



THE (UN)FAIR SEX

WHY WOMEN HAVE WORSE ASTHMA
AND WHAT WE CAN DO ABOUT IT

We work to stop asthma attacks and, ultimately, cure asthma by funding world-leading research and scientists, campaigning for change and supporting people with asthma to reduce their risk of a potentially life-threatening asthma attack.

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Foreword

The last year has clearly demonstrated the devastating, global impact of a respiratory viral infection. But it has also opened the world's eyes to the speed at which collaborative science can successfully identify causes and solutions. With funding to tackle COVID-19 released at an unprecedented pace and scale, innovations in both response and vaccine development have redefined the art of the possible. The power of science to resolve a crisis has been undeniably reaffirmed.

It's now time to harness this power to solve a huge problem in asthma: the fact that women have far worse health outcomes than men. Around the world, more women than men have asthma, they experience significantly higher numbers of asthma attacks, and they're more likely to die from them. Their working lives are also disproportionately impacted by living with the condition. Yet throughout the long history of asthma – first recognised over 2,000 years ago¹ – this potentially life-threatening condition has primarily been considered as affecting women and men in the same way. This, it is becoming clear, is not correct.

The 'one size fits all' approach to asthma diagnosis, management and treatment simply does not work for women with asthma. Instead, by understanding the role of sex hormones in asthma, there is the opportunity to have a transformative impact for 136 million women around the world.² But achieving this level of change demands that the asthma research community and its funders join forces to urgently understand the issue and collaborate to identify potential treatments.

Asthma UK recently brought together the foremost asthma experts from across the world to help us understand and articulate the research that's needed to correct these gender-based inequalities. This report summarises the latest science and outlines the immediate steps which can be taken to radically improve our understanding of why women often have worse asthma, and what can be done to reduce asthma attacks and save lives.

If we harness the powers of science and global collaboration, this kind of ambitious transformation for people's lives is within our reach. Now is the time to lead the way in unravelling the role of gender difference in one of the world's most widespread chronic conditions.



Sarah Woolnough

Chief Executive, Asthma UK

Executive summary

Globally, there are 136 million women with asthma.² Not only is the condition more common among women, but women are having more severe symptoms and are more likely to die from their asthma. In many cases, women experience a significant worsening of symptoms around menstruation and are at risk of potentially fatal asthma attacks every month.

The difference between how asthma affects men and women throughout their lives is striking. In childhood, asthma is more prevalent and severe in boys. However, after puberty, the situation reverses and asthma becomes more prevalent and severe among women.³⁻⁵ Furthermore, many women experience a change in symptoms at key moments of hormonal change – with some women also experiencing severe, life-changing deterioration of symptoms during and after menopause.

Asthma in women is clearly affected by cyclical hormone fluctuation, by birth control medication and hormone replacement therapy, and by pregnancy and menopause.³ These significant sex disparities, including differences in how often asthma occurs in women, the symptoms they present, response to therapies, and health outcomes, support the important role sex hormones play in the development of asthma.

There are multiple mechanisms through which sex differences in asthma may occur, yet they're poorly understood. They include sex-specific genetic differences in asthma risk, down-regulation of type 2 inflammation – a type of allergic response which exacerbates asthma – by the male androgen hormones, stimulation of type 2 inflammation by the female hormone oestrogen, and an increased susceptibility of women to develop late-onset asthma due to obesity.³

Understanding sex-related differences in asthma would pave the way for the development of new, more precise, targeted interventions and enable clinicians to utilise existing treatments more effectively. Globally, the impacts could be vast and transformative.

To enhance our understanding of the role of sex hormones in asthma we recommend the following:

Funders

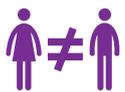


Immediate large-scale funding call: to investigate the influence of sex and gender differences on adult asthma.



Fund a global team science approach: develop a new funding call for an international public-private consortium.

Academia and industry partners must come together to break through the complex, pre-competitive knowledge gaps which must be filled before new, gender-based diagnostics and therapeutics can be identified and/or developed.



Look for gender inequality: mandate all future studies to analyse their datasets by gender to identify differences affecting women. Set up funding to enable the re-analysis of existing datasets.



Invest in leadership: appoint experienced leaders in major research bases to bring equality to asthma research and drive the creation of large collaborations aimed at deepening our scientific understanding of the role of sex hormones in asthma.



Develop infrastructure: invest in the creation of repositories of human clinical samples from well-defined healthy and asthmatic individuals to enhance research into mechanisms of asthma and translational research. Utilise -omics technologies to create stratified datasets to identify novel mechanisms and new therapeutic targets.



Connect high-value datasets: identify existing datasets that can be linked to create the numbers needed and leverage the power of data science to rapidly advance our understanding of the importance of gender difference in asthma.

Researchers, innovators and industry



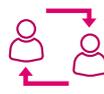
Map the way forward: publish a scientific roadmap for investigating sex hormones and asthma in women, identifying key research questions to answer with clear diagnostic and therapeutic goals identified.



Re-analyse historical data: encourage industry leaders, clinical trial companies, medical communication agencies and key opinion leaders to work together and re-analyse historical clinical trial data to find answers to some of the key questions.



Mobilise the community: set up an American Thoracic Society/European Respiratory Society Taskforce on sex hormones and asthma and agree how priority areas for research will be taken forward.



Create cross-disciplinary collaborations: drive the development of new collaborations across disciplines, particularly endocrinology, by hosting a symposium at major conferences or secure funding for a standalone Keystone Symposium or Gordon Research conference.



Engage innovators: leverage data collected by digital health companies who are supporting women through their menstrual cycles, and seek to co-create technological solutions that can improve the lives of women with asthma.

Current understanding of gender bias in asthma

“ I feel like you get brushed off because you're pregnant and random things happen when you are pregnant...”

Anon

There are over 262 million people with asthma;² a multifactorial disease with allergic, infectious and/or environmental triggers which have an effect on both the immune system and structural cells of the airways.

Clinical and epidemiologic studies in children and adults suggest a role for sex hormones in the development of asthma.³⁻⁵ The increase in asthma prevalence in females starting at puberty, and changes in asthma symptoms which are associated with fluctuations in hormones during menstruation, pregnancy, and menopause suggest a causative role for female sex hormones, such as oestrogen. The obesity-asthma association is also stronger among women than men.⁶ Finally, a drop in asthma incidence observed in and around puberty in males suggests a possible protective effect of male sex hormones such as testosterone.⁷

Results from animal asthma models support these findings; male mice develop less severe allergic asthma than female mice.⁸ Female sex hormones may therefore contribute to the onset, progression and exacerbation of asthma, whereas there is an accumulation of evidence that supports the protective action of male hormones, in particular androgen receptor signalling, during puberty and in adulthood.⁹

Asthma in women: the statistics

- Asthma is more prevalent and severe in women¹⁰
- Women are less likely to recover completely from asthma than men¹¹
- Poorly controlled asthma causes worse quality of life in women than men¹²
- Women have more frequent and severe asthma symptoms, poorer quality of life, greater healthcare utilisation, greater likelihood of hospitalisation, and a higher mortality rate than men¹³
- **Women aged 20-50 years are three times more likely than men to be admitted to hospital for asthma¹⁴**
- 20-25% of women with asthma have premenstrual asthma³
- 68% of women with premenstrual asthma have previously been hospitalised¹⁵
- 30% of women with asthma report worsening asthma severity and loss of disease control during pregnancy³
- **Asthma is 5-7 times more common in obese women (>11 years)¹⁶**

Asthma is more common among women than men

Asthma is caused by complex pathological processes that affect the airways. Before ten years of age, more boys than girls have asthma, but following puberty things change and women are twice as likely to develop asthma than men.¹⁷

Asthma is more severe among women than men and causes more death

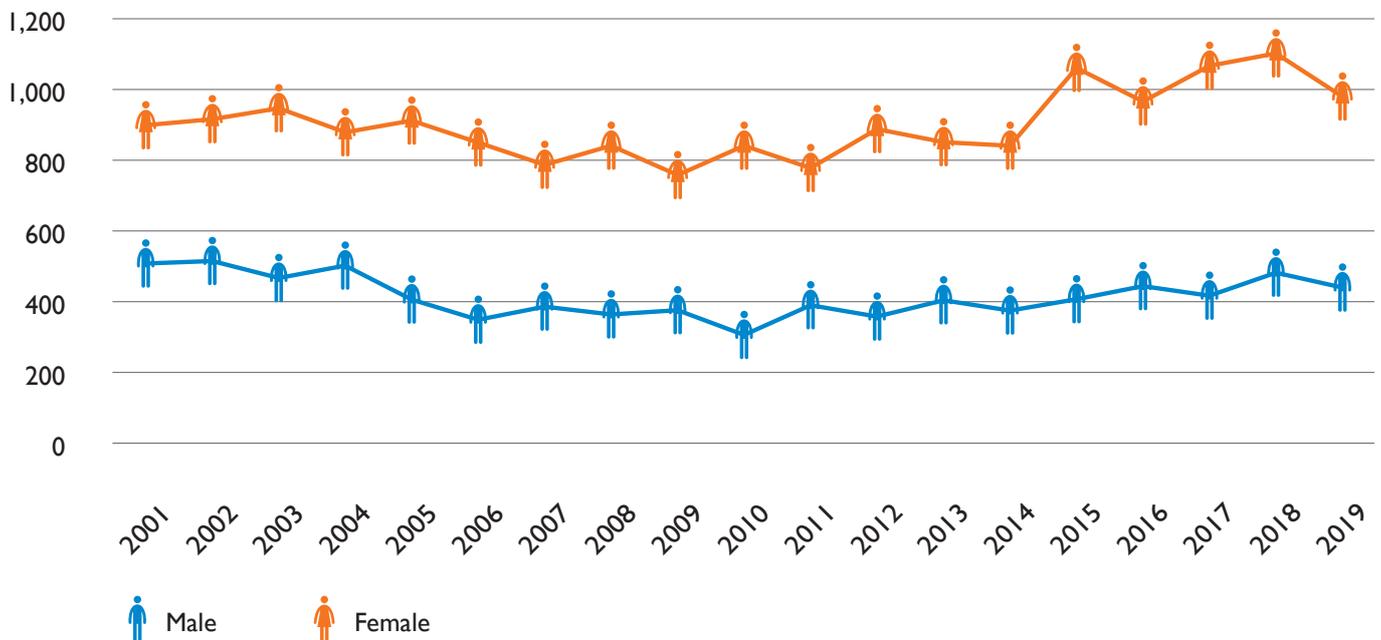
Rates of admissions to hospital for asthma are similar by sex in the early teenage years but are **three times higher in women than in men aged 20-50 years.**¹⁴ Women have more frequent and severe asthma symptoms, poorer quality of life, greater healthcare utilisation, greater likelihood of hospitalisation, and a higher mortality rate.^{13,17}

The menstrual cycle can play a key role in the development of asthma

Asthma is influenced by the rise of female sex hormones during puberty, and then fluctuating levels during monthly menstruation cycles. Female hormones can also trigger asthma symptoms during perimenopause (the time leading up to menopause).¹⁵

For many women asthma can deteriorate significantly during the perimenstrual period, a phenomenon known as perimenstrual asthma or PMA. Women with pre-menstrual worsening of asthma report that the most significant symptoms that worsen during this time are shortness of breath, wheezing and chest tightness. Of women with PMA, up to 68% have previously been hospitalised for their asthma. They also report increased use of oral corticosteroids and increased healthcare utilisation compared to women without PMA.¹⁵

Figure 1: Asthma mortality in the UK, 2001-19



Data via Office for National Statistics (ONS), National Records of Scotland and the Northern Ireland Statistics and Research Agency

Pregnancy and asthma symptoms

The effect of pregnancy on asthma is variable: symptoms worsen in about one-third of pregnant women and improve in about one-quarter. Mild asthma is likely to improve, whereas more severe forms of the disease frequently worsen. During the last 4 weeks of gestation, asthma generally improves, and exacerbations are not common during labour and delivery.¹⁸

“ I just thought this is weird, that whilst I am pregnant there is obviously something in my body that just reacts to my asthma... but I've never really understood why.”

Anon

The effect of menopause on asthma

Women with asthma may also experience different hormonal states as they transition through menopause. During the perimenopausal period there is a significant decline in lung function; however, once the menopause has occurred there appears to be a protective effect on asthma. Postmenopausal women present a significantly lower risk of developing asthma for the first time than premenopausal women of similar age. In contrast, the risk of severe asthma continues to increase in men after the age of 45 years.¹⁹

“ If I'm not mistaken during pregnancy it got worse... but that's what I can't understand, why it is better in menopause, not that I am complaining!”

Anon

How treatment with hormones affects the development of asthma

The effect of hormone replacement therapy (HRT) on asthma is controversial. HRT has been associated with an increased risk of hospital admission for asthma. However, neither the discontinuation nor re-initiation of HRT in the postmenopausal period was shown to have any effect on asthma.¹⁸

Studies have demonstrated a role for both exogenous oestrogen and progesterone in the management of PMA. Oral contraception reduces asthma symptoms, improves pulmonary function, and improves asthma control in women with PMA.¹⁸

The role of obesity in the development of asthma in women

Studies have shown an association between a high body mass index and asthma.²⁰ Obese patients have a higher risk of exacerbations and poorer asthma control; and positive effects of weight loss on outcomes related to asthma have been confirmed.²¹ According to the Global Burden of Disease Study 2017, a high body mass index has accounted for the most deaths caused by asthma since 2013 and contributed the most to disability adjusted life years since 2003.²² The obesity-asthma association is stronger among women than men.⁶

Case study: Diane Hobbs

Diane, aged 34 and living in Scotland, has had asthma since childhood.

I was first diagnosed at 4 years old, but later on, when I was a teenager, that diagnosis was changed to severe asthma. I kept a diary to try to work out what was triggering my attacks in the hope of trying to bring it under control, and that's when I discovered that all of the worst attacks followed my menstrual cycle.

Every month, I have a flare-up. I get itchy lungs, have difficulty breathing and I start to feel really poorly. Like clockwork, my peak flow will drop from 550 to 250, the wheezing starts and two days later I get my period.

When I first noticed this pattern, I immediately spoke to my doctor at the time. Instead of him taking my concerns seriously, he dismissed the idea that my asthma could be linked to my cycle. That doctor left me feeling shamed and confused and it meant I didn't feel comfortable enough to broach the subject again.

A few years later, when I had my two children, I noticed that during my pregnancy and the whole time I was breastfeeding my asthma symptoms practically disappeared. However, the moment I stopped breastfeeding and my menstrual cycle returned, the symptoms immediately reappeared.

After yet another hospital admission, my mum brought it to the attention of my new consultant who was shocked at the prior treatment I had received and started me on some hormone replacement therapy to try and improve my symptoms.

I feel like I have spent half of my life in the hospital and it is just so frustrating to go through these sudden, dramatic changes in my health.

Recent developments in the field and gaps in our knowledge

Findings from recent studies have suggested that increasing our understanding of how sex hormones are able to regulate asthma may lead to the identification of pathways to be targeted by new therapeutic drugs.

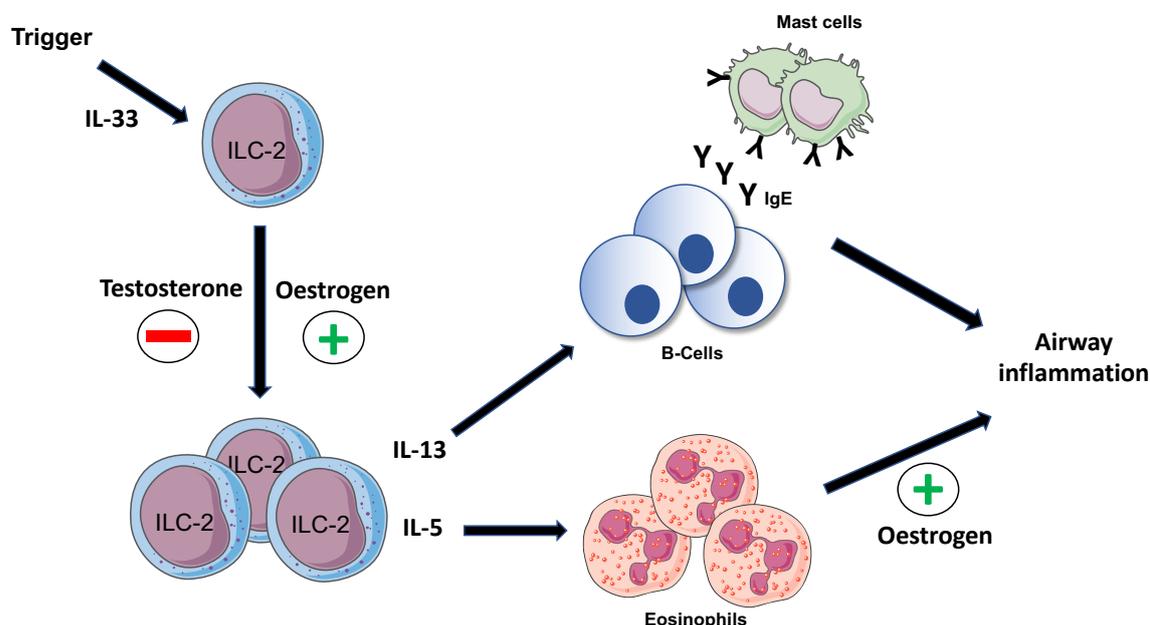
In late 2020, Asthma UK and the British Lung Foundation hosted a meeting to bring together global leaders in the field of sex hormones and asthma, together with industry and funders (see Acknowledgements). Participants explored four key areas of interest, identified some of the urgent research questions and discussed potential recommendations.

Recent developments: Sex hormones and airway inflammation

The effects of sex hormones on asthma symptoms and progression are complex.

Oestrogen receptors are found on numerous cells of the immune system, and oestrogen appears to promote an immunological response in the direction of allergy development.²³ This allergic sensitisation, at least in animal models, occurs not only following exposure to endogenous oestrogens but also exposure to xeno-oestrogens (i.e. foreign oestrogens) from environmental pollutants such as plastic and pesticides.²⁴

Figure 2: Regulation of airway inflammation by sex hormones



Innate lymphoid cells (ILCs) are recently discovered cells important in initiating inflammatory responses. Group 2 ILCs (ILC-2) are increased in allergic responses, with asthmatic women having higher circulating ILC-2 cells compared to asthmatic men. ILC-2s release cytokines, such as IL-5 and IL-13, which stimulate eosinophils, B-cells and mast cells, resulting in airway inflammation. Androgens (eg testosterone) negatively regulate ILC-2 cells, in turn reducing airway inflammation. Oestrogen has the opposite affect. Oestrogen may also directly affect the recruitment of eosinophils to the lungs. Adapted from *Sex hormones in asthma* presentation – Jean-Charles Guéry, Academia Europaea, Nov 6, 2018 and 'Hormones, sex and asthma,' – Dawn Newcomb et al., *Annals of Allergy, Asthma & Immunology*, 120:5 488-494 (2018). DOI: 10.1016/j.anai.2018.01.016.

Although present in both sexes, androgens play a role in male traits and reproductive activity (e.g. testosterone). Recent evidence suggests that increased androgen receptor expression is beneficial in asthma. In murine asthma models, loss of androgen receptor is associated with increased susceptibility to asthmatic airway inflammation and bronchoconstriction.²⁵⁻²⁷ **Strikingly, humans with androgen receptor deficiency (androgen insensitivity syndrome) also have an approximately three-fold increased asthma risk.**²⁸

Sex hormones regulate lymphocytes during airway inflammation

Collectively, **female sex hormones up-regulate whereas testosterone down-regulates important molecules of the inflammatory pathway.** Animal studies have provided evidence that oestrogen signalling through the alpha form of the oestrogen receptor enhances allergic airway inflammation via macrophage polarisation in the lung and bone marrow.²³ There appear to be several mechanisms by which androgens regulate airway inflammation. Dihydrotestosterone inhibits group 2 innate lymphoid cell (ILC-2) proliferation and IL-33 responses and decreases IL-5 and IL-13 secretion; it also affects macrophage polarization^{8,25-27,29} and inhibits human neutrophil migration.³⁰ This inhibition of the cells that orchestrate the allergic immune response may lead to the higher numbers of circulating ILC-2 cells in human females compared with males with asthma.²⁹

Oestrogen promotes and androgen reduces eosinophilia

Another type of immune cell involved in the development of asthma is the eosinophil, which is one of a subset of cells termed 'granulocytes'. In type 2 eosinophilic asthma, a cascade of processes directed by type 2 cytokine producing T-cells and ILC-2 cells influences the recruitment of eosinophils into the lungs.³¹ **Animal models have shown that oestrogen also has an effect on granulocytes during the development of asthma and lung**

function was improved when oestrogen was blocked.³² Conversely, lack of circulating androgen increased airway eosinophilia and androgen replacement reduced eosinophilia in a mouse model of asthma.²⁷

Sex hormones and the immune response in asthma: Knowledge gaps

To further our understanding of the role of sex hormones on the immune response during the development of asthma, some of the research questions that should be addressed include:

1. Do immune cell functions alter in parallel with sex hormone changes across the menstrual cycle in women with asthma?
2. Do environmental exposures to oestrogens, such as phytoestrogens, xenoestrogens/ BPA, exogenous hormone treatments or steroid medications alter immune cell function in asthma?
3. Do sex hormones affect the pathogenetic functions of immune and structural cells such as epithelial cells in the lung?
4. Does the effect of sex hormones on asthma differ depending on the underlying asthma endotype, especially for difficult to treat asthma endotypes such as neutrophilic asthma?

Recent developments: Sex hormones and airway structure/function

Inherent sex differences in the structure of the lung are apparent throughout the human life span.³³ At birth, the female lung is smaller than that of the male. During puberty, the influence of testosterone and the changing shape of the thorax and respiratory muscles in males generate higher respiratory pressures than in females. However, in adulthood, lung function is higher in women. As adults age there is a loss of lung function in both sexes; however, the rate of decrease in lung function is greater in men and women are older at the onset of this decline.³³

Protective role for oestrogen receptor beta?

Airway smooth muscle cells are major structural cells of the lung and a key contributor to the contractile nature of airways. Remodelling of airway smooth muscle is a critical feature of asthma that influences disease severity.³⁴ Human airway smooth muscle cells express both the alpha and beta forms of the oestrogen receptor and expression of both forms of the receptor is significantly higher in airway smooth muscle from asthmatic patients than non-asthmatic patients.³⁵

It is thought that the differential activation of oestrogen receptors may play a crucial role in regulating asthma. In animal models of asthma, mice lacking the oestrogen receptor beta showed exacerbated airway hyperresponsiveness and remodelling, while those lacking oestrogen receptor alpha showed reduced airway hyperresponsiveness and remodelling.^{36,37} **This “protective” role of the oestrogen receptor beta during asthma may make it a potential target for novel therapies to treat asthma.**²⁸

Sex hormones and airway structure/function in asthma: Knowledge gaps

In order to further our understanding of the role of sex hormones on airway structure/function during the development of asthma, the following research questions should be considered:

1. How do sex hormones influence airway structure or function in health vs. states of inflammation and/or asthma?
2. Beyond oestrogen, progesterone or testosterone, is there a role for hormonal metabolites in asthma?

Recent developments: Sex hormones and obesity-linked asthma

The links between obesity and asthma have been clear for some time. The prevalence of asthma is 9% in obese adults vs. 5% in non-obese adults,⁴⁰ being obese increases the relative risk of having asthma 2.7-fold.⁴⁰ The link between obesity and asthma in females is even more pronounced. In childhood, obesity is associated with higher asthma prevalence and morbidity in girls, but not in boys, and in females older than 11 years, **asthma is five to seven times more common in obese people compared to those of normal weight.**

Obese, non-eosinophilic asthma: A different phenotype?

Obesity-related asthma often appears to have a different clinical presentation to asthma in non-obese patients and may constitute a different type of asthma. Obesity is associated with chronic low-grade inflammation including the lungs. Obese asthma patients do not respond well to treatment with inhaled corticosteroids.⁴¹ There is also a subset of obese female asthma patients who have high percentages of sputum neutrophils and more severe asthma symptoms.⁴² Understanding these different phenotypes of asthma may lead to personalised and more effective treatment for people living with asthma.

Adipose hormone FABP4: A link between obesity and asthma?

Recent studies have identified that **fatty acid binding protein 4 (FABP4), one of the most abundant proteins in adipocytes⁴³ which is also expressed by eosinophils in allergen-exposed lungs, plays a proinflammatory role in the development of allergic asthma.**⁴⁴ In humans, serum levels of FABP4 increase with obesity and females exhibit higher circulating FABP4 levels than males,⁴⁵ perhaps suggesting differences in adipose depot contributions and/or the involvement of sex hormones in the regulation of secretion.⁴⁶

At a cellular level in a mouse model of allergic asthma, FABP4 appears to play a direct role in supporting eosinophil adhesion and migration. Genetic deficiency, or blocking FABP4 leads to decreased eosinophil recruitment to the lungs, markedly reduced airway inflammation and airway hyperresponsiveness.^{44,47} New data is emerging to show that asthmatic women have higher serum FABP4 levels than non-asthmatic women, and that the correlation is stronger in overweight and obese women than lean subjects.⁴⁸ Additionally, neutralization of FABP4 with monoclonal antibody is able to treat obesity and related complications such as diabetes, insulin-resistance and fatty liver disease.⁴⁹ FABP4 could therefore be a link between obesity and asthma and a potential target for novel treatments for a subset of people with obesity and asthma.

Sex hormones and obesity-related asthma: Knowledge gaps

To further our understanding of the role of sex hormones in obesity-related asthma, some of the research questions that should be addressed include:

1. How do sex hormones affect the role of obesity and metabolic syndrome in the inflammatory response in asthma?
2. Do current therapeutics used to treat obesity and/or type 2 diabetes alter lung inflammation and airway hyperresponsiveness differently in men and women?
3. By which mechanisms do adipose tissue molecules contribute to airway hyperresponsiveness?
4. What effect do common asthma comorbidities have on the action of sex hormones in asthma associated with obesity?

Recent developments: Androgens as a potential therapeutic target for asthma

There is evidence to suggest that regardless of patient gender increased androgen receptor levels in the airway are associated with better lung function, improved quality of life and lower fractional exhaled nitric oxide (FENO; a biomarker associated with lung inflammation).⁹ Increased levels of androgen receptor ligands, e.g. testosterone and dehydroepiandrosterone sulphate (DHEA-S), have also been found to be associated with lower asthma prevalence and better lung function.⁵⁰⁻⁵⁶

Higher levels of androgen are also associated with better lung function in children with asthma⁵⁷ and both boys and girls often outgrow severe asthma during the period of increased androgen levels during adolescence.⁵⁸

Inhaled corticosteroids (ICS) can decrease levels of androgen ligands such as DHEA-S. However, it is unlikely that increased ICS use accounts for the association between decreased androgens and increased asthma severity.

Recent data has shown that a mutation in the gene linked with high tissue androgen levels (HSD3BI) is associated with better lung function in patients with severe asthma, for both men and women.⁵⁹ Additionally, patients with non-severe asthma may also benefit from androgen supplementation.^{60,61}

Androgens as a potential therapeutic target for asthma: Knowledge gaps

To further our understanding of androgens as a potential therapeutic target for asthma, the following should be addressed:

1. Studies should be designed to understand the role of androgens in women with asthma in general, and in those with severe asthma in particular.
2. A study of DHEA treatment in women with very low DHEA-S levels and severe asthma should be carried out, particularly those with a high-risk HSD3BI genotype.

Discussion

Delivering better outcomes for women with asthma

For many women with asthma, the notion that their symptoms change with their menstrual cycle will not come as news, but as confirmation of what they always suspected. The stark differences in outcomes for women and changes in symptoms due to the menstrual cycle can often be clearly related to fluctuations in sex hormones. This paper articulates a clear need to understand the differences between women and men with asthma.

Recent research has shown how different sex hormones affect key processes: increasing and counteracting inflammation, worsening or reducing asthma symptoms. Oestrogen receptors if activated differently could significantly reduce airway hyperresponsiveness and lung remodelling, providing a protective effect against asthma. New findings on fatty acid proteins and their role in allergic asthma could provide new avenues of scientific discovery. The role of tissue androgens also suggests possible therapeutics could be within grasp.

Yet there is much more to be done. To achieve better outcomes for millions of women with asthma will require bold leadership and a collective response across multiple sectors.

Radical increase in funding to match ambition

In recent years, major research funders have called for a fundamental shift in the world of science and some are mandated for all research to analyse and account for the impact of gender. The European Commission has noted gender equality as a 'cross-cutting priority' for its forthcoming €95bn Horizon Europe research funding programme, requiring the integration of the gender dimension by default in research and innovation.⁶²

Similarly, the US National Institutes of Health's strategic objectives highlight the opportunity of leveraging a deeper understanding of biologic differences related to gender to devise more precise, targeted intervention strategies and further improve clinical outcomes; and utilising the power of data science to achieve this.⁶³ Building on this, the NIH has explicitly called for sex as a biological variable to be factored into research designs, analyses, and reporting in human studies.⁶⁴

These ambitions are important steps and should be matched by all research funders. However, these policy changes need to occur alongside the allocation of dedicated, large-scale funding to analyse the role of sex hormones on asthma outcomes.

Strengthening leadership and infrastructure

Large-scale funding could help to drive the creation of necessary academic leadership to drive forward the areas highlighted in this paper, which could bring us closer to new ways to manage asthma across a woman's life, accounting for the true impact of hormonal changes. To crystallise the steps towards better outcomes for women, we urge the development of a clear research roadmap, operationalised by an ATS/ERS Taskforce.

Tackling the challenge of gender inequality in asthma does not require starting from scratch. Existing datasets provide a wealth of information regarding the role of sex hormones in asthma. We suggest that all major asthma research groups should be encouraged to re-analyse their datasets by gender, and where possible investigate whether severity of asthma was affected by hormonal status.

Funding will also be required to develop key infrastructure that can accelerate scientific progress. New repositories of human clinical samples will be needed to compare healthy and asthmatic individuals, which can enhance the investigation

of the mechanisms outlined in this paper, and translational research which applies findings to real-world uses in healthcare. Industry- or academia-based -omics technologies could be leveraged to create highly stratified datasets to help identify novel mechanisms causing asthma in women and new therapeutic targets.

Additionally, leadership within the asthma research community could help to drive new collaborations across disciplines and sectors, including endocrinology, to gain from insights into other conditions with significant differences between the sexes, such as rheumatoid arthritis, autoimmune diseases and Long Covid.

Building on past drug trials and the present innovation

Meeting the challenge of improving outcomes for women with asthma will require significant investment and a team science approach. The complexity of this challenge means that academia cannot work alone. The expertise of global pharmaceutical companies must be leveraged to provide a deeper understanding of differences between sexes that can result in more precise interventions and improved outcomes.

New public-private partnerships should be developed to explore the pre-competitive knowledge gaps and revisit high-value datasets from asthma drug trials. Large-scale funding in alliance with industry could enable insight into the impact of sex hormones across diseases, resulting in considerable market opportunities. Research into women with asthma could ultimately provide the platform for the mass implementation of precision medicine, whereby treatment regimes move beyond one-size-fits-all for complex conditions and towards therapy that is hyper-personalised to the individual and their history.

To avoid the trap of applying age-old thinking to an historic injustice, it will be important to engage innovators, particularly from the fast-growing world of femtech, a market which is predicted reach \$60 billion globally by 2027.⁶⁵ Research into women with asthma could gain considerable insight from the vast datasets produced by existing applications that are helping women to track their menstrual cycle and its relation to overall health.⁶⁶ Additionally, the application of machine learning and other high-performance computing tools, which are already being applied to help women to predict the onset of menstruation,⁶⁷ could pave the way for accelerated improvement in outcomes.

Asthma affects 136 million women across the world, and yet we are only beginning to scratch the surface of the role of sex hormones in women's asthma. Understanding these differences and developing appropriate interventions could provide a high-impact, high-value demonstration of precision medicine. By investing in research and innovation into the impact of sex hormones on asthma, we can transform outcomes for women and, ultimately, save lives.

Recommendations

Funders

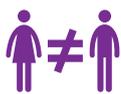


Immediate large-scale funding call: to investigate the influence of sex and gender differences on adult asthma.



Fund a global team science approach: develop a new funding call for an international public-private consortium.

Academia and industry partners must come together to break through the complex, pre-competitive knowledge gaps which must be filled before new, gender-based diagnostics and therapeutics can be identified and/or developed.



Investigate gender inequality in all studies: mandate all future studies to analyse their datasets by gender to identify differences affecting women. Set up funding to enable the re-analysis of existing datasets.



Invest in leadership: appoint experienced leaders in major research bases to bring equality to asthma research and drive the creation of large collaborations aimed at deepening our scientific understanding of the role of sex hormones in asthma.



Develop infrastructure: invest in the creation of repositories of human clinical samples from well-defined healthy and asthmatic individuals to enhance research into mechanisms of asthma and translational research. Utilise -omics technologies to create stratified datasets to identify novel mechanisms and new therapeutic targets.



Connect high-value datasets: identify existing datasets that can be linked to create the numbers needed and leverage the power of data science to rapidly advance our understanding of the importance of gender difference in asthma.

Researchers, innovators and industry



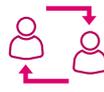
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