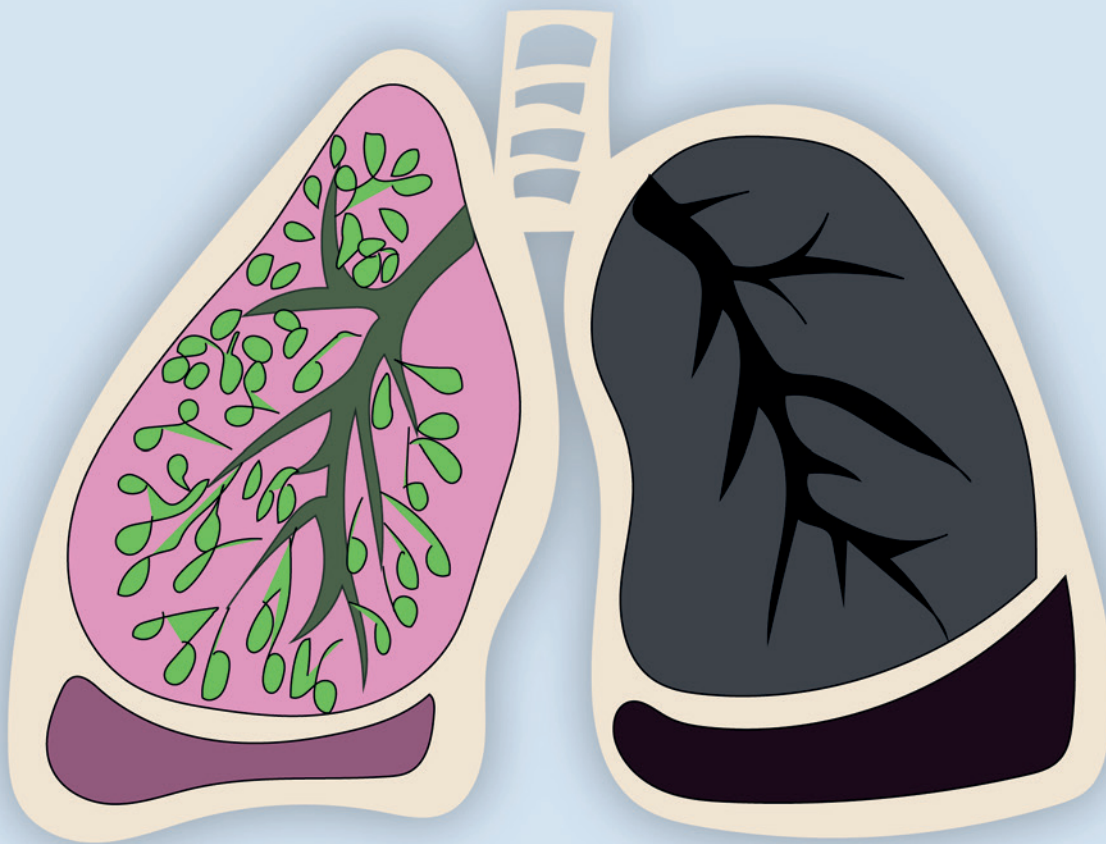




Key points

- CF and non-CF bronchiectasis are complex, multifactorial chronic pulmonary diseases with gender-specific differences in their prevalence, clinical presentation and disease severity.
- Microbiology and host physiology (immune and inflammatory responses) are essential aspects of bronchiectasis that are influenced by gender.
- Sex steroid hormones vary in type, fluctuating pattern and concentration throughout life and between the genders with a potential central role in bronchiectasis-related gender differences.
- Gender-focused clinical and/or therapeutic intervention has the potential to narrow the observed gender gap occurring in bronchiectasis-related lung disease.

Educational aims

- To summarise the existing knowledge base of gender-related differences in CF and non-CF bronchiectasis.
- To highlight key areas of importance in the diagnosis, monitoring and treatment of bronchiectasis that is amenable to clinical and/or pharmacological intervention to narrow the existing “gender gap”.



Gender differences in bronchiectasis: a real issue?

Gender differences in chronic respiratory disease, including cystic fibrosis and non-cystic fibrosis bronchiectasis are clinically apparent and of increasing importance. Differences in disease prevalence, severity and outcome are all described, however, the precise cause of the gender dichotomy and their associated underlying mechanisms have been poorly characterised. A lack of dedicated clinical and epidemiological research focused in this area has led to a paucity of data and therefore a lack of understanding of its key drivers. Diagnosis, disease pathogenesis and treatment response are all complex but important aspects of bronchiectasis with an evident gender bias. Broadening our understanding of the interplay between microbiology, host physiology and the environment in the context of chronic lung diseases, such as bronchiectasis, is critical to unravelling mechanisms driving the observed gender differences. In this review, epidemiological, biological and environmental evidence related to gender in bronchiectasis is summarised. This illustrates gender differences as a “real issue” with the objective of mapping out a future framework upon which a gender-tailored medical approach may be incorporated into the diagnosis, monitoring and treatment of bronchiectasis.



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CF and non-CF bronchiectasis are complex multifactorial chronic pulmonary diseases demonstrating gender differences in their prevalence, severity and infections, some of which are attributable to sex hormones <http://ow.ly/beDf30jsek4>

Cite as: Vidaillac C, Yong VFL, Jaggi TK, *et al.* Gender differences in bronchiectasis: a real issue? *Breathe* 2018; 14: 108–121.

Increasing epidemiological and biological evidence supports the influence of gender on disease pathogenesis and patient outcomes [1–3]. Sexual dichotomies plague most chronic respiratory disease states including asthma, chronic obstructive pulmonary disease (COPD) and bronchiectasis. Gender-related differences are described in disease prevalence, severity and outcome [1, 2, 4, 5].

Bronchiectasis is a complex multifactorial chronic respiratory disorder characterised by an abnormal, permanent and irreversible dilatation of bronchi. This anatomically abnormal state is accompanied by persistent airway inflammation, a chronic cough and excessive mucopurulent secretions [6, 7]. A key genetic related cause of bronchiectasis is cystic fibrosis (CF); a progressive

multi-systemic disease caused by a mutation to the CF transmembrane conductance regulator (CFTR), which codes for an apically based chloride ion channel. In addition to CF, bronchiectasis may also be driven by a range of non-CF related disorders or be idiopathic [8–11]. The diagnosis and management of CF-related bronchiectasis has matured. Significant improvements in radiology, awareness and specialist non-CF bronchiectasis services, including the publication of consensus international guidelines for its diagnosis and management, have all contributed to the increased prevalence of non-CF bronchiectasis [11, 12]. Despite this, delayed diagnosis or misdiagnosis remains a key issue affecting both CF and non-CF bronchiectasis [6, 7, 13].



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Age and ethnicity are recognised as independent risk factors for respiratory diseases including CF and non-CF bronchiectasis [14–16]. Importantly, gender also plays a central role (figure 1) [1, 17–19]. In CF, higher male prevalence is observed across age categories [5, 8, 27]. Conversely, in non-CF bronchiectasis, females are more likely to present earlier, while males surpass them in older age categories [1, 17, 28–30]. In terms of disease severity, females are reported to have more severe disease, poorer clinical outcomes, worse lung function and a survival disadvantage compared to males across all age groups in both CF and non-CF related bronchiectasis (figure 2) [1, 3, 31].

The sexual dichotomy in bronchiectasis is multifactorial. Inherent gender differences in lung anatomy affect the susceptibility to chronic lung diseases such as bronchiectasis [37]. Females have smaller lungs but importantly smaller conducting airways, a pseudostratified ciliated epithelial tissue with mucus-secreting properties [4]. Lung

physiology, and specifically microbiota composition, affects the severity and progression of chronic respiratory disease states with observed gender differences [1, 38]. The respiratory microbiome appears to have sex-specific signatures and is susceptible to a range of host immune and inflammatory consequences [39, 40]. Continuous chronic inflammation is reported as more deleterious in females potentially contributing to greater tissue damage and their observed worse disease severity [41].

Differences in genetics and sex steroid hormones, both type and concentration, are key components to the gender dichotomy observed in human health and disease [42]. These factors govern host physiology, immunity, microbiota and psychological or social behaviour [17, 43]. Women experience greater hormonal change through menstrual cycling, pregnancy and menopause over a lifespan and concentrations are generally higher than males. Hormone type and concentration are

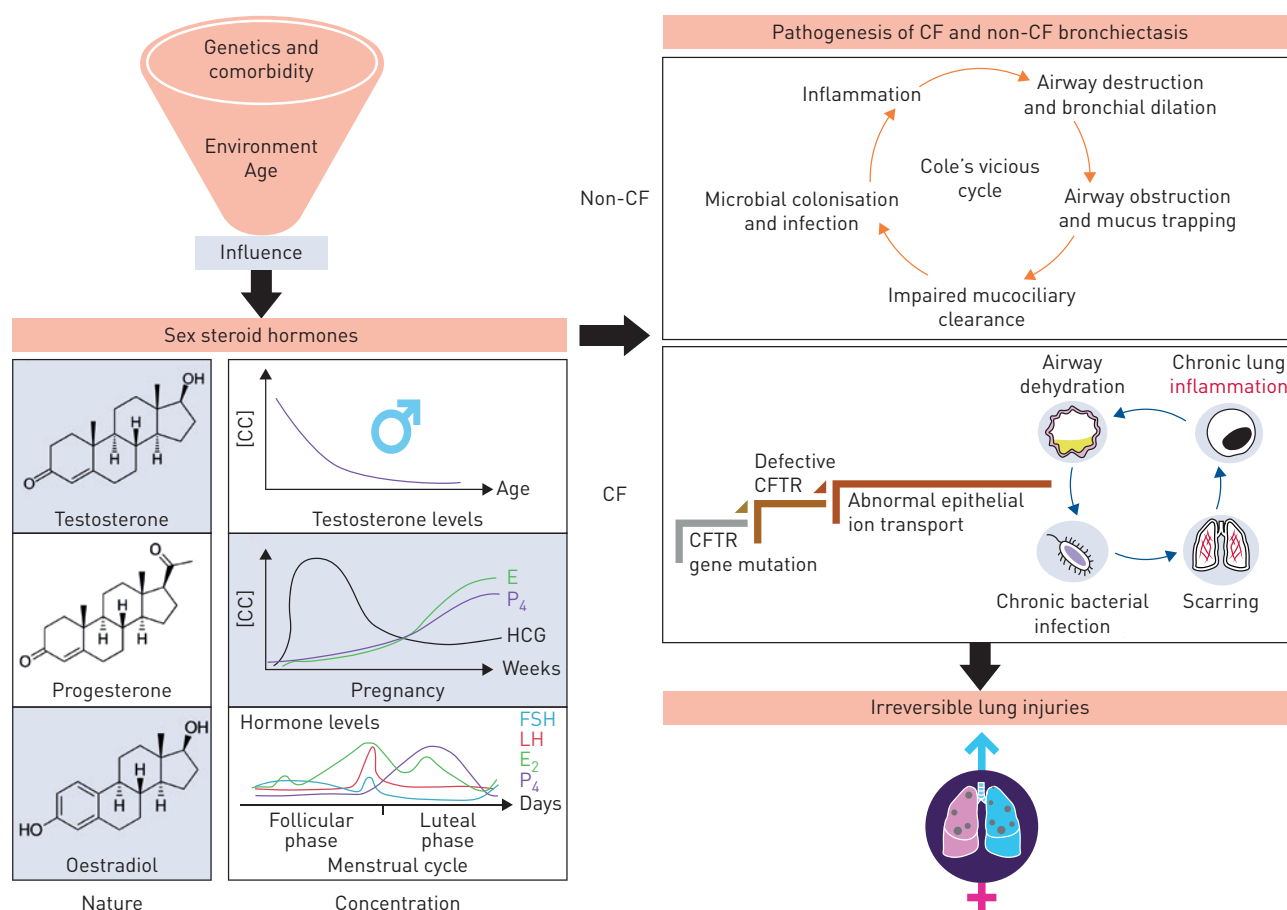


Figure 1 The pathophysiology of bronchiectasis may be influenced by sex steroid hormones, which potentially account for some of the observed gender dichotomy in CF and non-CF bronchiectasis. Bronchiectasis is the result of a “vicious cycle” of chronic inflammation and infection that leads to frequent and recurrent exacerbations [6, 7]. Sex steroid hormones potentially play an important role in the pathophysiology of the disease through anatomical variation, regulation of lung function and altering microbiota composition, as well as influencing host immune and inflammatory response [19, 20, 21, 22–24]. Age, environmental factors and comorbidities are also important key components, directly or indirectly affecting the nature and concentration of sex steroid hormones [CC] and, therefore, potentially influencing gender differences observed in bronchiectasis [19, 20, 21, 22–26]. E: oestrogens; FSH: follicle-stimulating hormone; LH: luteinizing hormone; HCG: human chorionic gonadotropin; E₂: oestradiol; P₄: progesterone.

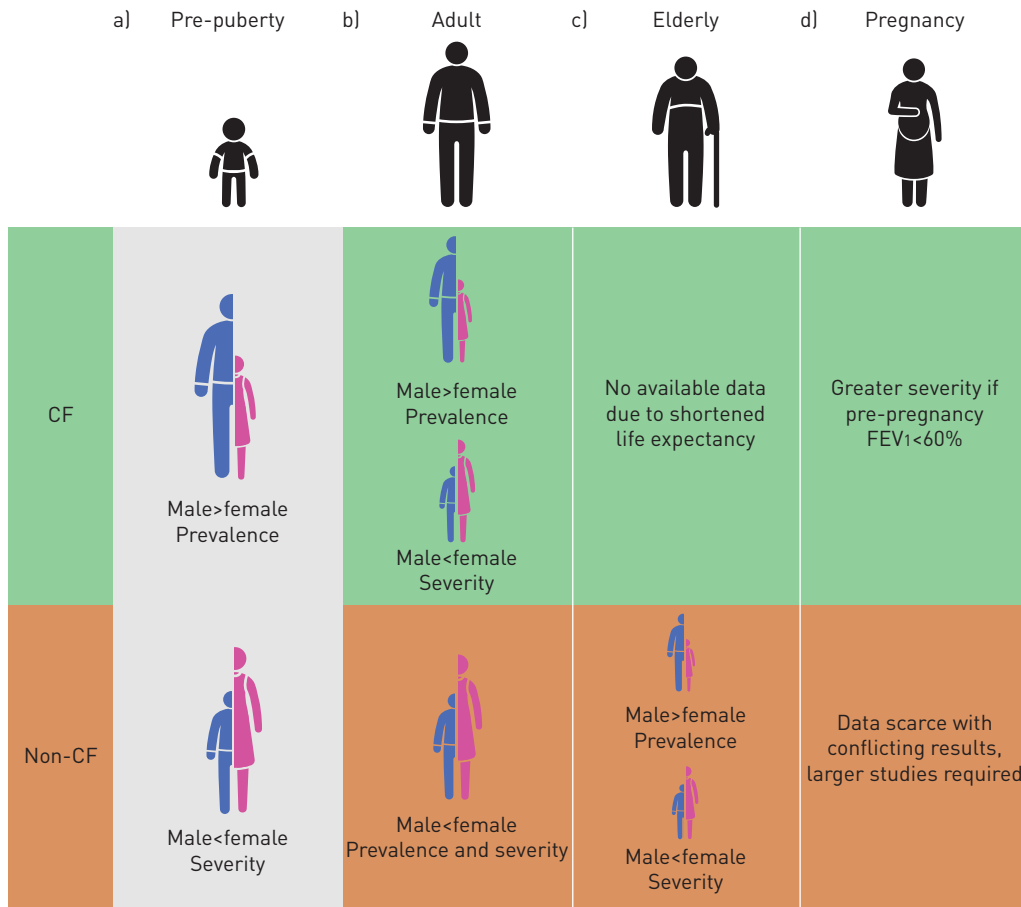


Figure 2 A summary of known gender differences in the prevalence and severity of CF and non-CF bronchiectasis by age and during pregnancy. Areas with no or sparse data are indicated. a) While data are sparse in paediatric populations, bronchiectasis confirmed by high-resolution computed tomography scans of the thorax suggest a 2:1 male:female ratio in patients aged <18 years [1, 18, 32]. b) Severity of bronchiectasis is greater in females than in males [1, 3, 31]. Prevalence of CF is reported to be higher in males, while females surpass males in non-CF bronchiectasis [3, 13, 20, 53, 54]. c) Prevalence and severity data are not available in the elderly due to a shortened life expectancy in CF. In non-CF bronchiectasis, prevalence is higher in males, although females present with clinically more severe disease [18, 21, 22, 33, 34]. d) Pregnancy is increasingly reported in CF patients. Although severity of the disease appears similar in pregnant and non-pregnant patients, poorer lung function prior to pregnancy appears to be a risk factor for complications and worse clinical outcomes during pregnancy [35, 36]. FEV₁: forced expiratory volume in 1 s.

thought to play crucial roles in disease pathogenesis and severity and therefore represent potential therapeutic targets to address gender-related disparities in respiratory medicine.

In this review, we present the current evidence base to support gender-related differences in prevalence, severity and treatment response in CF and non-CF bronchiectasis. Sexual dichotomies in bronchiectasis microbiology will be discussed, with specific focus on *Pseudomonas aeruginosa*, a major pathogen in bronchiectasis. The role of sex steroids on its regulation and that of the resident lung microbiota will be addressed. Potential clinical and therapeutic interventions to narrow the “gender-gap” will be outlined to map out a future framework upon which gender-tailored medical approaches may be incorporated into the diagnosis, monitoring and treatment of CF and non-CF bronchiectasis.

Gender differences in CF and non-CF bronchiectasis

Disease prevalence, severity and treatment

Bronchiectasis is characterised by the interplay between infection, inflammation and immunity, leading to airway damage and infection. It is the hallmark of lung disease in CF, where abnormal CFTR function dehydrates the airway lumen, thickens secretions and impairs mucociliary clearance, which in turn increases the risk of microbial colonisation and infection [44]. Non-CF bronchiectasis is similarly complex and its multifactorial pathogenesis has highly variable clinical presentations that sometimes overlap with other respiratory disease states [30]. Repeated

cycles of infection and inflammation coupled to mucus hypersecretion leads to obstruction and collapse of smaller airways further perpetuating more bronchiectasis (figure 1) [45].

CF-related bronchiectasis is predominantly a Caucasian disease, with highest prevalence reported in Europe, North America and Australia [44, 46]. CF is more prevalent in males across all age groups (figure 2) [31]. However, the prevalence of non-CF bronchiectasis varies with age, ethnicity and geography [14–16]. Recent work estimates a prevalence of 370–566 per 100 000 of the population in the USA and Europe; however, prevalence in the Asia-Pacific region is less certain due to a lack of published data. Frequencies are expected to be up to four-fold higher; however, existing data from Hong Kong and Australia are in contrast to this [17, 33, 47–49]. Non-CF bronchiectasis is an age-associated disease with highest prevalence in the age group >75 years [13]. Rates are higher in populations with poor healthcare access or significant childhood pulmonary infection [50].

Gender differences in bronchiectasis are reported [2, 19, 31, 38, 51, 52]. Females with CF have more severe disease, poorer lung function and earlier *Pseudomonas* colonisation and conversion to its more aggressive mucoid form [3, 20, 53, 54]. Females with non-CF bronchiectasis are more likely to present with disease especially that which is idiopathic or associated with asthma [13]. Prevalence of non-CF bronchiectasis is reported to be higher in males, especially when aged ≥ 65 years [18, 28, 29, 33, 34]. Explanations put forward include the overall lower life expectancy of females and higher proportions of smokers with COPD in the affected age group [29, 33, 55]. While data is scarce in paediatric populations, bronchiectasis confirmed by high-resolution computed tomography scans of the thorax suggest a 2:1 male:female ratio [1, 18].

While the prevalence of bronchiectasis is higher in males, disease is more severe in females [2, 13, 56, 57]. In CF and non-CF bronchiectasis, females have poorer prognosis [3, 5, 31, 38, 57, 58]. As early as the 1990s, the median survival in CF females was reported to be lower than that in males [59]. More recent work confirms this observation [31]. With improved overall CF survival due to advances in its diagnosis and treatment, most women now reach reproductive age and many conceive. Pregnancy brings with it fluctuating hormonal states and additional physiological stresses. In a study by COHEN *et al.* [60] more than 30 years ago, pregnant women with CF are reported to have severe pulmonary dysfunction associated with shortened gestation periods and increased perinatal mortality rates. With advances in our understanding of CF disease and improvement in its care, more recent work has shown that pregnant women with CF in fact do not experience worse survival; however, prospective work is desired to examine the precise effect of pregnancy on

CF progression and to unravel the specific role of sex hormones in pregnancy [35, 36]. Work performed by our group illustrates that oestrogen as 17β -oestradiol impairs immune responses in the CF airway and has a role in the mucoid conversion of *P. aeruginosa* [20, 61]. In addition, associations between oestriol, the major oestrogen during pregnancy, and airway *Pseudomonas* including its mucoid conversion post pregnancy have been suggested but require further exploration [20]. The role for hormones as modulators of CF disease is further suggested by fluctuating lung function and nasal potential differences over the course of a menstrual cycle, observations discussed later in this review [20, 21, 62, 63]. As non-CF bronchiectasis usually presents in females who have undergone the menopause, the role of oestrone, the major oestrogen of menopause, should be investigated in future studies as currently no evidence exists to link hormones to the severity of non-CF bronchiectasis in affected females.

There is little data available addressing the impact of gender on treatment responses in bronchiectasis [64]. A recent CF study focused on evaluating the lung microbiome as a marker of response to aztreonam did report gender-associated differences in treatment response and lung microbiome diversity [64]. Importantly, treatment adherence differs between genders with females demonstrating poorer overall adherence [65–71]. This likely contributes to gender-related differences in disease severity in bronchiectasis, for instance, significantly less women use inhalers appropriately and have poorer attendance at follow-up appointments for treatment and pulmonary rehabilitation [1, 72, 73].

Physical and biological mechanisms

Physical and biological mechanisms play key roles in the gender differences observed in CF and non-CF bronchiectasis. These include comorbidities, pulmonary anatomy and physiology, chronic infection and inflammation, impaired host defences and other environmental influences (figure 1) [74]. Many mechanisms are reported to the disadvantage of women with CF and non-CF bronchiectasis. These include earlier bacterial colonisation and conversion to mucoid *P. aeruginosa* phenotypes, nutritional deficiencies and disorders, delayed diagnoses, greater comorbidities and socio-cultural disparity [14, 51].

Sex-related differences in respiratory tract structure, function and microbiome composition predispose females to earlier infection. Females have smaller lungs and therefore smaller conducting airways. Goblet cells located at the surface of pseudostratified ciliated epithelia are responsible for mucus production and oestrogen regulates MUC5B gene expression augmenting mucin production [4, 75]. In addition, the female sex

hormones oestrogen and progesterone influence airway cilia beat frequency and function thereby affecting the mucociliary escalator [76]. Changes to the pathogenicity of CF-related pathogens correlates with clinical outcome and patient survival. Colonisation with *P. aeruginosa*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Aspergillus* species and non-tuberculous mycobacteria (NTM) occur in females at younger age, and correlate with lower life expectancy [31]. In NTM associated non-CF bronchiectasis, gender associations are observed with particular species: *M. kansasii* in men and *M. avium intracellulare* in women [77, 78]. Studies in mice reveal that lower oestrogen levels predispose to *M. avium intracellulare* lung infection, a potential association with the post-menopausal state [79]. One particular NTM-associated bronchiectasis phenotype coined Lady Windermere's syndrome is typically found in white, lean and tall women [80]. The recognised sex-related differences in microbial colonisation, infection and virulence can, at least in part, be attributed to differences in host immune response and bacterial pathogenicity; features influenced and regulated by sex steroid hormones [81, 82].

Nutritionally deficient diets unsurprisingly have an adverse effect on the course of chronic pulmonary disease [83–87]. They influence body mass index and lead to deficiency states that impact host homeostasis and physiological function [87, 88]. An Australian study illustrated that men with higher fat and energy intake had a longer median survival compared to females, while vitamin D deficient states, which are of higher prevalence in women and in non-CF bronchiectasis patients, correlate with disease severity [89, 90]. The greater the deficiency in vitamin D the greater severity of the disease. Concomitant disease occurring with non-CF bronchiectasis, such as rheumatologic or connective tissue disorders, are also of higher prevalence in women and further influences the observed gender dichotomies [1].

The delayed diagnosis of bronchiectasis observed in females results in a delayed initiation of appropriate therapy, and therefore disease progression, increased exacerbations and earlier microbial colonisation with *Pseudomonas* and other pathogens [17, 27, 91]. Gender bias in the diagnosis of CF and non-CF bronchiectasis is reported [27, 34, 91, 92]. In a study by Lai *et al.* [27], females with CF were diagnosed later. In another study, an overall delay of over a decade was observed in diagnosing non-CF bronchiectasis, with women being at a disadvantage [91]. Such differences are attributed to age of symptom onset, daily expectoration and poor pulmonary function, each illustrating gender-related differences [27, 91].

Social habits and behaviour are also important factors in gender-associated differences in bronchiectasis [56, 86]. Both impact disease manifestation and progression [56, 93]. Generally, males and females differ in perception of disease, a feature impacting their response to it [56, 93, 94].

Health perceptions are different to actual disease but have a direct bearing on quality of life [56, 86, 93, 95]. Women in general report more physical and emotional symptoms. In CF for example, patients with comparable disease based on lung function and BMI illustrate differences, *i.e.* females experience a poorer quality of life, concerns for a career and their general future [56, 86]. Males conversely scored poorly on body image perception [56, 86]. Behavioural characteristics of women with CF include a lack of participation in aerobic physical activity and limitation of their caloric intake, leading to inadequate airway clearance and nutritional deficiency [96–98]. In contrast, males participate in sports and have higher caloric intake, factors promoting better CF outcomes [86, 97, 98].

Environmental factors influence bronchiectasis outcomes. Tobacco smoking is reported to have a greater disadvantage for women, who typically experience faster pulmonary function declines compared to men, even when amounts of tobacco smoked are equal [74, 99]. The relatively smaller size of female lungs coupled to the differing detoxification approaches further translates into a greater and prolonged exposure to tobacco and its associated toxicity in females [74, 99].

The role of sex steroid hormones

Sex steroid hormones and, in particular oestrogens, have complex effects on the interaction between infection, immune function and inflammation. Oestrogen receptors are expressed on airway epithelial cells, and multiple studies have evaluated their effect on CF-related bronchiectasis [19–24]. Oestrogens directly regulate goblet cell expression and impact the post-translational modification of mucin, a key component of mucus [100, 101]. Both oestrogen and progesterone, through functional regulation of ion transporters, further dehydrate the airway-surface liquid, a crucial ingredient for optimal mucociliary clearance, which when impaired confers a susceptibility to microbial colonisation and infection [62, 102–106]. Testosterone and female sex steroid hormones also differentially regulate levels of CFTR expression in the lungs and other organs [107, 108]. RAMLI *et al.* [107] demonstrate that testosterone increases CFTR epithelial expression, an effect reversed by anti-androgen treatment with flutamide. Similar effects with oestrogen but not progesterone have also been described [108]. In previous studies we demonstrate that immune responses in the CF airway are further compromised by oestrogen which suppresses the protective acute inflammatory burst necessary to clear bacterial infection and prevent exacerbation [61]. T-helper-17-induced inflammation, further enhanced by oestrogen, is also associated with gender-related differences in CF [24]. The inflammatory function of oestrogen in the airway is complex and tightly balanced; anti-inflammatory but also able to induce tumour necrosis factor (TNF)- α

and IL-8 and promote neutrophil oxidative burst. Ovariectomised female mice treated with oestrogen were also more susceptible to *P. aeruginosa* with greater mortality [109].

In addition to regulating lung physiology and host immune and inflammatory response, female hormones also directly affect bacterial pathogenesis. Our group has shown that oestrogen promotes the conversion of *P. aeruginosa* from a non-mucoid to a more pathogenic mucoid phenotype, one associated with lung function decline [20, 45, 57, 110–112]. This mucoid drug-resistant switch is associated with alginate over production [20, 53, 113–116]. Chronic mucoid *P. aeruginosa* infection occurs earlier in women, further supported by the premature decline in female pulmonary function [3, 20]. Mucoid conversion and biofilm formation are mutually exclusive events and oestrogen independently promotes *P. aeruginosa* biofilm formation through inhibitory effects on antimicrobial peptides, such as lactoferrin [24, 116].

A significant increase in female CF exacerbations occurs post-puberty as a direct consequence of menstrual hormonal fluctuation [117]. SWEZEY *et al.* [63] further illustrate that nasal potential differences, a measure of ion transport across respiratory epithelia, varies through the menstrual cycle of females with CF. In menstruating CF women, infective exacerbations associate with elevated systemic oestrogen, and mucoid *P. aeruginosa* is selectively isolated at this time [20]. Further work dissecting out mechanisms through which sex steroids regulate host physiology and bacterial pathogenicity are now warranted.

Sex hormones are delivered to host tissues through sex hormone binding globulin, which exhibits a higher binding affinity for the male hormone testosterone compared to oestrogen. Therefore, greater unbound and biologically active sex hormones are available in females potentially explaining the larger gender-related disadvantage females experience in terms of lung physiology and pathology [118]. Oestrogen exists in multiple forms: oestrone (E_1), oestradiol (E_2), oestriol (E_3) and oestetrol (E_4). E_1 is predominant in menopause, while E_2 and E_3 are most abundant in pre-menopausal and pregnant women, respectively. E_4 is found in pregnancy. The variability of oestrogen receptor affinity for the different oestrogens, their potency and subsequent metabolism can further explain potential variations in their *in vivo* biological activity across women of different age groups [119]. Endocrine-related disorders are common in CF and several studies report that up to a quarter of men with CF have low testosterone, which in turn affects disease progression through loss of body mass and bone mineral density [120–127]. High testosterone coupled to low oestradiol and progesterone are also reported in non-ovulating female CF patients with uncertain effects on disease outcomes [121].

In vivo oestrogen concentrations are affected by exogenous exposure or consumption [25, 26]. This is a relevant topic as it is now evident that synthetic and natural oestrogens entering the food chain pollute our environment [25, 26]. While consequences on human health are debated, their consequence in respiratory disease and specifically bronchiectasis is yet to be explored [25]. Certain environmental factors induce variation to their production and metabolism, which potentially contributes to gender-related disparities in bronchiectasis [128, 129].

Overall, a sufficient body of evidence now exists, particularly in CF, to suggest that the shifting hormonal state in the female airway bears a substantial effect on lung pathology and worsens bronchiectasis outcomes [117]. Hormonal therapy represents a potential strategy to improve clinical outcomes by interrupting endogenous oestrogen. In this context we demonstrated that oral contraceptive use influences the need for antibiotics in CF exacerbations [20]. Further prospective and randomised controlled clinical trials are necessary before such approaches can be clinically applicable [130].

The lung microbiome in CF and non-CF bronchiectasis

Structure and composition of the lung microbiome: is there a gender bias?

The lung microbiome is a dynamic microbial community, consisting of bacteria, viruses and fungi, each influenced by its host and the environment. There are an increasing number of studies assessing its composition and associated disease progression in bronchiectasis. Its structure, composition and diversity demonstrate marked inter-patient variability in CF and non-CF bronchiectasis [32, 131–134]. Most studies show that the lung microbiome is patient specific with its diversity dependent on patient age, lung function and bronchiectasis severity [135–139]. In cross-sectional studies assessing more than 200 CF patients (children and adults), four dominant genera were reported across age groups and include *Streptococcus*, *Rothia*, *Veillonella* and *Actinomyces* [135]. Pathogenic organisms detected include *Pseudomonas*, *Burkholderia*, *Stenotrophomonas* and *Achromobacter*. The first two dominate in older patients, while *Streptococcus* is found at high frequency in children [135]. In paediatric non-CF bronchiectasis, *Haemophilus*, *Moraxella* and *Neisseria* are more abundant compared to *Pseudomonas* and *Staphylococcus* [32]. In contrast, adults with non-CF bronchiectasis illustrate microbiome profiles dominated by *Haemophilus*, *Pseudomonas* and *Streptococcus* [140]. Other common pathogens in this setting include *Klebsiella*

pneumoniae, *Acinetobacter* spp. and *Stenotrophomonas maltophilia* [140, 141]. Importantly, lung microbiome diversity does not correlate with pulmonary function, a feature in contrast with CF. Treatment variability in bronchiectasis potentially explains the observed differences in lung microbiome structure and diversity; however, when exacerbation-associated microbiomes are assessed they surprisingly do not differ to the stable state [140, 142]. Geographic variability and antibiotic-related change to microbiome composition are other key factors for CF and non-CF bronchiectasis where antibiotic usage is high [143]. Analyses from a large CF cohort illustrates that the relative abundance of the opportunistic pathogens *Pseudomonas* and *Staphylococcus* were somewhat reduced following antimicrobial treatment, whereas commensal bacteria *Streptococcus* and *Prevotella* dramatically decreased. Following antibiotic withdrawal, the relative abundance of pathogens was restored while commensal bacteria remained in low abundance [144].

Gender differences in bronchiectasis airway microbiology and microbiome composition remains a key question with a lack of dedicated research (figure 3). In recent CF studies assessing the lung microbiome as a marker to identify responders to aztreonam therapy, gender was interestingly cited as a confounding parameter [64]. In this study, males had significantly higher Shannon diversity indices that correlated with a reduced proportional abundance of *Pseudomonas* and increased abundance of *Streptococcus*, *Dialister*, *Shuttleworthia* and *Stenotrophomonas* (figure 3). In contrast, females had a higher abundance of *Pseudomonas* and trended toward improved

responsiveness to aztreonam. Significant gender variation was detected in microbiome composition; however, the authors could not exclude the possibility that such differences were simply due to interpatient variability [64]. As discussed above, females with CF acquire and convert to mucoid *P. aeruginosa* in advance of males [20, 53, 57, 110]. Beside *Pseudomonas*, *S. aureus*, *H. influenzae*, *Achromobacter xylosoxidans*, *Aspergillus* species and NTM all occur in CF females at an earlier time-point compared to males, with the largest age differences observed with atypical mycobacteria [31]. In non-CF bronchiectasis, post-menopausal women are reported to have greater NTM susceptibility [78, 145]. In a retrospective review, *P. aeruginosa* is also described as the predominant pathogen in females with non-CF bronchiectasis, while in contrast, males were dominated by *H. influenzae* [52]. The lower abundance of *H. influenzae* in females here may be linked to the protective role of oestrogen as proposed in a separate body of research [146]. Like CF, mucoid conversion of *P. aeruginosa* appears to occur more frequently in females with non-CF bronchiectasis; however, not all studies are congruent on these findings [54, 112].

***P. aeruginosa*: a biomarker of severity in bronchiectasis and a pathogen that responds to sex steroid hormones**

Pulmonary infection is a major risk factor for the development of bronchiectasis [147, 148]. The impaired airway mucus clearance provides a

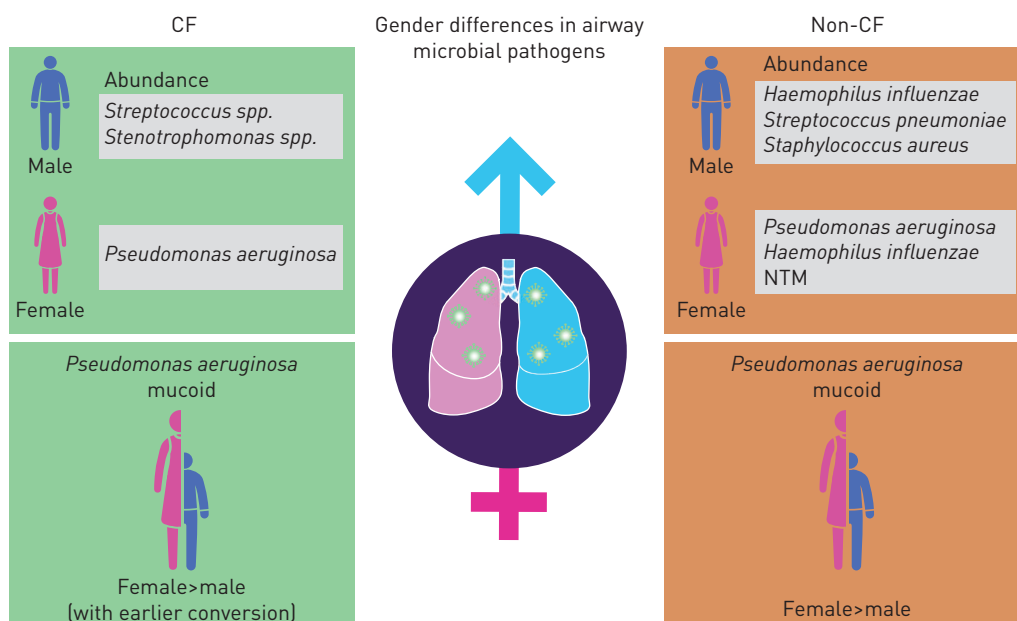


Figure 3 Gender differences in the lung microbiome in CF and non-CF bronchiectasis. The nature of respiratory pathogens predominant in patients with CF and non-CF bronchiectasis is gender specific [32, 135–138]. Females have higher risks of *Pseudomonas aeruginosa* colonisation and mucoid conversion in both CF and non-CF bronchiectasis [54, 111].

favourable environment for microbial colonisation by opportunistic pathogens, including *P. aeruginosa* [149, 150]. *P. aeruginosa* is a recognised marker of bronchiectasis severity and is associated with increased hospitalisations, exacerbations and greater mortality [141, 150–154]. This versatile genetically flexible pathogen can modulate its gene expression to increase survival potential in the presence of environmental challenges including the host immune response, oxygen depletion and the threat of antimicrobial therapy [155–159]. Excess inflammation in bronchiectasis causes oxidative stress, that itself exerts a mutagenic stress on DNA and promotes the development of hyper-mutable *Pseudomonas* strains [160–162]. Adaptive mutations aid *P. aeruginosa* persistence in lung niches [154, 157, 159, 163–165]. The detection of small colony variants in CF associates with poorer prognosis and increased levels of the biofilm signalling molecule cyclic-di-GMP, exopolysaccharide production and enhanced biofilm formation [166, 167]. In non-CF bronchiectasis, *P. aeruginosa* is the leading coloniser [140, 168]. Despite this, emerging data in CF and non-CF bronchiectasis suggest the value of comprehensive molecular analysis of this organism, particularly in the setting of multispecies communities where social interaction shapes virulence [136, 159, 169–172]. These data should be related to its potential to respond to hormones, which in turn may explain gender-related differences in the organism's genetic composition, flexibility and transmissibility [173–175].

P. aeruginosa in CF and non-CF bronchiectasis is phenotypically diverse [150, 174, 176]. It utilises a range of virulence mechanisms that all have the potential of influence by sex hormones [53, 113, 141, 156, 163, 176]. *Pseudomonas* virulence changes over time and with disease progression; for example, flagellar expression, which is essential for motility, reduces over time in CF and non-CF bronchiectasis [156, 176]. Woo *et al.* [176] illustrate that in bronchiectasis, *P. aeruginosa* strains have comparable levels of proteases and elastases and similar capacities for motility and biofilm formation. However, lipase production, an enzyme used by the bacteria to break down lipids from lung surfactant, is reduced in non-CF bronchiectasis isolates compared to CF [176].

Sex steroids, directly and indirectly, influence the pathogenesis of bronchiectasis by altering the ecological interaction between airway microbes (commensal or pathogenic) and their host (figure 1) [177]. Host hormones cross-talk with bacteria influencing their survival, virulence and pathogenesis [178–180]. Lyte and co-workers [181, 182] demonstrate that *P. aeruginosa* growth can be induced by stress hormones. Increased densities of *P. aeruginosa* promote quorum sensing, alginate production and biofilm formation, all crucial virulence traits ensuring the bacteria's persistence and survival [163, 183, 184]. Oestrogens, and 17 β -oestradiol in particular, promote *P. aeruginosa*

mucoïd conversion and emerging work suggests that the hormone (and its metabolites) may even act as quorum sensing inhibitors [31, 179, 185, 186].

Narrowing the gender gap: potential clinical and therapeutic interventions

Addressing sex-related dichotomies observed in pulmonary disease including bronchiectasis are believed to have the potential to confer therapeutic and prognostic improvements. Clinical and therapeutic interventions aimed at addressing biological and/or behavioural parameters may contribute to narrowing the emerging “gender gap” in chronic respiratory disease and infection [21]. Therefore, in addition to age, ethnicity, geography and nutrition, gender should also be considered an important factor in the management of CF and non-CF related bronchiectasis.

In bronchiectasis, females generally have worse clinical outcome, poorer lung function, more severe infections, and increased exacerbations and mortality [1, 3, 19, 187]. Improving patients' quality of life and clinical symptoms, particularly breathlessness and cough, reducing exacerbations and lowering the airway microbial load remain the core principles of bronchiectasis management [188]. However, females seek medical attention later and underestimate their symptoms, with consequences for the severity of their disease and potentially treatment response [189]. Raising awareness of bronchiectasis may reduce diagnostic delays observed in females and encouraging females to seek appropriate medical care and treatment can potentially assist in narrowing the gender gap in terms of clinical outcome [188].

Treatment approaches for bronchiectasis are complex and have been reviewed elsewhere [190–192]. Some believe that management strategies should be gender oriented; however, little data to support such an approach exists. Future studies should address differences in treatment efficacy and response between the genders and examine potential strategies to narrow the “gender gap”. Interestingly, a gender-specific aztreonam response favouring females has been reported in CF; however, reasons to explain this are unclear [64]. Gender associated differences in microbiology, pharmacology, metabolism, immune response and inflammation are all targetable possibilities. In addition to variation in antibiotic response, HEIRALI *et al.* [64] showed that anti-microbial susceptibility profiles varied between genders suggesting that further work is required to better understand the potential to stratify our antibiotic approach by gender. Anti-inflammatory therapies exhibit gender-specific effects [41]. In prior work unrelated to bronchiectasis, females with asthma or COPD report greater oral corticosteroid use but persistently worse clinical

outcomes [41]. Mechanisms driving the observed gender-related differences in bronchiectasis have important consequences for therapy. Menstrual cycle variation in asthma, for instance, is a relatively well-recognised phenotype with small studies illustrating the potential benefit of exogenous hormone administration [193, 194]. While it is unlikely that menstrual cycling influences non-CF bronchiectasis (as most disease is detected in the post-menopause state), its effect in menstruating CF patients is emerging [20, 62, 63]. Furthermore, sub-phenotypes of bronchiectasis may exist that can be stratified by gender and the dominant hormone, whether pre- or post-menopausal. Use of the oral contraceptive pill appears to lower exacerbation rates and the need for antibiotics in CF but further studies are required to confirm this [20]. Women receiving hormone replacement therapy demonstrate better immune function through increases in cell proliferation and elevated TNF- α , however, how this translates to female post-menopausal non-CF bronchiectasis remains to be established [75]. Importantly, if hormonal manipulation is to be seriously considered as a potential adjunctive therapeutic approach in bronchiectasis, their adverse long-term consequences must be examined. Tamoxifen, a selective oestrogen-receptor modulator is experimentally suggested to be of benefit in primary cell cultures from women with CF and is shown to restore the epithelial airway-surface liquid by interfering with calcium signalling [62, 106].

Research focusing on CF and non-CF bronchiectasis is clearly necessary in the context of the gender-related differences already established in these diseases. A better understanding of infection and immune and inflammatory mechanisms in relation to gender will be necessary if we are to successfully narrow the bronchiectasis “gender gap”.

Conclusion

The inherent heterogeneity in bronchiectasis, CF and non-CF represents a clinical and therapeutic challenge. The global move toward personalised medicine combined with the identification of

Self-evaluation questions

1. Gender differences exist at multiple levels in both CF and non-CF bronchiectasis such as:
 - a) Prevalence of the disease
 - b) Severity
 - c) Microbial pathogenesis
 - d) All of the above
2. As part of the sexual dichotomy observed in bronchiectasis, the female sex hormone oestrogen plays a key role in the regulation of:
 - a) Transepithelial water and ion transport in the airway, thereby modulating the viscosity of the airway-surface liquid
 - b) *Pseudomonas* mucoid conversion
 - c) Anti-inflammatory airway responses
 - d) All of the above
3. A gender gap exists at the microbiome level in CF-related bronchiectasis. Which of the following is correct about this observation?
 - a) *Pseudomonas aeruginosa* is more prevalent in males and is associated with poorer lung function
 - b) *Mycobacterium kansasii* is more prevalent in females
 - c) The lung microbiome diversity is unaffected by disease progression
 - d) *Streptococci* are relevant in observed gender-related differences

genotypes, phenotypes and other biological parameters in bronchiectasis is of great interest particularly in the context of gender-associated alterations in disease [195, 196]. There are clear gender associated differences in disease portending to worse clinical outcomes for female patients. The role of sex steroid hormones in the microbial endocrinology space is emerging and how this affects the airway microbiology in bronchiectasis is an important avenue for future work. However, a gender-tailored clinical and pharmacological approach may be necessary before we can consider this. An important recent statement by Melinda Gates must be acknowledged: “We cannot close the gender gap without first closing the data gap”. Therefore, dedicated gender-focused research is necessary to better understand its role and impact in bronchiectasis and permit us to effect appropriate intervention to address this “real issue”.

Support statement

S.H. Chotirmall is supported by the Singapore Ministry of Health’s National Medical Research Council under its Transition Award (NMRC/TA/0048/2016) and the Lee Kong Chian School of Medicine, Nanyang Technological University Start-Up Grant.

Conflict of interest

None declared.

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Suggested answers

1. d.
2. d.
3. d.

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