. Luder E, Ehrlich RI, Lou WYW, Melnik TA, Kattan M. Body mass index and the risk of asthma in adults. *Respir Med* 2004; **98**(1):29–37.
90. Chen Y, Dales R, Jiang Y. The association between obesity and asthma is stronger in nonallergic than allergic adults. *Chest* 2006; **130**(3):890–5.
91. Varraso R, Siroux V, Maccario J, Pin I, Kauffmann F. Epidemiological Study on the Genetics and Environment of Asthma. Asthma severity is associated with body mass index and early menarche in women. *Am J Respir Crit Care Med* 2005; **171**(4):334–9.
92. Hallstrand TS, Fischer ME, Wurfel MM, Afari N, Buchwald D, Goldberg J. Genetic pleiotropy between asthma and obesity in a community-based sample of twins. *J Allergy Clin Immunol* 2005; **116**(6):1235–41.
93. Sengler C, Lau S, Wahn U, Nickel R. Interactions between genes and environmental factors in asthma and atopy: new developments. *Respir Res* 2002; **3**(1):7.
94. Barr RG, Cooper DM, Speizer FE, Drazen JM, Camargo Jr CA. β 2-Adrenoceptor polymorphism and body mass index are associated with adult-onset asthma in sedentary but not active women. *Chest* 2001; **120**(5):1474–9.
95. Faggioni R, Feingold KR, Grunfeld C. Leptin regulation of the immune response and the immunodeficiency of malnutrition. *FASEB J* 2001; **15**(14):2565–71.
96. Halle M, Persson PB. Role of leptin and leptin receptor in inflammation. *Am J Physiol Regul Integr Comp Physiol* 2003; **284**(3):R760–2.
97. Mai XM, Böttcher MF, Leijon I. Leptin and asthma in overweight children at 12 years of age. *Pediatr Allergy Immunol* 2004; **15**(6):523–30.
98. Guler N, Kirerleri E, Ones U, Tamay Z, Salmayenli N, Darendeliler F. Leptin: does it have any role in childhood asthma? *J Allergy Clin Immunol* 2004; **114**(2):254–9.
99. Sood A, Ford ES, Camargo Jr CA. Association between leptin and asthma in adults. *Thorax* 2006; **61**(4):300–5.
100. Li YF, Gilliland FD, Berhane K, McConnell R, Gauderman WJ, Rappaport EB, Peters JM. Effects of in utero and environmental tobacco smoke exposure on lung function in boys and girls with and without asthma. *Am J Respir Crit Care Med* 2000; **162**(6):2097–104.
101. Lødrup Carlsen KC, Løvik M, Granum B, Mowinkel P, Carlsen KH. Soluble CD14 at 2 yr of age: gender-related effects of tobacco smoke exposure, recurrent infections and atopic diseases. *Pediatr Allergy Immunol* 2006; **17**(4):304–12.
102. Holmen TL, Barrett-Connor E, Clausen J, Langhammer A, Holmen J, Bjermer L. Gender differences in the impact of adolescent smoking on lung function and respiratory symptoms. The Nord-Trøndelag Health Study, Norway, 1995–1997. *Respir Med* 2002; **96**(10):796–804.
103. Satoh H, Hasegawa T, Suzuki E, Terada M, Nakayama H, Toyabe S, Akazawa K, Kondoh A, Arakawa M, Yoshizawa H, Gejyo F. Gender differences in susceptibility of asthma to active smoking. Questionnaire based analysis in the Niigata Prefecture, Japan. *Allergol Int* 2005; **54**(3):401–10.
104. Hellings PW, Vandekerckhove P, Claeys R, Billen J, Kasran A, Ceuppens JL. Progesterone increases airway eosinophilia and hyper-responsiveness in a murine model of allergic asthma. *Clin Exp Allergy* 2003; **33**(10):1457–63.
105. Mitchell VL, Gershwin LJ. Progesterone and environmental tobacco smoke act synergistically to exacerbate the development of allergic asthma in a mouse model. *Clin Exp Allergy* 2007; **37**(2):276–86.
106. Jaakkola JJK, Jaakkola N, Piipari R, Jaakkola MS. Pets, parental atopy, and asthma in adults. *J Allergy Clin Immunol* 2002; **109**(5):784–8.

107. Chen Y, Dales R, Tang M, Krewski D. Sex-related interactive effect of smoking and household pets on asthma incidence. *Eur Respir J* 2002;**20**(5):1162–6.
108. Mendonça EMC, Algranti E, de Freitas JBP, Rosa EA, dos Santos Freire JA, de Paula Santos U, Pinto J, Bussacos MA. Occupational asthma in the city of São Paulo, 1995–2000, with special reference to gender analysis. *Am J Ind Med* 2003;**43**(6):611–7.
109. Bakke PS, Gulsvik A. Work-related asthma: prevalence estimates by sex, age and smoking habits in a community sample. *Int J Tuberc Lung Dis* 2000;**4**(7):649–56.
110. Colilla S, Nicolae D, Pluzhnikov A, Blumenthal MN, Beaty TH, Bleeker ER, Lange EM, Rich SS, Meyers DA, Ober C, Cox NJ Collaborative Study for the Genetics of Asthma. Evidence for gene–environment interactions in a linkage study of asthma and smoking exposure. *J Allergy Clin Immunol* 2003;**111**(4):840–6.
111. Gohlke H, Illig T, Bahnweg M, Klopp N, André E, Altmüller J, Herbon N, Werner M, Knapp M, Pescollenderung L, Boner A, Malerba G, Pignatti PF, Wjst M. Association of the interleukin-1 receptor antagonist gene with asthma. *Am J Respir Crit Care Med* 2004;**169**(11):1217–23.
112. Ramadas RA, Sadeghnejad A, Karmaus W, Arshad SH, Matthews S, Huebner M, Kim DY, Ewart SL. Interleukin-1R antagonist gene and pre-natal smoke exposure are associated with childhood asthma. *Eur Respir J* 2007;**29**(3):502–8.
113. Martin AC, Laing IA, Khoo SK, Zhang G, Rueter K, Teoh L, Taheri S, Hayden CM, Geelhoed GC, Goldblatt J, LeSouëf PN. Acute asthma in children: relationships among CD14 and CC16 genotypes, plasma levels, and severity. *Am J Respir Crit Care Med* 2006;**173**(6):617–22.
114. Choudhry S, Avila PC, Nazario S, Ung N, Kho J, Rodriguez-Santana JR, Casal J, Tsai HJ, Torres A, Ziv E, Toscano M, Sylvia JS, Alioto M, Salazar M, Gomez I, Fagan JK, Salas J, Lilly C, Matalana H, Castro RA, Selman M, Weiss ST, Ford JG, Drazen JM, Rodriguez-Cintrón W, Chapela R, Silverman EK, Burchard EG. CD14 tobacco gene–environment interaction modifies asthma severity and immunoglobulin E levels in Latinos with asthma. *Am J Respir Crit Care Med* 2005;**172**(2):173–82.
115. Osman M. Therapeutic implications of sex differences in asthma and atopy. *Arch Dis Child* 2003;**88**(7):587–90.
116. Hartl D, Koller B, Mehlhorn AT, Reinhardt D, Nicolai T, Schendel DJ, Griese M, Krauss-Etschmann S. Quantitative and functional impairment of pulmonary CD4⁺CD25^{hi} regulatory T cells in pediatric asthma. *J Allergy Clin Immunol* 2007;**119**(5):1258–66.
117. Weiner P, Magadle R, Massarwa F, Beckerman M, Berar-Yanay N. Influence of gender and inspiratory muscle training on the perception of dyspnea in patients with asthma. *Chest* 2002;**122**(1):197–201.
118. Wickman M, Melén E, Berglind N, Lennart Nordvall S, Almqvist C, Kull I, Svartengren M, Pershagen G. Strategies for preventing wheezing and asthma in small children. *Allergy* 2003;**58**(8):742–7.
119. Mai XM, Becker AB, Sellers EAC, Liem JJ, Kozyskyj AL. The relationship of breast-feeding, overweight, and asthma in preadolescents. *J Allergy Clin Immunol* 2007;**120**(3):551–6.
120. Mandhane PJ, Greene JM, Sears MR. Interactions between breast-feeding, specific parental atopy, and sex on development of asthma and atopy. *J Allergy Clin Immunol* 2007;**119**(6):1359–66.
121. Gilliland FD, Berhane KT, Li YF, Gauderman WJ, McConnell R, Peters J. Children's lung function and antioxidant vitamin, fruit, juice, and vegetable intake. *Am J Epidemiol* 2003;**158**(6):576–84.
122. Romieu I, Varraso R, Avenel V, Leynaert B, Kauffmann F, Clavel-Chapelon F. Fruit and vegetable intakes and asthma in the E3 N study. *Thorax* 2006;**61**(3):209–15.
123. Raby BA, Lazarus R, Silverman EK, Lake S, Lange C, Wjst M, Weiss ST. Association of vitamin D receptor gene polymorphisms with childhood and adult asthma. *Am J Respir Crit Care Med* 2004;**170**(10):1057–65.
124. Szalai C, Kozma GT, Nagy A, Bojszko A, Krikovszky D, Szabó T, Falus A. Polymorphism in the gene regulatory region of MCP-1 is associated with asthma susceptibility and severity. *J Allergy Clin Immunol* 2001;**108**(3):375–81.
125. Weiss ST, Raby BA. Asthma genetics 2003. *Hum Mol Genet* 2004;**13**(1):R83–9.
126. Wills-Karp M, Ewart SL. Time to draw breath: asthma-susceptibility genes are identified. *Nat Rev Genet* 2004;**5**(5):376–87.
127. Nicholson PJ, Cullinan P, Newman Taylor AJ, Burge PS, Boyle C. Evidence based guidelines for the prevention, identification, and management of occupational asthma. *Occup Environ Med* 2005;**62**(5):290–9.
128. Dehner W. Beitrag zur Pathologie des Asthma bronchiale. *J Mol Med* 1927;**6**(30):1412–7.
129. Rosenberg HF, Phipps S, Foster PS. Eosinophil trafficking in allergy and asthma. *J Allergy Clin Immunol* 2007;**119**(6):1303–10.
130. Osler W. *The principles and practice of medicine: designed for the use of practitioners and students of medicine*. 4th ed. New York: D Appleton and Company; 1901.
131. Shepherd JM, Duddleston DN, Hicks GS, Low AK, Russell LD, Brown CA. Asthma: a brief overview. *Am J Med Sci* 2002;**324**(4):174–9.
132. Caracta CF. Gender differences in pulmonary disease. *Mt Sinai J Med* 2003;**70**(4):215–24.
133. Dombrowski MP. Asthma and pregnancy. *Obstet Gynecol* 2006;**108**(3 Pt 1):667–81.
134. Salvi SS, Babu KS, Holgate ST. Is asthma really due to a polarized T cell response toward a helper T cell type 2 phenotype? *Am J Respir Crit Care Med* 2001;**164**(8 Pt 1):1343–6.
135. Wolthers OD. Eosinophil granule proteins in the assessment of airway inflammation in pediatric bronchial asthma. *Pediatr Allergy Immunol* 2003;**14**(4):248–54.
136. Heaton T, Rowe J, Turner S, Aalberse RC, de Klerk N, Suriyaarachchi D, Serralha M, Holt BJ, Hollams E, Yerkovich S, Holt K, Sly PD, Goldblatt J, Le Souef P, Holt PG. An immunoepidemiological approach to asthma: identification of in-vitro T-cell response patterns associated with different wheezing phenotypes in children. *Lancet* 2005;**365**(9454):142–9.
137. Douwes J, Pearce N. Asthma and the westernization 'package'. *Int J Epidemiol* 2002;**31**(6):1098–102.
138. Mead MN. Environmental roots of asthma. *Environ Health Perspect* 2005;**113**(1):A32–3.
139. Pearce N, Douwes J. The global epidemiology of asthma in children. *Int J Tuberc Lung Dis* 2006;**10**(2):125–32.
140. Barbato A, Turato G, Baraldo S, Bazzan E, Calabrese F, Tura M, Zuin R, Beghé B, Maestrelli P, Fabbri LM, Saetta M. Airway inflammation in childhood asthma. *Am J Respir Crit Care Med* 2003;**168**(7):798–803.
141. Baker KM, Brand DA, Hen Jr J. Classifying asthma: disagreement among specialists. *Chest* 2003;**124**(6):2156–63.
142. Busse W, Banks-Schlegel S, Noel P, Ortega H, Taggart V, Elias J, NHLBI Working Group. Future research directions in asthma: an NHLBI Working Group report. *Am J Respir Crit Care Med* 2004;**170**(6):683–90.