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REVIEW

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Sex disparities in cystic fibrosis in the era of highly effective modulator treatment

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Abstract

Cystic fibrosis (CF) is a genetic disorder characterized by progressive lung disease and extra-pulmonary manifestations with notable sex disparities in disease outcomes. In this review we summarize the underlying mechanisms driving this sex disparity, with a particular focus on the role of sex hormones on CF lung disease pathophysiology. We explore how the introduction of highly effective modulator therapies (HEMT) may impact sex differences in outcomes and assess whether they have the potential to close the sex gap. While treatment with HEMT has led to better outcomes in the CF population as a whole, females with CF continue to experience worse pulmonary morbidity than males. There is a need for continued research in this area, particularly into the influence and therapeutic potential of sex hormones.

Keywords Sex, Hormone, Disparity, Cystic fibrosis, Modulator

Introduction

Cystic fibrosis (CF) is an autosomal recessive disease caused by genetic defects in cystic fibrosis transmembrane conductance regulator (CFTR) protein causing impaired chloride (Cl^{-1}) transport across surface epithelium [1]. CF affects all exocrine organs, but most of the morbidity and mortality is related to lung disease. Despite equal prevalence, female people with CF (PWCF) have worse clinical outcomes [2, 3]. This phenomenon was first described in the 1990s by Rosenfeld et al. [4] and despite unprecedented improvements in overall life expectancy for PWCF, females continue to die younger than their male counterparts [5]. In addition to risk factors such as low socioeconomic status, poor nutrition and acquisition of CF-comorbidities including CF related diabetes (CFRD) and liver disease, female sex is an independent risk factor for death [2, 3]. Over the last decade the treatment of CF has been revolutionized by the introduction of small molecule drugs targeting the basic protein defect termed CFTR modulators. Despite the success of these therapies, their impact on the sex disparity in CF remains unclear and the mechanisms underpinning this dichotomy are likely multifactorial. In this review we will summarize the underlying biological mechanisms driving the sex differences, with a particular focus on the role of sex hormones in CF lung disease pathophysiology. We will then explore the potential impact highly effective modulator therapies (HEMT) may have in closing the gap, highlighting key areas of further research including additional therapeutic targets.

Proposed mechanisms for sex disparity in outcomes in CF

To gain further understanding of the observed sex disparity in CF, a variety of mechanisms have been proposed and explored. The sex dichotomy likely results from a complex interplay of biological mechanisms related to sex assigned at birth, and societal and behavioral factors related to gender. The contribution of psychosocial factors has been reviewed in detail elsewhere [6–8]. In

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this review we will only discuss hypothesized biological mechanisms such as differences in CF related co-morbidities, anatomy, microbial acquisition and immune response, with a particular focus on the role of endogenous sex hormones (Table 1).

Cystic fibrosis related diabetes (CFRD) is a distinct subtype of diabetes mellitus resulting from a combination of defective CFTR protein in pancreatic epithelial cells causing pancreatic exocrine and beta islet cell damage [9], intra-islet inflammation, and dysregulation of the incretin hormonal axis [10]. Insulin insufficiency induces a catabolic state, causing protein and muscle breakdown, resulting in a reduced body mass index (BMI) [11]. CFRD is more common in female PWCF and associated with a more severe decline in lung function and greater mortality than in male PWCF who develop CFRD [12–14]. This sex difference in clinical outcomes in PWCF and CFRD was first highlighted by Milla et al., who identified worse survival in females with CFRD. This group postulated that this sex difference may be the result of an interaction between female sex hormones and diabetes promoting a proinflammatory state [12]. Interestingly, in a later study by this group, the sex difference had disappeared, felt to be a result of improved diagnosis and more aggressive treatment [15]. In more recent work, including a 2015 study by Stephenson et al. using the Canadian CF registry, an incidence of CFRD of 30% in females versus 17% in males was reported, with a hazard ratio for death of 1.28 in females with CFRD [14]. Thus, further supporting the CFRD-sex interaction. This highlights the importance of research in this area to address conflicting data and to investigate potential mechanisms including the hypothesized impact of sex hormones. The treatment goals for CFRD focus on managing postprandial hyperglycemia, preventing calorie loss, and maintaining body mass [16], as poor nutrition and low BMI are linked to reduced lung function and higher mortality in CF [17, 18]. Historically, female PWCF had lower BMIs than male PWCF or non-CF females [19]. However, CF registry data over the last several years has demonstrated improving BMI percentiles in both sexes, with overweight and obesity emerging as problems in CF. This is an issue that predates the introduction of HEMT [20–22].

There are also morphometric differences between the sexes which have functional and clinical implications. For example, females have fewer bronchioles, smaller airway diameter and smaller lung volumes priming them to be more susceptible to airflow limitation [23, 24]. Furthermore, geometric factors such as sharp airway branch points or branch patterns such as bifurcations in females could contribute to impaired mucociliary clearance in CF with the potential to increase susceptibility to pulmonary infections [25]. This is a general mechanism implicated in the sex disparity seen in other chronic lung diseases such as asthma and chronic obstructive lung disease and a direct association with worse pulmonary outcomes for female PWCF has not been studied.

Pulmonary exacerbations (PEx) represent important clinical events in the lives of PWCF due to the associated impact on quality of life, lung disease progression and increased mortality [26–28]. Female PWCF have been shown to experience more frequent PEx than males and have worse associated clinical outcomes [17, 29–31]. Following a PEx, female PWCF require longer

Table 1 Summary of proposed biological mechanisms for the sex disparity in CF outcomes

	Mechanism (references)
Anatomical	- Reduced airway diameter and lung volumes in females [23, 24] - Sharp airway branch points and airway bifurcations in females [25]
Genetic	- Sex-biased expression of genes related to CFTR and inflammation [35] - Increased immunity genes on X chromosome [37]
Microbiology	- Earlier acquisition of common CF pathogens in females [17, 32, 33] - Earlier acquisition of *P.aeruginosa* [17, 32, 33] - Female PWCF have more frequent PEx than males [17, 29–31]
CFRD	- CFRD more common among females [12–14] - Associated with greater decline in lung function and mortality in female PWCF [12–14] - Insulin insufficiency induces catabolic state leading to low BMI [11]
Sex hormone related	- Estrogen alters ion transport across the epithelium via inhibition of CaCC mediated Cl^- secretion [43], reduced CFTR expression [44] and increased ENaC expression at apical cell membranes [46] - Estrogen increases mucin production (MUC5B) [48] - Progesterone reduces ciliary beat frequency [47] - Estrogen induces mucoid conversion of *P.aeruginosa* [32, 34] - Estrogen inhibits lactoferrin, supporting biofilm development. [52, 53] - Estrogen promotes *P.aeruginosa* motility, adherence and secretion of pyocyanin [49, 54] - Estrogen reduces neutrophil chemotaxis via downregulation of IL-8 [61]

duration and more complex treatment regimens compared to males and are less likely to recover lung function to their pre-exacerbation baseline [17, 29–31]. This may in part be explained by the earlier acquisition of pathogens in female PWCF, including *Pseudomonas aeruginosa (P.aeruginosa), Methicillin-resistant Staphylococcus aureus (MRSA), Hemophilus influenza (H.Influenza), Achromobacter xylosoxidans (A.xylosxidans), Aspergillus species* and *non-tuberculous mycobacterium (NTM)* [17, 32, 33]. The earlier colonization with *P.aeruginosa* is of particular importance, as female PWCF also demonstrate earlier conversion to a more virulent mucoid phenotype of *P.aeruginosa* which in turn is associated with an increased rate of lung function decline and increased morbidity [32, 34].

These mechanisms do not fully explain the sex differences in outcomes in CF. This was highlighted by Harness-Brumley et al. in a large registry study, which demonstrated female sex remained an independent risk factor for death despite accounting for variables such as CFRD and infection with common CF pathogens [17]. In attempt to investigate sex specific differences at a molecular level, a 2023 study by Gartner et al., analyzed RNA sequencing data from whole blood of PWCF. They identified a CF-specific sex-bias in the expression of number of genes involved in pathways related to CF pathology [35]. They propose higher expression of genes, such as CFTR and epidermal growth factor receptor (EGFR) as a mechanism which may confer male advantage in CF and in the case of CFTR, may allow for some compensation for protein mutations. Given that loss of normal CFTR activity has been shown to increase airway epithelial interleukin (IL)-8 production via activation of the pro-inflammatory EGFR cascade [36], male-biased expression of such genes may result in less IL-8 production and less inflammation. They also identified sex differences in genes involved in the proinflammatory IL-17 pathway and the cAMP pathway which affects ciliary beat frequency [35]. These results are limited by low numbers but should prompt further research, potentially leading to targets for sex specific therapies. Additionally, female PWCF have a greater number of immunity genes on the X chromosome promoting pro-inflammatory responses. This may be protective in acute infection but could be a disadvantage in chronic infection leading to persistent airway inflammation [37].

Clinically, the emergence of sex differences in outcomes occurs post-puberty where female PWCF experience greater exacerbation rates than males, despite having similar rates pre-puberty [33]. This has prompted researchers to explore the mechanistic role of sex hormones in the sex disparity seen in CF. We will explore further in the next section how sex hormones, particularly estrogen, have been shown to play a significant role in CF lung disease pathophysiology, and as such provide a plausible mechanism for the observed disparity via their impact on pulmonary outcomes.

Influence of sex hormones on CF lung disease pathophysiology and pulmonary outcomes in PWCF

The primary female hormones are estrogen (active form 17β-estradiol) and progesterone, while male hormones are androgens, which include testosterone, dehydroepiandrosterone (DHEA), and dehydroepiandrosterone- sulphate (DHEA-S). Sex hormones play a key role from early on in fetal lung development, with the placenta producing estrogen and the fetal testes secreting testosterone. These hormones continue to affect respiratory function throughout life and influence many chronic respiratory diseases, including CF [38].

The effects of sex hormones are mediated via their receptors. Estrogen receptor 1 (ESR1) and Estrogen receptor 2 (ESR2) are ligand-activated transcription factors, meaning they bind to estrogen and then move to the cell nucleus to regulate the expression of genes involved in cell cycle regulation and inflammation, while G protein-couple estrogen receptor (GPER) is a 7 transmembrane G protein-coupled receptor which interacts with EGFR and affects cell signaling pathways [35]. Both ESR1 and ESR2 are expressed in normal lung tissue but ESR1 and its gene targets have been shown to be upregulated in PWCF compared to non-CF controls [39].

In CF, defective CFTR results in loss of normal anion transport across epithelial surfaces resulting in thick mucus accumulation. CF lung disease is characterized by a vicious cycle of impaired mucociliary clearance and mucus plugging with recurrent infection and sustained excessive inflammation [40]. Sex hormones have been shown to negatively influence factors that play a direct role in CF lung disease, including airway surface liquid (ASL) dynamics and mucociliary clearance, airway infection and immune response (Fig. 1).

Impact of sex hormones on ASL dynamics and mucociliary clearance in CF

ASL is a protective aqueous film covering the airway epithelial cell surfaces which is maintained at an optimum height of 7–10 μm in normal healthy lungs [41]. Its main functions are as a barrier defense against inhaled pathogens and to facilitate ciliary beating [42]. ASL hydration relies on transepithelial Cl^- secretion, sodium ($Na+$) absorption and subsequent movement of water by osmosis. ASL height is reduced in the CF airway and is further reduced by estrogen effects on ion channels located on the apical and

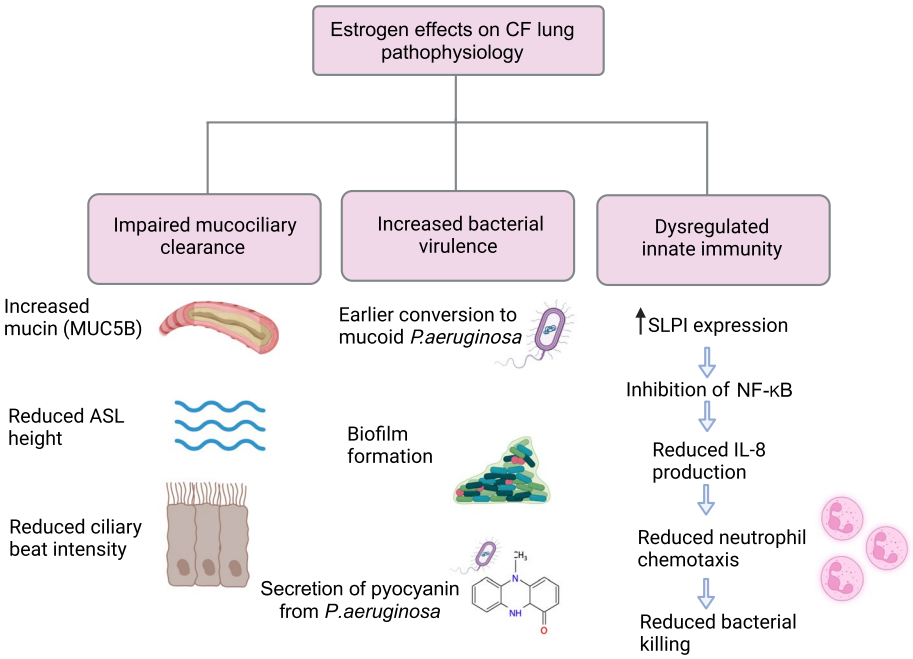

Fig. 1 Effects of estrogen on CF lung pathophysiology

basolateral cell membranes. Estrogen lowers intracellular calcium (Ca2 +) levels by inhibiting UTP-sensitive Ca2 + entry into the cell thereby reducing calcium-activated Cl^- secretion directly via calcium activated Cl^--channel (CaCC) and indirectly via calcium-dependent K + -channels [43]. Estrogen also inhibits CFTR Cl^- secretion both directly by reducing CFTR expression [44] and indirectly by inhibiting cAMP dependent K + channels [45]. Additionally, estrogen promotes Na + absorption via EGFR transactivation and PKCδ-mediated ENaC insertion leading to increased Na + and water absorption and airway surface dehydration [46]. The cumulative effect being decreased ASL height and increased mucus viscosity with resultant impaired mucociliary clearance. While less studied, the progesterone receptor (PR) has been shown to localise to motile cilia of airway epithelia, and progesterone to inhibit ciliary beat frequency [47]. Interestingly, this effect was blocked by concurrent exposure to estrogen suggesting that the relative balance of sex hormones could influence airway epithelial function [47]. In addition to female sex hormones impairing mucus clearance, estrogen binding to ESR1 in airway epithelial cells increases mucin (via upregulated MUC5B expression) production from the submucosal glands [48]. The combination of suboptimal mucociliary clearance and hypersecretion of mucus results in mucus plugging in CF airways, predisposing to recurrent infection and inflammation.

Impact of sex hormones on airway infection in CF

Bacterial colonisation and infection leading to PEx are a major complication of CF lung disease. As previously mentioned, female PWCF become colonised with airway bacteria earlier and have increased rates of PEx [17, 32, 33]. *P. aeruginosa* is an opportunistic pathogen, known to employ numerous virulence factors to promote its persistence in the CF airway. The microenvironment of CF lungs can induce non-mucoid *P.aeruginosa* to produce alginate, converting it the more virulent mucoid form, which is associated with accelerated lung function decline and increased morbidity [32, 34]. The MucA gene is a key regulator of alginate biosynthesis and when mutated by exposure to hydrogen peroxide permits mucoid conversion [34]. Female PWCF acquire both non-mucoid and mucoid *P. Aeruginosa* younger than males [32, 49, 50] which is likely explained by the presence of a steroid binding protein present in *P. aeruginosa* which has a higher affinity for estrogen than other steroid hormones [51]. When studied by Chotirmall et al., estrogen and not testosterone, was found to drive mucoid conversion in *P. aeruginosa* through alginate production and selection of MucA mutations, facilitated by estrogen-induced hydrogen peroxide production [34]. *P. aeruginosa* further evades host defenses and antibiotics by forming a biofilm which provides an extracellular matrix

that enhances pathogen adherence. Estrogen has been shown to support biofilm development through its effects on alginate and inhibition of lactoferrin (LTF), an antimicrobial peptide [52, 53]. Tyrell et al. investigated the effect of estrogen on a number of known *P.aeruginosa* virulence factors and found that estrogen induced bacterial motility observed as swarming and twitching, adherence to bronchial epithelial cells and secretion of pyocyanin, a potent toxin with downstream immunomodulatory effects [49, 54]. This ability of estrogen to modify bacterial behavior selects for a more virulent, difficult to treat form, which may contribute to lung disease progression and mortality in female PWCF (Fig. 1).

Impact of sex hormones on airway inflammation and immune response in CF

Estrogen receptors are expressed by numerous immune system cell types, including T-cells, B-cells, dendritic cells, macrophages, neutrophils and natural killer cells [55]. As such, estrogen plays a complex immunomodulatory role, suppressing inflammation in some situations while enhancing it in others. T-cells form part of the adaptive immune response and are responsible for recognizing and responding to pathogens. Females have greater T-cell numbers than males [56]. Interestingly, regulatory T-cell numbers increase during the follicular phase (estrogen high) of the menstrual cycle before falling in the luteal phase (estrogen low), indicating that immune responses may vary in accordance with the menstrual cycle [57]. Estrogen inhibits the expression of CD16 on monocytes and macrophages, leading to a decrease in the production of proinflammatory cytokines IL-1β, IL-6, and tumour necrosis factor (TNF), as well as reduced bacterial killing [58]. The net effect of androgens on adaptive immune function is suppressive with less T- and B-cell proliferation [59]. Testosterone suppresses the innate immune response by suppressing expression of Toll-like receptor 4 by macrophages and monocytes [60].

Clearly the effects of sex hormones on different immune cells has implications on disease outcomes for both sexes. In CF, estrogen downregulates the innate immune response via inhibition IL-8 which is responsible for neutrophil chemotaxis. It does this via increased expression of secretory leukocyte protease inhibitor (SLPI) in bronchial epithelial cells resulting in the downregulation of IL-8 production via the Toll-like receptor (TLR)–nuclear factor-κB (NF- κB) signaling pathway [61] (Fig. 1). In addition to reduced neutrophil chemotaxis, estrogen can also impair neutrophil mediated bacterial killing. Wang et al. described this in a *P.aeruginosa* infected CF mouse model. They reported elevated levels of IL-17 and IL-23, indicative of neutrophil oxidative burst, but an overall increased bacterial burden compared to controls [52]. This suggests increased host inflammation without effective bacterial clearance with a presumed net effect of increased lung injury.

Impact of sex hormone variation on pulmonary outcomes in CF

The direct relationship between sex hormones and pulmonary function remains unknown but evidence suggests variability in lung function throughout the menstrual cycle [62]. Studies have shown a higher percentage predicted forced expiratory volume in one second (ppFEV1) during the luteal phase compared to during ovulation [63]. PEx are more frequent during high estrogen states with the majority occurring during the follicular phase of the menstrual cycle [34]. In addition, post-pubescent female PWCF experience greater exacerbation rates than male PWCF, with a trend towards a greater rate of lung function decline [33].

Given the apparent adverse effects of estrogen surges on airway inflammation and infection in CF, it might be reasonable to hypothesize that altering the physiological rise and fall of estrogen and progesterone with a hormone based oral contraceptive pill (OCP) would have a positive effect on clinical outcomes. In fact, the evidence for this is conflicting. A small prospective study comparing ovulation phase ppFEV1 pre and post OCP demonstrated an improvement in ppFEV1 of 2.5% after commencing the OCP and a significant reduction in sputum bacterial load and inflammatory markers once an OCP was initiated [62]. Similarly, a retrospective analysis of adolescent females with CF showed that at 18 years old, the ppFEV1s in females taking an OCP for three or more years was higher than in those who were not taking an OCP (85% vs 71%) [64]. They did not find a significant difference in the rates of nebulised antibiotic usage or hospitalisations for PEx between the two groups [64]. A study of the Irish CF registry found a statistically meaningful reduction in antibiotic usage (used a surrogate marker for PEx) among females taking an OCP [34]. Conversely, a large retrospective analysis of 700 female failed to demonstrate statistically significant differences in rates of antibiotic usage or FEV1 decline in females taking the OCP [65]. These discordant results may in part be due to the array of OCP formulations with varying concentrations of sex hormones available. There is a need for additional studies to address this conflicting data, which in addition to assessing the potential impact of estrogen, should also investigate the impact of progesterone and sex hormone level fluctuation on pulmonary outcomes.

Pregnancy is a period where estrogen and progesterone are both elevated. In relation to impact of pregnancy on CF clinical outcomes, studies have overall demonstrated no significant difference in lung

function decline between pregnant and non-pregnant PWCF [66, 67]. Despite demonstrating that pregnancy did not impact lung function decline in female PWCF, the Epidemiological Study of CF did show increased PEx rate, health related visits and intravenous antibiotic days in pregnant PWCF versus non-pregnant PWCF [68]. This is most likely a consequence of multiple factors including increased frequency of follow-up and lower threshold for aggressive treatment for PEx in pregnant PWCF. However, it does further support the theory that high estrogen states negatively impact pulmonary health outcomes in female PWCF.

There is limited information on the natural course of the menopause transition for female PWCF, given estrogen levels decline it might be assumed clinical outcomes improve. In non-CF postmenopausal females, studies have demonstrated an association with a drop in lung function and accelerated rate of lung function decline during the menopause transition [69, 70]. This may be related to sex hormone fluctuations during the menopause transition, with some females experiencing an initial rise in estrogen before it declines [71]. A 2023 study in the United States (US) surveyed female PWCF across several centres, identifying 39 perimenopausal or postmenopausal participants, 97% of which reported experiencing typical menopausal symptoms. Importantly, 30% of participants reported experiencing worse CF symptoms during menopause and 42% in the post-menopause phase. Clinical parameters such as lung function or weight were not recorded but given the association of menopause onset and CF symptom deterioration there is a probable impact of sex hormone variation on pulmonary health outcomes that requires further research.

In summary there is convincing data from in vitro studies that sex hormones influence CF lung disease pathophysiology, playing a potential role in the sex differences seen in CF. In particular, estrogen driven mucous production, diminished ASL height and impaired mucociliary clearance are compounded by estrogen mediated dysregulated immune response to virulent bacterial pathogens. This in turn may lead to increased PEx and as such worse outcomes for female PWCF (Fig. 1). It is important however to acknowledge the conflicting clinical data discussed, highlighting the limitations of in vitro mechanistic studies which may not fully reflect the complexity of in vivo physiology. The interplay with other sex hormones including progesterone requires consideration, in addition to the potential contribution of other endocrine and metabolic pathways to the sex disparity in CF outcomes.

Impact of CFTR modulator therapy on sex disparity in CF outcomes

The overall survival of PWCF has dramatically increased with the regulatory approval of genotype-specific therapies (CFTR modulators), focused on restoring the defective CFTR protein expression and functionality. The CFTR modulators in current use consist of two main groups, potentiators, such as Ivacaftor, which improve the function of the ion channel at the cellular surface and correctors such as Lumacaftor, Tezacaftor and Elexacaftor, which improve protein folding and allow trafficking to the cell surface [72, 73]. In 2012, Ivacaftor was the first HEMT approved for use in PWCF with a single G551D variant [74]. The most recent combination therapy, Elexacaftor/Tezacaftor/Ivacaftor (ETI) is approved for PWCF with a at least one copy of F508del [75–77], meaning 80% of PWCF in Europe, are now genetically eligible for HEMT. ETI has been demonstrated to be the most efficacious combination to date with unprecedented improvements in sweat chloride concentration (41.8 mmol reduction) and clinical predictors of disease severity including lung function (ppFEV1 14.3% higher) PEx rate (63% lower) and BMI [75–77].

In the era of HEMT, a key question is whether the sex disparity in CF outcomes will persist. Interestingly the most recent 2023 UK CF registry report demonstrates the gap in predicted survival of male and female PWCF is narrowing [20]. This is promising, but it will take some time before the potential survival benefit conferred from long-term treatment with HEMT can be accurately assessed. The impact of CFTR modulators on sex differences in outcomes is largely dependent on the underlying mechanisms and the degree to which CFTR dysfunction contributes (Fig. 2). CFTR correction in the lungs could help reduce the sex disparity as data shows that time to death post-lung transplant in CF was similar for both sexes, despite females undergoing transplant at a younger age [78]. To explore this theory further, sex specific clinical response to treatment needs to be assessed, of which there is limited data. As Ivacaftor has been in use for over 10 years, Holtrop and colleagues used data from the United States CF Foundation Patient Registry (CFFPR) to evaluate whether sex differences in outcomes persist following its initiation. They compared changes in key markers of disease severity; lung function, PEx rate and presence of *P.aeruginosa*, in male and female patients before and after Ivacaftor initiation. Male PWCF demonstrated a greater decline in PEx than female PWCF following Ivacaftor treatment, with no significant difference seen in rate of lung function decline or presence of *P.aeruginosa* [79]. Similar findings following ETI initiation were described in a 2023 study by Wang et al. assessing the impact of ETI on clinical outcomes based on sex.

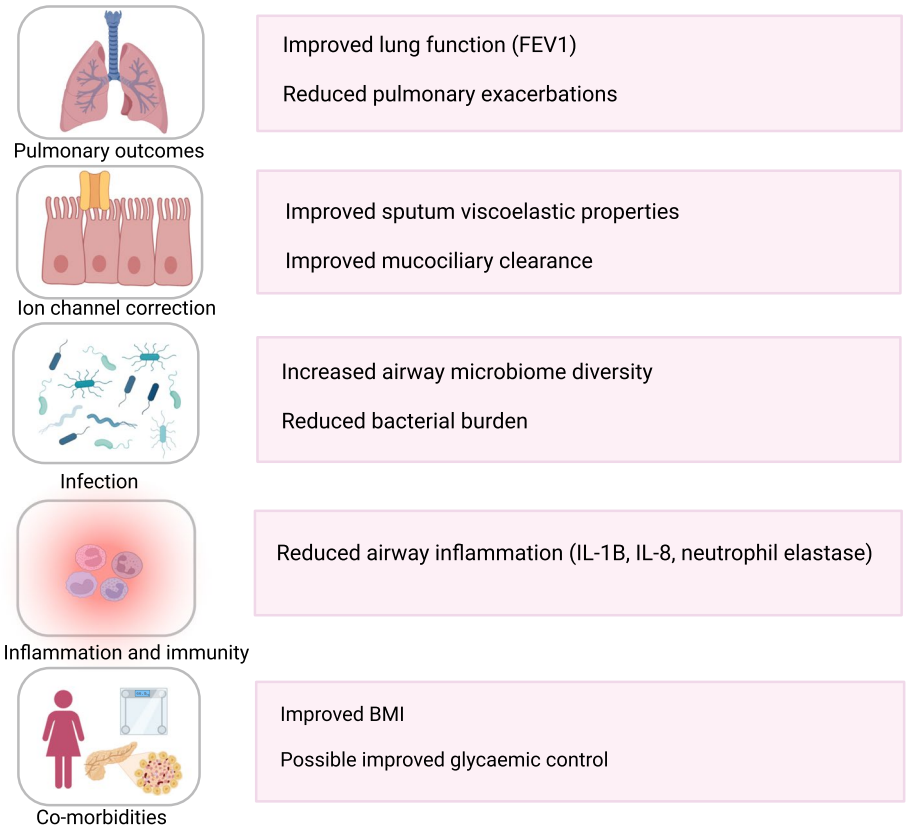

Fig. 2 Potential impact of CFTR modulators on sex disparity in CF

This single centre study of 251 PWCF, also reported that females continue to have more PEx than males (25% reduction compared to 43% reduction). In addition, they found that post-ETI, the presence of *P.aeruginosa*, change in BMI or ppFEV1 did not significantly differ by sex [80]. Interestingly, as the change in lung function pre- and post-ETI can be attenuated by prior CFTR modulator use, this group carried out a sub analysis on ETI-naïve PWCF. This demonstrated a trend towards males achieving greater improvements in ppFEV1 after starting ETI [80]. As aforementioned, sex differences in PEx rates between female and male PWCF are well established, with sex hormones implicated given the post-puberty onset [33]. This persistent difference in PEx rate despite initiation of HEMT is highly relevant given the association of PEx with accelerated loss of lung function and earlier mortality [28, 81]. It suggests female PWCF may continue to have worse clinical outcomes than male PWCF despite ETI and that further research to elucidate the potential mechanisms remains of critical importance.

We have highlighted in the previous section how sex hormones contribute to the sex disparity in outcomes via influence on key areas implicated in CF lung disease pathophysiology; impaired mucociliary clearance, infection and inflammation. We now consider what impact, if any, HEMT has had on these mechanisms. ETI has been demonstrated to improve sputum viscoelastic properties and mucociliary clearance following initiation of therapy [82, 83]. In terms of infection, despite showing improvements in airway microbiome diversity and reduction in bacterial load, harmful pathogens including *P.aeruginosa* persist in the upper and lower airways of PWCF on ETI treatment [84–87]. Given the described effect of estrogen on bacterial virulence factors in the CF airway, female PWCF may remain at a disadvantage in terms of bacterial infection, even with ETI treatment. In terms of inflammation, despite studies demonstrating a significant reduction in airway inflammation at 1 year on ETI treatment [83, 85], sputum inflammation markers remain above that found in healthy controls [83], and comparable to that in found in non-CF bronchiectasis, an inflammatory lung disease control [85]. In female PWCF this residual inflammatory burden may be further aggravated during high estrogen states, which have been associated with worse pulmonary symptoms and increased inflammatory markers in sputum leading to a potential increased risk of PEx [62].

Further to the impact on CF lung disease, ETI has improved extrapulmonary complications in PWCF, potentially reducing sex disparities. Notably, BMI increases have been observed in both clinical trials and real-world settings, regardless of CFRD status [76, 88, 89]. While addressing low BMI is beneficial given its association with poor health outcomes, rising reports of obesity and metabolic complications in PWCF on ETI are concerning CF care providers [22, 90]. ETI's impact on glucose homeostasis remains uncertain. Small studies have shown HbA1c improvements without corresponding changes in continuous glucose monitoring (CGM) or oral glucose tolerance test (OGTT) [91–93]. Since CFRD-related hyperglycemia is typically postprandial and transient, HbA1c's utility in this cohort is limited. Insulin remains the only recommended CFRD treatment [16], therefore, insulin requirements are a more reliable marker of disease activity. Data regarding the impact of ETI on insulin requirements is variable. Lurquin et al. reported insulin dose reductions in 88% of CFRD patients post-ETI [94], whereas Amini et al., found no significant change after three years on ETI [88].

An alternative method to assess response to CFTR modulator treatment is via sweat chloride (SC) measurement which is an accepted marker of in vivo CFTR function. It is used in clinical trials and in many CF centers to monitor the degree of CFTR restoration following modulator initiation [80, 95–97]. A study by Secunda and colleagues in PWCF commenced on Ivacaftor reported a greater decline in SC in females following treatment initiation [98]. This was further supported by a study assessing the CFTR combination Lumacaftor/Ivacaftor, which again demonstrated a greater reduction in SC in female PWCF at 6-months post treatment initiation. The reduction in SC was not accompanied by sex-specific improvements in ppFEV1 in either study [98, 99]. The interim results of CHEC-CF, a large epidemiological study assessing SC response to CFTR modulation in CF did not demonstrate any association with sex and degree of SC response [96]. In this interim analysis patients included were on Ivacaftor or dual CFTR combination therapies, no patients were on ETI [96]. In terms of ETI impact, the recent PROMISE study, a large prospective observational study of PWCF starting ETI, showed female PWCF experienced a greater reduction in SC. In contrast to previous studies, they also described a significant link between SC response and ppFEV1[100]. The novel findings in this study may be attributed to several factors, including the large sample size, genotype heterogeneity, prior CFTR modulator use, and the substantial effect sizes observed with ETI [100]. Further research is needed to fully understand whether SC can serve as an indicator of clinical response to HEMT. Additionally, it is important to explore the potential reasons behind the correlation seen between sex and SC response. This may be a result of sex-specific pharmacokinetics that may lead to variations in drug plasma concentrations, as well as possible interactions between sex hormones and drug efficacy [101]. Interestingly, a study recently identified elevated levels of miR885-5P (a microRNA) in females compared with male PWCF. The miR885-5P inhibits Ras-related C3 botulinum toxin substrate (RAC1), which is a CFTR regulatory protein. This is relevant as higher RAC1 levels are likely to lead to a greater CFTR modulator response which suggests that males may have a better response than females [102].

Summary and future considerations

While HEMT has significantly advanced CF care and increased life expectancy in the CF population as a whole, early data in this field suggests sex specific disparities persist. Given these therapies remain relatively new in terms of duration of widespread use, longitudinal data is required to appropriately address this question. There is convincing data supporting sex hormones as a key driver of the sex difference in clinical outcomes seen in CF, that warrants further research. A particular area of importance is the relationship with airway infection and inflammation and how this may explain the persistent higher PEx rate in female PWCF following ETI. It will be important to assess whether there is a difference in female PWCF initiated on therapies as adults with established disease, versus children, who with early initiation of modulator therapy may stand to have no CF associated lung damage. In addition, assessing what impact ETI has, if any, on key timepoints associated with hormonal fluctuations including puberty and menopause is necessary. A prospective study Maternal and foetal Outcomes in the Era of Modulators (MAYFLOWERS) study is ongoing, designed to help address some of these pressing questions related to pregnancy and CFTR modulator therapies (NCT04828382). It is likely that in some female PWCF additional therapies will be needed. Thus, further research on the efficacy of hormone-based therapies and the potential of additive anti-inflammatory therapies targeting downstream pro-inflammatory consequences mediated by estrogen receptor activation is required.

Finally, the sex specific response to CFTR modulator therapies requires further investigation including sex-specific data on drug pharmacokinetics, dosing and adverse events including during times of hormone level variation such as menstruation, pregnancy and menopause. The aim of which to inform prescribing and sex-specific clinical guidelines and a more personalized approach to treatment.

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E.McN and M.C wrote the manuscript text and E.McN prepared Fig. 1 and Table 1. All authors reviewed the manuscript.

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Competing interests
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