8 March, 2022

Advocacy statement of the European Respiratory Society on women and respiratory diseases

In all of human history, there has never been a better time to be born female[1]. The number of women dying in pregnancy or childbirth has dropped significantly. Mortality rates for girls under five have been cut in half. Women are living longer, healthier lives than ever before. Despite this, we observe a disturbing increase in many respiratory diseases among women.

More than ever, we need to consider the female aspects of respiratory disease. What are the factors behind women becoming more susceptible and experiencing more severe disease? Are societal or scientific factors more important? Do we need a special focus on the female respiratory system and lung?

This statement illustrates the situation across a selection of diseases, risk factors, diagnostics and care pathways. We have commissioned some of the Society's leading experts to summarise the position in their field. As both evidence and awareness of sex and gender differences in lung diseases increases, the case for action in this area becomes louder. The European Respiratory Society (ERS) is particularly concerned by the rise in respiratory disease in women and we call for a more intense focus at all levels to address this.

Our recommendations:

- Faster fostering of research into the rise of respiratory disease in women**.**
- Prevention, diagnosis and treatment of respiratory disease requires the implementation of sex, gender and diversity sensitive best practices and guidelines. Medical practice needs to urgently up the game and ERS urges a mindset change.
- New approaches to sex and gender at many levels, from medical training to clinical medicine, epidemiology, drug development and basic research are needed.
- The latest advances in precision medicine and digital health must be calibrated to effectively address female respiratory disease.
- In addition, greater inclusion of women at the highest levels of respiratory medicine must be accelerated. ERS will set up a diversity taskforce to address this and other aspects related to the modernisation of respiratory medicine.

Our findings:

- Scientific evidence suggests that gender is an important factor for the incidence, susceptibility, and severity of respiratory diseases. It has also been shown to influence key domains of research, lung health, healthcare access and healthcare delivery. Therefore, the unique biology of women must be considered while prescribing medications and treatment plans.
- Gender differences in respiratory diseases are linked to a variety of molecular, physiological and genetic factors. On a molecular level, gender differences in lung diseases are thought to be predominantly associated with sex hormones, also called sex steroids. Though the precise

[1] *The Full Participation Report,* home to 850,000 data points, spanning more than 20 years, from over 190 countries tells us that in all of human history, there has never been a better time to be born female

role of sex-specific genetic factors in the individual susceptibility to airways disease remains uncertain, an increasing number of observations point in this direction, especially in asthma and chronic obstructive pulmonary disease (COPD).

- Females are more likely to develop asthma, have a higher prevalence and are more likely to die from asthma. Several mechanisms have been suggested to explain the gender-related differences in the prevalence, pathophysiology, clinical presentations and treatment response, although definitive reasoning has yet to be elucidated.

- More significant gender differences can be observed in the clinical expression of COPD that result from various environmental, behavioural, genetic and biophysiological factors. These differences have been discussed and investigated for more than two decades; however, they have received limited attention. Yet, COPD gender variances could contribute to differences in treatment response and could facilitate a more personalised disease management.

- The gender disparities in pulmonary vascular diseases are ambivalent. On one hand, women are more at risk of developing pulmonary artery hypertension (PAH), possibly due to complex mechanisms of oestrogen and metabolism dysregulations. Nevertheless, women have better survival rates because of greater right ventricle adaptation to elevated pulmonary arterial pressure.

- Differences between genders in intensive care suggest that an understanding of the role of gender on outcomes should be multi-directional. Understanding the factors that generate these differences at genetic, molecular, clinical and social levels should improve care and access to it, for all.

- Gender differences could also be observed in the risk factors for lung diseases. For example, strategies to reduce the tobacco industry marketing and use of cigarettes / novel electronic nicotine delivery systems (ENDS) to reduce smoking-associated disease in women clearly need to consider gender and social context.

- Gender differences also persist in diagnostics and therapeutics. Gender inequalities in access to diagnostics and therapeutics are different in different parts of the world. They can depend on the structure of the society, the education level of females compared to males, on social class, and access to healthcare. While there has been more recent research into gender inequality in cardiovascular disease, very little has been published on the issue of gender inequality in respiratory diseases field.

- Finally, we must continue to strive for equity in healthcare for every patient. As we emerge into a more digital world, it will be important to assess willingness and ability to be engaged and have more equitable access to improved healthcare systems where no people, regardless of their sex, gender and background, are left behind.

Full chapters

This statement is supported by a longer paper, which compliments the new *European Respiratory Review (ERR*) series focusing on the role of sex and gender-related factors in respiratory health, and is a collaborative effort exploring the angle of sex/gender in relation to respiratory health with a particular focus on women within nine chapters dedicated to: molecular and genetic background,

asthma, COPD, interstitial lung disease, gender and pulmonary vascular diseases, intensive care, risk factors, diagnostic and therapeutic inequalities, lung cancer, and patient perspective. The full chapters are available here:

1. Molecular and genetic background

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Gender differences in respiratory diseases are linked to a variety of molecular, physiological and genetic factors [1]. On a molecular level, gender differences in lung diseases are thought to be predominantly associated with sex hormones, also called sex steroids [2, 3]. Sex hormones include androgens, estrogens and progestogens, and all classical hormone receptors (androgen receptor (AR-A and AR-B), estrogen receptor (ER-α and ER-β), progestogen receptor (PR-A and PR-B), and G-protein coupled estrogen receptor (GPER)) are present in the lung [4-7], and they play an important role in lung development, maturation and homeostasis. While most of the effects of sex hormones on the lung have been attributed to gonadal hormones, it is important to note that the lung is able to synthesize these hormones locally. Clinical and experimental animal studies support the notion that estrogen and its receptors promotes lung development and maturation [8], whereas androgens exhibit an inhibitory role. However, androgens and their receptor also support the developing lung during branching morphogenesis [7]. Moreover, testosterone, produced by the foetal testes, inhibits surfactant production, which thus starts later in male compared to female neonatal lung [9, 10]. The early appearance of surfactant in female lungs might contribute to the observed higher airflow rate and lower airway resistance compared with neonatal males [11]. Although the impact of sex hormones and their receptors at birth results in smaller female lungs with fewer respiratory bronchioles compared to males, female lung maturation is enhanced due to earlier surfactant production. Throughout puberty, menstrual cycles, pregnancy, menopause and with age, sex hormones fluctuate and may have varying effects on respiratory homeostasis (reviewed in [2, 12]). Sex hormones remain active in the lung throughout lifetime and can modulate lung function in both a beneficial or detrimental way [13, 14], thereby setting the stage for lung health and disease.

In addition to their role in lung development and maturation, sex hormones are implicated in pulmonary immune and structural cell responses [15]. Bronchial epithelial cells express both ER-α and ER-β and are thus involved in estrogen signaling [16]. Estrogens are capable of inducing nitric oxide in bronchial epithelial cells via non-genomic mechanisms and can thus potentially modulate

bronchodilation [16]. As mentioned previously, sex hormones influence the maturation of alveolar type II cells and consequently surfactant production and lung maturation in early life [9, 10]. Similar to bronchial epithelium, alveolar epithelial cells express both ER-α and ER-β, as well as AR and PR [17]. Interestingly, progesterone has been shown to influence cilia function in females, which can affect mucociliary clearance [18], and thus has large implications for the development of lung diseases. Most immune cells, including T lymphocytes express sex hormone receptors. Female sex hormones favor a T helper (Th) 2 immune responses, whereas androgens favor Th1 responses or suppress inflammation. During the luteal phase and pregnancy, estrogen levels are high and shift the immune response to a Th2 phenotype, which can have implications for asthma exacerbations, as they are often observed during these time periods [19]. It is important to note that the influence of sex hormones on immune and structural cells and their function is highly dependent on the concentration, timing, duration and context of the exposure [2, 20]. These factors can be difficult to control in clinical settings and many experimental protocols and this should be taken into account when reviewing such experimental/study protocols.

The precise role of sex-specific genetic factors in the individual susceptibility to airways disease remains uncertain, although an increasing number of observations point in this direction, especially in asthma and COPD. Genetic variability predisposing to respiratory disease has been well described in asthma and COPD pathogenesis [21-23], and recent reports highlighted the sex-specific genetic differences in both [12 14, 24, 25]. Single Nucleotide Polymorphisms (SNP) in several genes including *TSLP*, *IFNG*, *IRF1*, *RAP1GAP2*, Vitamin D receptor, and β-adrenergic receptor have been linked to sex-specific variations in asthma susceptibility and pathogenesis, and lung function [26-30]. Moreover, polymorphisms in sex hormone signaling, such as a SNP in *ESR1*, ER-α, and a missense variant in *HSD3B1(1245)* (enzyme responsible for conversion of *dehydroepiandrosterone* (DHEA) to testosterone) were associated with enhanced asthma and glucocorticoid resistance, respectively [31, 32]. Using SNP-by-sex genome wide association study *CELSR1*, a lung development gene, was recently identified to play a role in sexually dimorphic COPD susceptibility [25, 33]. However, follow-up studies are required to enhance the functional understanding of this variation.

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2. Asthma

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Asthma is a common chronic disease, affecting over 300 million people worldwide, and results in a considerable socio-economic burden [1]. Gender related differences in the prevalence and severity of asthma have been observed related to the different stages of life [2]. In the Severe Asthma Research Program, asthma was more prevalent in pre-pubertal and pubertal boys compared to girls (11.5 vs. 9.9%) [3]. After puberty, the prevalence of asthma remains similar between men and women until after 40 years of age, when it becomes more prevalent and severe in women [4], and in older years, asthma has been observed to be more severe in men [5]. Data from the American Lung Association suggest overall, females are more likely to develop asthma, have a higher prevalence and are more likely to die from asthma [6]. Several mechanisms have been suggested to explain the gender related differences in the prevalence, pathophysiology, clinical presentations and treatment response, although definitive reasoning has yet to be elucidated. A key mechanism that has been explored is airway hyper-responsiveness (AHR): a characteristic feature of asthma. Leynaert and colleagues assessed the frequency of AHR in both women and men aged 20 - 44 years and observed the metacholine provocation dose of <4mg was higher in women versus men (odds ratio [OR] 3.77, 95% confidence interval [95% CI] 2.37–6.00 in Paris; OR 1.82, 95% CI 1.14–2.93 in Montpellier) [7]. The difference between genders did not disappear after adjusting for respiratory symptoms, body mass index, and lung function. Similarly, a Canadian study reported AHR was more prevalent in women than in men and hypothesized hormonal factors, environmental conditions and tobacco smoke exposure, could explain the difference [8]. Hormonal fluctuations during different stages in life and during the menstrual cycle have, naturally, been investigated in the pathophysiology of asthma in women, although studies are not concordant in their findings. Asthma symptoms have been reported to be aggravated during the premenstrual phase, in phases within the menstrual cycle, and there are reports of worsening symptoms during the peri-menstrual phase with increased healthcare resource utilization [9, 10, 11]. Matteis and colleagues observed bronchoconstriction (decreased FEV_1) during the follicular phase of the menstrual cycle, which was associated with decreased sputum cAMP levels

[12]. Other studies, however, have not shown hormonal changes relating to fluctuations in pulmonary function and asthma symptoms [11, 13]. In post-menopausal women, Oguzulgen and colleagues observed women using hormone replacement therapy had a higher risk of a new diagnosis of asthma, or worsening symptoms of pre-existing asthma, compared to women without exogenous hormone exposure [14]. Changes in inflammatory markers have been seen and related to worsening asthma symptoms that coincide with fluctuations in physiological hormone levels, where sputum eosinophils, exhaled nitric oxide and serum leukotriene C4 concentrations have been reported to be higher in women with severe symptoms [15,16]. Exposure to tobacco smoke has been investigated to explain the gender differences. In a large multicenter study, AHR was greater in women and smoking individuals had greater AHR compared to non-smokers [17]. Gold and colleagues investigated tobacco exposure during childhood and observed those who smoked during adolescence had a 1.09% percent slower growth of FEV_1 per-year in girls (95 percent confidence interval 0.70 to 1.47), and 0.20% slower growth in boys (95 percent confidence interval, -0.16 to 0.56) when compared to non-smoking adolescents [18]. From an anatomical perspective, post-mortem data show lungs in girls are smaller and lighter than boys [19], although the FEV_1/FVC ratio is lower in boys and men than in girls and women [20], and this highlights the concept of 'dysanapsis'; that is, individuals with larger lungs do not necessarily have larger-diameter airways when compared to individuals with smaller lungs. Genetic studies have been undertaken to understand the cause of asthma and identify specific therapies, but have been inconclusive overall, without any observed gender differences [21]. Women report experiencing more symptomatic asthma with greater use of rescue medication compared to men with the same pulmonary function, resulting in a poorer quality of life and greater healthcare resource utilization [22]. Osborne and colleagues in a longitudinal study observed women aged 15–34 years reported more symptoms than men and, a similar trend was seen in those aged 35–55 years [23]. Data from the American Lung Association consistently show females have a higher asthma attack prevalence rate than males, and this has been seen year-on-year over the last two decades [6]. In summary, although gender related differences have been observed in the field of asthma, little is understood of the underlying mechanisms. Future research is needed to address the importance of the many associations seen related to gender and to determine if such differences are relevant in the everyday management of patients with asthma.

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3. Does COPD have a gender?

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Gender-related differences in airway behavior and clinical manifestations of airway disease occur across the human life span and can be attributed to both biological and sociocultural factors (1). Chronic obstructive pulmonary disease (COPD) is a progressive respiratory disease characterized by persistent irreversible airflow obstruction (2). It is one of the most prevalent health conditions and a major cause of morbidity and mortality around the globe (2). For many years men were considered to use all tobacco products at higher rates that women, and therefore COPD was regarded as a disease that mainly affected elderly men. The past two decades the number of women with COPD is growing and nowadays the mortality rate from COPD in women has surpassed that in men in the USA (2), as women with severe COPD have a higher risk of hospitalization and death from respiratory failure and comorbidities (4). Moreover, in many developed countries COPD has become more prevalent in females than males (5). Yet, women are less likely to be diagnosed with COPD than men with the same degree of lung function impairment and even though spirometry reduces the risk of underdiagnosis and gender bias, it is underused (6).

Various environmental factors may have an impact on COPD gender differences. In a study of 811 nonsmoking women in Japan, those who were exposed to environmental tobacco smoke from their husband had the lowest FEV_1/FVC (7). Moreover, a higher proportion of them had airway obstruction when compared to nonsmoking women who were exposed to environmental tobacco smoke from housemates other than their husbands (eg, parents, siblings, and dependants) (7). These findings suggest that tobacco control in husbands is the most important measure to prevent airway obstruction of nonsmoking women at home (7). Moreover, women in developing countries who cook over a wood stove for years and inhale the smoke can develop COPD and experience the same clinical characteristics, diminished quality of life and increased mortality rates as tobacco smokers (8). Similarly, exposure to cooking oil fumes may exacerbate the progression of chronic bronchitis in nonsmoking women (9).

Further evidence suggests that women experience more COPD exacerbations, having poorer health status and reporting greater dyspnea (10–12). A cohort of 22,429 COPD patients (48% women) demonstrated that despite the evidence of milder disease (as measured by lung function) at the time of COPD diagnosis, women were at greater risk of moderate or severe exacerbation with shorter time to first exacerbation and increased frequency of these events compared with men (13). The

differences were more prominent in the younger age group (40-65 years), in individuals with preexisting asthma, in GOLD groups B, C, D and in individuals with moderate to severe airflow limitation (13). Moreover, the annual rate of moderate or severe exacerbations was higher in women compared with men in the first 3 years of follow-up (13). Similarly, the TORCH study demonstrated that women had a shorter time to first exacerbation and were at a higher risk of exacerbation than men (11). A post hoc analysis from the IGNITE program also reported that a higher percentage of women had experienced at least one exacerbation in the previous year compared with men (14). The higher exacerbation rates observed in females may be attributed to differences in disease expression or differences in symptom reporting patterns (15). Indeed, women tend to report a higher degree of dyspnea, a symptom that often precedes an exacerbation (15,16). Nevertheless, they are less likely to self-medicate or seek medical assistance within 24 hours prior to emergency hospital admission because of underestimating the severity of their symptoms due to fear of stigmatization or dismissing symptoms as a "smoker's cough" (17–19). Psychologically, women with COPD demonstrate higher levels of anxiety and depression and worse symptom-related quality of life than male patients (20). Anxiety and depression also appear to increase the risk of hospitalization in women (21). On the other hand, in hospitalized patients with COPD there are significantly higher anxiety scores in women than men (21,22).

A recent analysis of the 3CIA study including data from 17,139 patients (31.2% women) from 22 COPD cohorts indicated that women were younger, had lower pack years, greater FEV1%, lower BMI and greater number of exacerbations (15). On symptoms, women reported more dyspnea, equal cough and less expectoration. Regarding prognosis, 5-year survival was higher in COPD females (86.9%) than in males (76.3%), $p<0.001$ (15). The crude and adjusted RR and 95% CI for death in males was 1.82 (1.69-1.96) and 1.73 (1.50-2.00) respectively (15). Sputum production is a strong marker for morbidity, low FEV_1 (23) and mortality (24) in COPD, and the fact that is considerably less common or lower among women with COPD may contribute to under-diagnosis of COPD among women (25).

Furthermore, gender differences can be detected in various genetic factors that may lead to the development of COPD. Alpha-1-antitrypsin deficiency (AATD) is a rare genetic condition caused by mutation of the SERPINA1 gene with clinical manifestations of COPD and liver cirrhosis (26). Data from the German AATD registry indicated that there were no significant differences in age, COPD exacerbation rate or quality of life (based on the SGRQ) between female and male AATD-COPD individuals (27). Nevertheless, the number of pack-years and BMI were significantly lower in female AATD-COPD patients and the time between the first symptom and the establishment of the correct diagnosis was significantly longer in female AATD-COPD patients (14.47 ± 16.46 years) as compared to male patents (12.39 ± 14.38 years, $p=0.04$) (27). Additionally, there is an association between accelerated telomere shortening and progressive worsening of alveolar gas exchange, lung hyperinflation and clinical outcomes in COPD patients and shorter telomeres increase the risk of all-cause mortality in COPD (28). Yet, telomere length is considered to be longer in females than males, but the association between gender and telomere length may vary by age (29).

Histologically the pattern of COPD differs between men and women, with women presenting severe COPD with relatively less emphysema (and smaller hole size) and more small airway disease (smaller lumen size and thicker airway walls) than men (30,31). COPD associated with indoor air pollution also demonstrates small airway disease than emphysema compared with COPD associated with cigarette smokers and this may indicate the predominance of this risk factor in women (32). In a study of a mouse model exposed to chronic cigarette smoke, female animals were more prone to develop small airway remodeling and peripheral airway obstruction than male animals, who developed mainly emphysema (33). However, ovariectomy and tamoxifen (estrogen receptor-α blocker) both produced

the male pattern in females, indicating that female sex hormones are responsible for these histological differences in response to chronic smoking (33). In female mice, cigarette smoke was associated with the activation of transforming growth factor-β (TGF-β), increased oxidative stress and decreased expression of antioxidants and this was reduced in ovariectomized animals or after tamoxifen treatment (33). Up-regulation of TGF-β increases the expression of NAPDH oxidase-4 (NOX-4), which produces reactive oxygen species and thus leads to lung fibrosis and airway smooth muscle proliferation (34,35). In turn, oxidative stress and reduced antioxidants increase TGF-β resulting in a vicious cycle of progressive fibrosis, accounting for the accelerated progression of COPD in females (36).

Still, most data for gender differences in COPD exist in regard to smoking. Overall female smokers are about 50% more likely to develop COPD than male smokers (33). On the other hand, women tend to smoke less than men indicating that they may be more susceptible to the lung-damaging effects of smoking (3–9). In a large Norwegian study of 954 subjects with COPD (38.9% women), when compared to males, female COPD patients demonstrated greater lung function reduction and more severe disease, despite their younger age, later age of smoking onset and fewer-pack years (38). A meta-analysis of longitudinal studies demonstrated a faster decline in lung function of female smokers aged >45-50 years as compared with male smokers (5). A systematic review of 11 studies indicated that female smokers had a faster annual decline in FEV_1 than male smokers, even when they smoked less cigarettes (8). Indeed, the airways of women are anatomically smaller for the same lung volume, and therefore there might be a proportionally greater exposure to every cigarette, as there is a greater concentration of tobacco smoke per unit area of small airway surface (40). Furthermore, females may biologically be more susceptible to the adverse effects of smoking than men, due to sex differences in cigarette smoke metabolism (different expression and activity of cytochrome P450 enzymes) (41) or due to other dimensional, immunological and hormonal determinants (1). Additionally, the gender genotype might play an important role, as in families of individuals with severe early-onset COPD, a female predominance among COPD cases was observed (42). When it comes to smoking cessation, studies have shown that women tend to quit less frequently and have a lower success in long-term smoking cessation than men (43). This may be because women tend to have less symptomatic benefit when they quit smoking (40). However, sustained female quitters have better improvement in their lung function measures (2.5 greater improvement of FEV_1% predicted than men during the first year) (44).

To conclude, there are significant gender differences in the clinical expression of COPD that result from various environmental, behavioral, genetic and biophysiological factors. These differences have been discussed and investigated for more than two decades; however, they have received limited attention (16,45,46). Yet, COPD gender variances could contribute to differences in treatment response (14,47) and could facilitate a more personalized disease management (10,48). Therefore, there is an unmet need for appropriate identification and management of women with COPD in clinical practice, as barriers to their treatment include greater under-diagnosis than in men, fewer spirometry tests and medical consultations (49). Subsequent management should consider gender-specific issues, such as differential incidences of comorbid conditions, potentially higher symptom burden, and a higher risk of exacerbations (19). COPD treatment and smoking cessation management should be personalized to the individual woman and reviewed regularly to optimize patient outcomes (19). Finally, awareness of COPD in women should be raised and women should be empowered through education in order to take control of their disease (19).

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4. Sex and gender in interstitial lung diseases

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Interstitial lung diseases (ILD) comprise a heterogenous group of lung diseases and even within these diseases much variability in disease behavior exist. Some of this variation can be explained by differences in biological sex and behavioral gender. Awareness of these influences is of great importance to optimize research and care. Two recent reviews on this topic provide more in-depth information, here we provide a short overview (1. PMID: 34789464; 2. PMID: 34353457)

A well accepted concept in the pathogenesis of many ILDs there is the interplay between a trigger (such as smoking or inhalation of substances) and a susceptible host (with genetic susceptibility or autoimmunity). Both gender and sex may affect this complex interplay which is also reflected in epidemiological data for the different ILD.

In idiopathic pulmonary fibrosis, older age, male sex and smoking are associated with a higher incidence as well as shorter survival (3. PMID: 26425858). Occupational exposure to substances as asbestosis, coal and silicosis is a prevalent cause of ILDs (4. PMID: 33153688). Around the world men are more often working in this kind of industries than women. Nevertheless, women may work in specific industries using silicosis or indium-tin oxide (touch screens) and one should be equally aware of occupational exposures in women to avoid diagnostic delays (5. PMID: 30869783). Furthermore, domestic exposure to biomass fuel is still much higher in women and associated with domestic pneumoconiosis or “hut lung” (6. PMID: 23880681). Smoking is in general more seen in men, which is also reflected in the higher prevalence of smoking related ILD in men. Another exposure related ILD is chronic hypersensitivity pneumonitis (HP) which occurs more or less gender-balanced. Interestingly, the cause of HP may differ between men and women, with men having more metal-work and farming related HP (1. PMID: 34789464)

An important group of ILDs are related to connective tissue diseases (CTD-ILD). It is well accepted that immune responses differ by sex (7. PMID: 27546235), which likely related to the higher prevalence of women with CTD-ILD as can be seen in diseases as systemic sclerosis, systemic lupus erythematosus, and Sjogren’s syndrome. Although rheumatoid arthritis (RA) is more prevalent in females, RA-ILD is more prevalent in males, even if corrected for smoking (8. PMID: 33059295). If this effect is caused by sex dependent genetic and hormonal differences is not yet elucidated.

One of the ILD’s that is predominantly seen in females of childbearing age is lymphangioleiomyomatosis (LAM), which is likely reflecting the role that oestrogens are believed to play in the pathogenesis of this disease (9. PMID: 29874537). Though cases of LAM in males have been reported.

Familial ILDs can be the cause of multiple different mutations. An important group are the telomere related gene mutations (TRG), which are associated with shortening of telomere length. Although TRG mutations are mostly located on autosomes, men affected are usually younger than women and have significantly shorten telomeres (10. PMID: 19458273). It is believed that gender dependent environmental factors such as smoking and occupational exposure may cause progressive telomere shortening. Whilst on the other hand there are data that androgen may lead to telomere elongation (11. PMID: 27192671), suggesting that women may be partially protected from telomere shortening. The interplay between sex hormones, genetic variations and environmental factors in ILD is still largely unknown and a field of future study.

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5. Gender and pulmonary vascular diseases

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Pulmonary vascular diseases include both pulmonary embolism (PE) and pulmonary hypertension (PH). PE is frequent, and usually presents acutely. Its prevalence increases with age, and the disease is equally distributed between both genders (1). However, anticonception pill, hormonal replacement therapy and pregnancy represent female-specific risk factors for PE. Pregnancy-related PE is one of the leading causes of maternal death in high-income countries and occurs in around 0.03% of all pregnancies (2). Guidelines for prevention, diagnosis and treatment of pregnancy-related PE have been recently published (3,4). They consistently recommend prophylactic anticoagulation during pregnancy and postpartum, in patients with previous venous thromboembolisms (VTE), unprovoked or oestrogen-related. Outside of pregnancy context, women are tested for PE at higher rates than men and an invasive workup is required more often in females (1). Among patients with confirmed PE, women tend to have more severe features yet may be less likely to receive invasive interventions. Females have more bleeding complications, but mortality does not differ (1). Males, for their part, have a higher rate of recurrence justifying extended anticoagulation in most of them (5,6).

PH, currently defined by a mean pulmonary arterial pressure (PAP) >20 mmHg and a pulmonary vascular resistance ≥3 WU (ref 10), frequently complicates the course of severe lung and heart diseases. Pulmonary arterial hypertension (PAH) is a subcategory of PH, whose definition also requires a pulmonary arterial wedge pressure (PAWP) ≤15 mmHg. It can be either idiopathic (iPAH), heritable or associated with drugs or other conditions such as connective tissue diseases, congenital heart diseases, portal hypertension, or HIV infection. The disease specifically affects small pulmonary arterioles and is characterized by endothelial dysfunction, smooth muscle cell proliferation and progressive pulmonary vascular remodelling (7). PAH is a rare chronic condition with a higher incidence in women than in men (female predominance 56-86%), and a more distinct difference at a younger age (ratio 2,3:1 in favour of women). This contrast seems to fade in postmenopausal women (ratio 1,2:1 in favour of women) (8–15). Furthermore, the penetrance of heritable PAH in subjects carrying mutations in the gene encoding bone morphogenetic protein receptor type II (BMPR-II), is significantly higher in women (42%) than in men (14%) (16,17). Hormonal status appears to influence prognosis since PAH in men and postmenopausal women is associated with a worse prognosis and shorter survival rates when compared with younger women (18–23).

These observations have prompted research into the pathophysiological effects of sex hormones in the development of PAH, in particular oestrogens. Mainly the effects of oestrone (E1) and 17β-oestradiol (E2) were the subjects of investigation. The former is produced by aromatase in extragonadal tissues and is predominant in men and postmenopausal women, while the latter is produced in gonadal tissues and is predominant in premenopausal women (24,25). Oestrogens are metabolized by CYP1A1 and CYP1B1 enzymes, resulting in the active metabolites 16α-OH-E1 and 16α-OH-E2 (26). CYP1A1 and CYP1B1 expression is elevated in PAH patients (27,28). Study findings in humans support the importance of altered oestrogen metabolism in PAH. A small study showed decreased E1 and increased 16α-OH-E2 levels in female iPAH patients (29). Male iPAH patients showed increased E1, E2 and 16α-OH-E2 levels (29–31). Remarkably E1 concentrations were higher in iPAH men than women, oppositely to the situation in healthy humans, with higher E1 concentrations in women. Furthermore, increased 16α-OH-E2 levels were linked to a reduction of cardiac output in women (29).

Moreover, differences in right ventricle (RV) function between genders have caught attention. As PAP rises, RV function and its adaptation to increased afterload are major determinants of survival. Initially RV contractility is enhanced, and RV hypertrophy develops (32–35). In PAH patients, women exhibit better RV contractility, systolic and diastolic cardiac function compared to men (36). Typically, RV function has worsened less in women at the time of PAH diagnosis (22,37,38). After start of treatment, RV ejection fraction increases in women (+3,6%) while it diminishes or remains unchanged in men (-1%) (22). Furthermore, efficacy of PAH therapy is influenced by gender. Endothelin receptor antagonists show better responses in women compared to men, with larger improvement of 6-minute walking distance (39). PDE-5 inhibitors on the other hand are more effective in men and postmenopausal women (40–42). No difference in the efficacy of prostanoids has been reported, though data are limited (43). These differences may contribute to the better prognosis observed in PAH women.

Devastating effects of pregnancy have been reported in PAH. Pregnant patients with PAH cannot cope well with pregnancy-induced increases in plasma volume and cardiac output, leading to disease progression and right heart failure (44,45). It is unclear whether the impact of sex hormones on vascular remodelling are responsible for PAH worsening during pregnancy or if this is merely a volume-dependent issue.

In conclusion, women are more at risk of developing PAH, possibly due to complex mechanisms of oestrogen and metabolism dysregulations. Nevertheless, women have better survival rates because of greater RV adaptation to elevated PAP.

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6. Intensive Care

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Women comprise half the world's population but account for 35-45% of Intensive Care Unit (ICU) admissions[1]. Is this a result of inequitable access, or other causes such as differences in disease prevalence and severity? Many factors could influence outcomes including the well-recognised fact that presentation of illness in women may differ from men, and trial studies with no gender balance at inclusion have meant that results obtained from male patients are extrapolated to females. But could other factors related to implicit bias be present? A range of cohort studies has been carried out in an attempt to untangle these features; often with conflicting results.

In a meta-analysis and systematic review[1], most studies included showed higher illness severity scores on admission to ICU, and higher risk-adjusted mortality at discharge and 1 year, in women compared to men. Difficulties in interpretation include the fact that the terms 'sex' and 'gender' were often used interchangeably, and sex-disaggregated age was only given in some studies, while even fewer reported on sex-disaggregated co-morbidity scores. No study considered non-binary sex or gender[1]. Menopausal status was often poorly ascertained.

Although over 500,000 ICU patients were included in the studies for the meta-analysis, clear information on outcomes from specific conditions was not available. In the one study that showed excess ICU mortality in males this was associated with older age (>75 years) and longer ICU stay[2]. Male patients in this study comprised 61.7% admissions and 66% ICU bed days, which could indicate differences in selection criteria. In a Swedish study that showed no sex difference in risk adjusted ICU mortality for the cohort as a whole, risk adjusted mortality from cardiac arrest was lower in males aged less than 45 years, and for the patients admitted with multiple trauma, male sex was associated with higher nurse workload and longer ICU stay[3].

Todoraov et al have recently carried out a Bayesian analysis of the provision of Intensive care based on analysis of a national registry of critically ill patients[4]. In keeping with the meta-analysis, they showed a lower likelihood of women being admitted to ICU despite being more severely ill. Women aged <45 years had the same admission probability as men, but had more severe illness at the time of admission. Mortality odds were significantly higher in women than men per unit increase in Simplified Acute Physiology (SAPS II) score. Overall men had a higher rate of mechanical ventilation, vasoactive therapy and renal replacement therapy, whereas women were more likely to receive non-invasive ventilation. While this was influenced by age and women aged <45 years were more likely to receive invasive mechanical ventilation, the trend was opposite in women > 65 years.

These findings prompt a discussion as to whether bias in ICU triage systems and admission criteria contribute to these outcomes. It has been observed that SAPS II and Sequential organ failure assessment tool (SOFA) perform differently in men than women - which should not come as a surprise, as sex is not included as a variable. Further studies on ICU risk-based prediction and assessment scores related to gender are urgently needed. It should be noted too, that ceiling of therapy (treatment limitation) advance directives are more frequent in women[5], and less aggressive treatment preferences impact on ICU admission and the level of interventions. Clearly if outcomes are worse for the reasons described above, this may feed into a circular loop of information provided to patients and surrogates, and further influence decision-making.

Having said that, looking at specific conditions, management and outcomes vary. Women receive less appropriate management of respiratory distress syndrome then men[5], but may fare better with outcome from an ICU admission for acute severe COPD[6]. There is no difference in outcome from sepsis by sex, but women may have less timely initiation of antibiotics[5]. Women are more likely to develop hypoactive delirium while receiving Intensive Care, and have worse functional outcomes after discharge[5]. Most of these results come from large heterogeneous, retrospective studies. The French and European Outcomes Registry in Intensive Care Unit study (FROG-ICU study)[7] - a prospective study examining long term outcomes – found that ICU, 28-day and 1 year mortality did not differ significantly between men and women when adjusted for age and illness severity, but here too women comprised only one third of the recruited population.

It should also be understood that while the number of women entering medical school is equal or exceeds that of men, Critical Care remains a clinical medical speciality which has one of the lowest number of women. A Canadian study showed that only 20% of the critical care faculty and 28% if critical care trainees were women[8], with even fewer in clinical or research leadership roles. Far less are first or last author on Critical Care medicine publications[9]. These figures are not atypical for Europe too, although the tide may be turning, and more equal female representation is seen in Respiratory High Dependency Units. There is active work in progress attempting to address inequalities[8;10], and discern their impact on clinical care delivery.

Importantly, an understanding of the role of gender on outcomes should be multi-directional. Male gender is major risk factor for severe illness in covid pneumonia, and other illnesses, and social deprivation magnifies many inequities. Trans patients are significantly disadvantaged across medical care[11]. Understanding the factors that generate these differences at genetic, molecular, clinical and social levels should improve care and access to it, for all.

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7. Lung cancer

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In their monocentric observational study entitled 'Carcinoma of the Lung in Women' from 1965, *Vincent et al.* already pointed out sex-specific characteristics in lung cancer when describing different histological distributions in female and male patients (Vincent, Satterfield et al. 1965). Since then, we have gained increasing knowledge about considerable peculiarities of lung cancer in women which will be emphasized in this chapter.

Recent epidemiology data from the International Agency for the Research on Cancer and the World Health Organization estimated that 2.21 million patients were diagnosed with lung cancer worldwide in 2020, while 1.80 million patients died. Lung cancer in women accounted for about one third of these new cases and deaths with approx. 771.000 and 607.000 women affected, respectively. Among all female cancers, lung cancer represented the third and second most common entity relating to incidence and mortality rankings (International Agency for Research on Cancer and World Health Organization 2022). The incidence rate of lung cancer among women in the EU in 2020 was expected to be close to 45 per 100 000, less than half the rate among men. Yet, the gender gap has been narrowing with the decreasing incidence rates for men and increasing for women reaching almost similar level in Scandinavia (Organization for Economic Co-operation and Development, 2020)

Regarding lung cancer stages at diagnosis, population-based data, available up to 2018 from national lung cancer registries, generally indicated higher proportions of early stages in women compared to men. A reverse correlation was seen in locally advanced disease stages, while being ambiguous among countries in metastasized lung cancer as the most diagnosed stage for both sexes (Araghi, Fidler-Benaoudia et al. 2021, National Cancer Institute 2022). Historically, adenocarcinomas have comprised the most frequently diagnosed histological subtype in female lung cancer populations worldwide. Incidence rates still increase in most countries according to published data. In women, pulmonary

adenocarcinomas rates exceed those in squamous and small cell lung cancer (SCLC) to a significantly larger extent than in men (Lortet-Tieulent, Soerjomataram et al. 2014, Barta, Powell et al. 2019).

While women and man share similar risk factors, biological sex- and gender role-based differences may attribute for the distinct tumour biological and clinical behaviour in female lung cancer disease. Despite effective primary and secondary prevention programmes in place, smoking still remains the most prevalent risk factor for the development of lung cancer in women. It has been unclear whether women are more susceptible to the carcinogenic potential of smoking despite less tobacco consumption than men. Contrasting male smokers and female never-smokers, previous case-control studies detected higher mutation rates of the glutathione s-transferase Mu 1 gene relating to less protection against oxidative stress and more DNA adducts, higher inducible activity of the cytochrome P450 subtype CYP1A1 and less DNA repair capacities, and more inhibitory mutations of the tumour suppressor gene TP53 in female smokers. Conversely, similar, or even increased risks for lung cancer evolution were reported in smoking men when the duration and amount of inhaled tobacco smoke was accounted for by prospective cohort studies (Rivera 2013, Tsai, Chu et al. 2021, Ragavan and Patel 2022).

Other reported lung cancer risk factors in women encompass genetic alterations, hormonal differences, life-style factors including increased consumption of saturated fats and lack of exercise as well as environmental exposure to second-hand smoke, indoor cooking fumes, radon, and asbestos. In addition, hormone replacement therapies, chronic infectious (i.e., human papilloma virus (HPV), tuberculosis, and non-tuberculosis mycobacteria) and other pre-existing lung diseases (i.e., COPD, emphysema) have been named (Rivera 2013, Baiu, Titan et al. 2021, Tsai, Chu et al. 2021, Ragavan and Patel 2022).
In addition to the already named genetic alterations, lung cancers harbouring activating driver mutations of the epidermal growth factor receptor (EGFR) gene, the Kirsten rat sarcoma (KRAS) and BRAF protein genes as well as anaplastic lymphoma kinase (ALK) gene translocations and ROS1 fusions are more frequently detected in women than in men (Baiu, Titan et al. 2021, Tsai, Chu et al. 2021, Ragavan and Patel 2022).
The negative effect of hormonal differences as well as hormonal replacement therapies on the development and progression of lung cancer in women remains still under debate. Nuclear oestrogen receptors α and β are expressed in lung cancers of both sexes. Beside their physiological function, oestrogen pathways have been linked also to carcinogenesis in lung cancers (Rivera 2013, Rodriguez-Lara and Avila-Costa 2021). The meta-analysis by *Greiser et al.* from 2010 concluded a 27 % risk reduction for all types of lung cancer in women who used oestrogen replacement for any duration, the same replacement therapy was correlated with an accountable risk of 76 % in non-smoking women with subsequent adenocarcinomas (Greiser, Greiser et al. 2010). In the more recent Cochrane-review, *Marjoribanks et al.* calculated an increased risk ratio of 1.91 (95% confidence interval 1.24-2.93) for non-small lung cancer (NSCLC) death in combined oestrogen and progesterone replacement therapy based on one study with 16,608 women, but showed similar risks ratios for SCLC death in combined hormone replacement as well as death in all lung cancer types in sole oestrogen replacement when both comparing against hormone-naïve women (Marjoribanks, Farquhar et al. 2017). Consequently, several clinical trials are on-going in NSCLC women that investigate the clinical benefits of antioestrogens (i.e., fulvestrant, tamoxifen), also in combination with EGFR tyrosine kinase inhibitors (TKI) (Rodriguez-Lara and Avila-Costa 2021).
Evidence on the association of HPV in the evolution of lung cancer in women pointed either towards a causative role with detection of several high-risk HPV-types in lung cancer specimens, or as sole commensal in both malignant and benign lung tissues (Ragin, Obikoya-Malomo et al. 2014, Zhang, Chen et al. 2019, Tsai, Chu et al. 2021, Ragavan and Patel 2022).

In recent years, low dose CT (LDCT) lung cancer screening programs have been established for high-risk groups defined by age and smoking history but not gender-related differences. Given higher incidence of lung cancer in never-smokers in female, this disproportionately affects women who also tend to start smoking at an older age and smoke less intensely than men. Meanwhile, women seem to receive greater benefit from LDCT screening with significant decrease of mortality (women HR 0.31; 95% CI 0.10-0.96; p=0.04 vs men HR 0.94; 95% CI 0.54-1.61; p=0.81), earlier stage at diagnosis and more frequent surgical eligibility (Becker et al. 2020; de Koning et al. 2020). In addition, detection of a solitary pulmonary nodule in women is a better predictor of lung cancer than in men (relative risk of lung cancer 13.7 vs. 6.2) (Chilet-Rosell et al. 2019). This suggests a greater protective effect and warrants further investigation for possible differences in screening standards and risk prediction in women population

Significant gender-related differences in lung cancer surgery utilization and outcomes have been observed. *Shugarman et al.* found women to be 25% less likely to receive timely lung resection (Shugarman et al. 2009). The fact that women undergo appropriate surgical intervention for NSCLC at lower rates compared to men has been at least partly related to physician bias (Ferguson et al. 2017). Meanwhile, most studies show that women have a long-term survival advantage after lung cancer resection with decreased rates of postoperative morbidity and mortality including lower in-hospital and 30-day mortality (Wainer et al. 2017). It might be in part linked to the general gender-related health risks as women undergoing resection tend to be younger and healthier than their male counterparts, but also to a higher proportion of women having stage I disease (Tong et al. 2014, Lautamaki et al. 2021). However, some authors reported more unplanned readmissions within first 30 days following discharge in women suggesting different postoperative symptom experiences (Nelson et al. 2017).

Limited evidence exists on sex-specific effects of stereotactic radiotherapy in localized stages favouring neither female nor male lung cancer patients.

Chemotherapy in advanced NSCLC showed a better response and longer overall survival in women than in men. Outcomes in PD-1 and PD-L1 checkpoint inhibitor monotherapies were inferior in women to which lower tumour mutational burden than in men might have contributed. On the contrary, meta-analyses on women receiving combined immunochemotherapies demonstrated more favourable effects when compared with male lung cancer patients. TKI-therapies in molecular altered NSCLC signalled a trend towards better progression-free and overall survival in women, yet statistically not significantly different as in men (Tsai, Chu et al. 2021, Ragavan and Patel 2022).

Based on the body of evidence on prognosis, lung cancer in women is generally associated with a better overall survival than in men (Baiu, Titan et al. 2021). In their analysis of the Surveillance, Epidemiology, and End Results Program (SEER) cancer registry data, *Wang et al.* identified surgical resection as the most relevant prognostic factor to 1-year overall survival, likewise the loco-regional lymph node status as most contributing factor to 3- and 5-year overall survival. Remarkably, the multivariate statistical models in women outnumbered those in males with prognostic accuracies of 0.8297 and 0.7329, respectively (Wang, Liu et al. 2021).

Regarding the patient perspective, *Ruano-Ravina et al.* observed in their recent multi-centric case-series of 13,590 Spanish lung cancer patients some marked differences in patient-reported symptoms at diagnosis. In stage I/II NSCLC, pain was more frequent in women than in men, whereas haemoptysis and coughing was stated less often in more advanced stages (Ruano-Ravina, Provencio et al. 2021).

Notably, *Vavalà et al.* envisaged in their review the perspective of 'women living with lung cancer as a chronic disease'. Long-term survival may occur especially in women as a result of either earlier lung cancer detection by LDCT screening or the significantly higher prevalence of targetable molecular alterations with reported survival times in female ALK-positive, stage IV NSCLC-patients of more than 10 years. Yet, quality of life in survivorship may be significantly impaired by prolonged physical and psychological symptoms related to tumour or therapy, social and spiritual burden as well as the apparent lung cancer stigma as a self-inflicted disease (Vavalà, Rigney et al. 2020).

Addressing lung cancer research, *Mendis et al.* assessed 35 clinical trials relating to US cancer drug approvals between 07/2008 to 06/2018. Female lung cancer patients were reportedly enrolled to a lesser extent than men into these clinical trials based on female-male incidence ratios (OR 0.77; 95% CI 0.75-0.80) (Mendis, Anand et al. 2021). Of note, female researches were underrepresented in global lung cancer research according to the systematic assessment of female authorships and those of their male counterparts by *Bendels et al.* (Bendels, Brüggmann et al. 2017). Equally, the survey-based study by *Banerjee et al.* indicated that female oncologists were less likely to hold leadership roles (Banerjee, Dafni et al. 2018).

As a conclusion, more than 50 years after the publication by *Vincent et al.* (Vincent, Satterfield et al. 1965), the current understanding of lung cancer in women is moving towards an independent tumour entity distinctive from lung cancer in men. Future clinical trials, modes of outcome reporting as well as clinical practice guidelines in lung cancer will clearly benefit from addressing the already evident differences between female and male patients more specifically. Focussed research seems necessary to better explore various sex- and gender role-based effects and their interactions which may result in more comprehensive pictures of lung cancer in women as well as in men.

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8. Risk factors

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- **Smoking and Women**
  Jonathan Grigg

The WHO reports that over 200 million of the world's one billion smokers are women, and that the tobacco industry aggressively targets women in order to increase its consumer base (1). Indeed, WHO youth smoking trend data show that similar numbers girls and boys smoke, a trend that is expected to continue as these young people become adults (1). The global tobacco industry watchdog STOP in its report "Women and the Tobacco industry " identified four main areas where the tobacco industry targets women and facilitates smoking uptake and smoking-related diseases (2). First, women are targeted in its marketing campaigns, often delivered via women. For example, Phillip Morris International funded a US women's think tank, which promoted its heated tobacco product. Social media is also used by the industry. Hunt *et al* (3) reported that the Twitter accounts the world's largest tobacco companies, @InsidePMI (Philip Morris International) and @BATPress (British American Tobacco) posted multiple tweets in March 2019 celebrating International Women's Day and the International Week of Women, using the hashtags #IWD2019 and #BalanceForBetter and that these tweets, drawing on women's equality, gender empowerment and equal pay, used emerging cultural contexts to build positive associations with smoking as a feminist act. The second area identified by the STOP report was that the tobacco industry co-opts sponsorship of women-related initiatives, such as PMI's "empowering women" campaign, to obscure the lethality of cigarettes to women (2). Third, while outwardly supporting gender equity in labour practices, tobacco companies benefit from poor working conditions on tobacco farms, and the industry continues to resist paying compensation to women who suffer from tobacco use. Finally, there are smoking-related diseases specific to women. For example, women who smoke are more likely to experience delays in conceiving, smoking increases the risk of premature delivery, stillbirth, and risk of cervical cancer (1). Even for some non-gender-specific disease such as lung cancer, for the same level of lifelong exposure to cigarettes, women have a higher relative risk compared with men (4). The mechanisms underlying this increased risk remain unclear, but hormonal regulation of genes governing metabolism of tobacco carcinogens and DNA repair, activation of growth promoting pathways, and the interaction between stroma and epithelial cells may all play a role (5).

Strategies to reduce the tobacco industry marketing and use of cigarettes / novel electronic nicotine delivery systems (ENDS) in order to reduce smoking-associated disease clearly need to consider gender and social context. Indeed, Margaretha Haglund, ex President of the International Network of Women Against Tobacco recently stated that "There is no magic bullet to reduce smoking prevalence in women". A Canadian focus group study concluded that an ideal smoking cessation program for women includes a women's centred approach with sufficient variety and choice, free pharmacotherapy, non-judgmental support, accessible services and clear communication of program options and changes (6). There are, however, actions that should be applied globally. For example, Margaretha Haglund considered that "all countries need the same thing - implementation of the WHO Framework Convention on Tobacco Control (FCTC), at its highest level"(2)

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- **Air pollution and respiratory disease – gender differences**
  Zorana Jovanovic Andersen

Air pollution is a major health risk factor contributing to morbidity and mortality from respiratory, cardiovascular, and metabolic disease, as well as lung cancer.[1] Every year, air pollution leads to 6.7 million premature deaths globally[1] and 373,000 of these in Europe, as well as serious aggravations of lung and heart diseases that affect millions of children and adults.[2] Because of the links with multiple diseases and the ubiquitous nature of the exposure, air pollution is the 4th leading risk factor for morbidity and mortality, surpassed only by high blood pressure, tobacco use, and poor diet.[3]

Respiratory disease patients, both children and adults, are arguably the most susceptible to the adverse effects of air pollution.[4,5] Air pollution affects lungs starting in pregnancy and throughout the entire lifetime, contributing to suppressed immune system,[6–9] inflammation and oxidative stress effects, impaired lung growth in children,[10,11] lung function decrements in children and adults, and carcinogenic effects.[12,13] Thus, long-term exposure to air pollution increases risk of development of asthma in children,[14] and adults,[15] chronic obstructive pulmonary disease,[16] acute lower respiratory infections, and lung cancer,[17,18] and ultimately increases the risk of premature death due to respiratory disease.[19] Furthermore, air pollution presents a substantial burden in the daily life of respiratory disease patients, where exposure to short-term peaks in air pollution can trigger exacerbations of manifest disease, such as asthma attacks, increased use of relieve medication, emergency room visits, hospitalizations, and even death.[4,5]

There are notable gender differences in exposure to air pollution, as well as response and susceptibility to air pollution.[20] Gender determines exposure to outdoor and indoor air pollution according to where people spend time (mostly at home, more typically women, or divided between home and work, more typically for men) and to their activity patterns, including, for example, participation in sports outdoors (jogging, walking), transportation modes (using active travel modes

such as cycling or public transport, or driving a car), and exposure through work, where men typically work more often in occupations related to high exposure to air pollution, including construction, wood processing/furniture production, welding, mining, transportation, etc., whereas women are more exposed to chemicals at work (hair dresser, beauty, painters, chemicals/ceramics production) and through use of personal care and cleaning products.

Women, who are generally homemakers, have the greatest exposures to household air pollution.[21] Nearly half of the world population, or 3.8 billion people, cook with solid fuels (wood, coal, agricultural waste, animal dung),[1] and many use it for heating. In Eastern and Southern Europe use of solid fuels for heating and cooking is still a major contributor to air pollution. These fuels are smoky, often used in an open fire or simple stove with incomplete combustion, and produce huge concentrations of air pollution indoors when smoke is poorly vented. Accordingly, stove-replacement interventions have effectively reduced exposures and improved women's health in these settings.[22,23]

Epidemiologic studies of air pollution effects on respiratory health report significant modification by sex, although results are not uniform, and go in both direction, showing stronger effects for men and women for different respiratory outcomes.[20] In summary of results presented by Clougherty, studies of children suggest stronger effects due to air pollution among boys in early life and among girls in later childhood, especially lung function and asthma. It still remains unclear whether differential effects of air pollution are attributable to socially derived gendered exposures, to sex-linked physiological differences, or to some interplay or the two. Possible sources of difference in air pollution response between women and men, may vary by life stage, co-exposures, hormonal status, or other factors.

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9. Diagnostic and therapeutic inequalities

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Access to therapeutics requires a diagnosis, diagnosis will only be established after appropriate diagnostic procedures, diagnostics will only be initiated if symptoms are reported.
Gender inequality in access to diagnostics and therapeutics has been a topic of interest for some decades; however, little has been published with regard to respiratory diseases.

It is likely that gender related inequalities differ depending on gender specific roles in the society. There still are areas in the world where women and girls are valued less within the society than men and boys; these inequalities are influenced by education level and socioeconomic status.

It has also been reported that symptoms are viewed differently in women and men with subsequent underdiagnosis and undertreatment in women - a phenomenon which has been named Yentl syndrome. Yentl syndrome has been described originally for cardiac disease and is defined as undertreatment of women compared with men which occurs unless women present with signs and symptoms of similar nature and severity compared to men. This phenomenon has been reported for childhood asthma with underdiagnosis and undertreatment in girls compared to boys in a Swiss population (Kühni Pediatr Pulmonol 1995) with several potential explanations: symptoms reported by girls differ from those reported by boys and are thus not diagnosed as asthma; boys' lifestyle with regard to sports and parental expectations is different even in Western Europe – with a more sedentary life style in a majority of girls who are therefore less likely to experience and report symptoms which would be a pre-requirement for access to diagnostics and therapeutics. However, while the issue is being discussed in clinical practice, scientific evidence remains scarce.

In contrast, it has been reported from Scandinavia that (adult) women report more symptoms and seek access to healthcare more easily then men, thereby have more access to specialist care and state-

of-the-art medication (Hakansson ERJ 2021; Sundh Eur Clin Respir J 2017). When and why there is an age-related shift in access to diagnostics and therapeutics has not been investigated.

More generally it can be assumed, that gender inequalities in access to diagnostics and therapeutics are different in different parts of the world, depend on structure of the society, education level of females compared to males and on social class and access to healthcare. Gender inequality exists in many countries, starts at or even before birth and has been shown to be associated with increased female child mortality in the under-5-year-olds (BMJ 2018). According to the WHO, with lower social class, inequality between the two sexes increases with a disadvantage for women. While there has been more recent research into gender inequality in cardiovascular disease, very little has been published with regard to gender inequality in respiratory diseases.

There are several topics of interest for future research: age-related changes in symptom perception and symptom reporting; how this may affect access to diagnostics and subsequently therapeutics; how the pattern of gender inequalities differs between different countries within Europe and beyond; how this may be influenced by local politics, education policies and the local health care system…..

It should be discussed if, when, for whom and how screening for respiratory disease would help to increase gender equality in access to appropriate respiratory care…

10. Patient Perspective

Kjeld Hansen, Pippa Powell, Jessica Denning
European Lung Foundation

It is in the mission statement of the European Lung Foundation to advance respiratory diagnosis, treatment and care. When considering gender and respiratory health we must consider if and how gender creates barriers or opportunities to achieving our mission. As such it is also essential to us to eliminate any barriers created by gender and seize any opportunities we can to advance good lung health for all.

It is clear that the current focus of gender in respiratory healthcare is on improving the representation of women, this is important, and we have much to do until we reach equality. However, the very perspective of gender as binary can be considered a barrier in itself. Gender diversity is not new nor is it uncommon, with younger generations changing perceptions. People who are gender non-binary, trans and intersex, are more likely to face discrimination and inequity in healthcare and are less likely to feel comfortable accessing it [1]. There is therefore a need to further develop gender diverse approaches to healthcare and the European Lung Foundation will work to advance this agenda.

There are many ways that gender impacts individuals living with lung disease. This includes gender norms, the impact of gender on socialisation, gender roles, gender expression, power relations, how illness is experienced and health behaviours [2]. In this section we intend to explore those factors in relation to prevention and early diagnosis, as well as the lived experience of people with lung disease and their involvement in healthcare.

Gender differences in the prevention and early diagnosis of lung disease

Even before someone is diagnosed with a lung disease, there are significant differences between the genders. Here we need to consider issues such as:

- differences in smoking rates and exposure (currently far fewer women than men use tobacco, but women are often exposed to tobacco smoke in the home and workplace) [2]
- exposure to tobacco smoke and pollutants in pregnancy and its impact on the lung health of the foetus at birth and across the life span, therefore the birthing parent's role in the future lung health of their children [3]
- differences in exposure to household pollution (1.8 million people will still rely on biomass for cooking and heating in 2040 – and the majority of those doing the cooking will be women) [4]
- differences in workplace exposure – men traditionally work in higher-risk settings (e.g. factories, building sites); however, women are often unaware of the levels of risk in their workplace and training in these sectors is lacking (hair and beauty sector) [5]
- difference in uptake of vaccines - in the case of the flu vaccine, women being more vaccine hesitant but also more likely to receive the vaccination than men [6]

  Early diagnosis of lung disease is vital to ensure that damage can be reduced or halted, making screening programmes and activities (including spirometry and lung cancer screening) vital for the future lung health of populations. There are significant differences in rates of uptake when looking at gender and so, as we develop prevention campaigns, invitations to health screening should be specifically co-designed with a target audience, taking gender and other factors into consideration.

Gender in patient involvement

The exclusion of women from clinical trials is well documented [8]. While efforts have been made to improve the gender balance in clinical research there is still some way to go. Despite this, women seem to be more engaged with patient and public involvement in research although data on this are sparse.

Involving patients and the public in research and guideline production is necessary to ensure that the needs and requirements of people living with the conditions are recognised and addressed. With healthcare professionals and researchers engaging more readily with public involvement comes the responsibility to ensure the involvement addresses the needs of everyone. The most likely to be engaged with research are white and middle class with good health literacy [9]. Women are often well represented however recruitment of gender diverse groups is low.

ELF facilities 13 patient advisory groups across a range of lung diseases. Across these groups there are roughly 181 members; 72% (n=132) are female, 32% (n=59) are male. There is a clear disparity between male and female involvement in ELF PAGs. The only disease areas where there is a predominance of men is in conditions that are more common in males. An example of this is in the sleep PAG where men account for 75% of the group. Even within this group, the men are all from patient organisations, demonstrating that unlike the women in other PAGs, unaffiliated men are still difficult to engage in activities such as being in PAGs. It is interesting to note that while men may be historically more represented in medical research, with patient and public involvement becoming more and more integrated into clinical trials and with fewer men taking up these positions, how might it affect men in clinical trials moving forward?

Disease area	Number of members	Men	Women
Sarcoidosis	13	6 (46%)	7 (54%)

Bronchiectasis adult	19	4 (21%)	15 (79%)
Bronchiectasis child	15	2 (13%)	13 (87%)
Pulmonary Fibrosis	12	7 (58%)	5 (42%)
PCD	12	5 (42%)	7 (58%)
Sleep disordered breathing	12	9 (75%)	3 (25%)
COVID-19	31	12 (39%)	19 (61%)
Cough	13	3 (23%)	10 (77%)
Lung Cancer	11	3 (27%)	8 (73%)
Severe asthma	9	1 (11%)	8 (89%)
Asthma	4	0 (0%)	4 (100%)
COPD	6	2 (33%)	4 (67%)
Aspergillosis	13	3 (23%)	10 (77%)
United PAG (Across disease areas)	11	2 (18%)	9 (82%)
Average	181	59 (33%)	122 (67%)

Table 1 – Male and female representation in 13 ELF PAGs.

Similarly, gender differences have been seen in ELF survey participation, for example, in a survey about using an app to obtain information on COVID-19, 68.4% of respondents were female. In another survey about the needs and priorities of people with experience of lung cancer, 83.25% of respondents were female. It should be noted that there we distinct differences between languages with 51.98% female respondents in the Spanish survey, suggesting that cultural aspects play a large role.

The future of gender and respiratory diseases

We must continue to work for equity in healthcare. As we emerge into a more digital world it will be important to assess the willingness and ability to participate online between people of different genders and backgrounds to ensure individuals are not left behind.

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