Women and Lung Disease
Sex Differences and Global Health Disparities

Kent E. Pinkerton[1], Mary Harbaugh[2], MeiLan K. Han[3], Claude Jourdan Le Saux[4], Laura S. Van Winkle[1], William J. Martin II[5], Rose J. Kosgei[6], E. Jane Carter[7], Nicole Sitkin[8], Suzette M. Smiley-Jewell[1], and Maureen George[9]

[1]University of California, Davis, Davis, California; [2]Public Advisory Roundtable of the American Thoracic Society, New York, New York; [3]University of Michigan, Ann Arbor, Michigan; [4]University of Texas at San Antonio, San Antonio, Texas; [5]Ohio State University, Columbus, Ohio; [6]University of Nairobi, Nairobi, Kenya; [7]Brown University, Providence, Rhode Island; [8]Yale University, New Haven, Connecticut; and the [9]University of Pennsylvania, Philadelphia, Pennsylvania

Abstract

There is growing evidence that a number of pulmonary diseases affect women differently and with a greater degree of severity than men. The causes for such sex disparity is the focus of this Blue Conference Perspective review, which explores basic cellular and molecular mechanisms, life stages, and clinical outcomes based on environmental, sociocultural, occupational, and infectious scenarios, as well as medical health beliefs. Owing to the breadth of issues related to women and lung disease, we present examples of both basic and clinical concepts that may be the cause for pulmonary disease disparity in women. These examples include those diseases that predominantly affect women, as well as the rising incidence among women for diseases traditionally occurring in men, such as chronic obstructive pulmonary disease. Sociocultural implications of pulmonary disease attributable to biomass burning and infectious diseases among women in low- to middle-income countries are reviewed, as are disparities in respiratory health among sexual minority women in high-income countries. The implications of the use of complementary and alternative medicine by women to influence respiratory disease are examined, and future directions for research on women and respiratory health are provided.

Keywords: health disparity; chronic obstructive pulmonary disease; sexual minority women; complementary and alternative medicine

Biological Differences Based on Sex

Some pulmonary diseases occur disproportionately or almost exclusively in women. These diseases may be underdiagnosed by clinicians, either due to their relative rarity or to clinical manifestations that mimic those seen with other respiratory diseases. One patient (M.H.) diagnosed with lymphangioleiomyomatosis (LAM), describes the diagnostic delays in recognizing her rare lung disease, which occurs mostly in women of childbearing age:

> My story begins 31 years ago on the day I was diagnosed with a profile of someone who has a spontaneous pneumothorax. I had several episodes of respiratory disease events that were not elucidated until a lung biopsy through bronchoscopy 19 years later confirmed the diagnosis of LAM, a disease almost exclusively found in women. My LAM remains in the high-moderate range, and I do not require oxygen unless I go to higher altitudes. Fatigue is frequently a problem for those with LAM, but now that I am retired, I am better able to manage my issues with fatigue. My LAM has been managed appropriately, my progression has been very slow, and I continue to live a full and satisfying life. As a patient, I wish my disease had been diagnosed appropriately sooner. It is important that physicians are aware of this rare disease to help women like me manage their life accordingly.

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Correspondence and requests for reprints should be addressed to Kent E. Pinkerton, Ph.D, Center for Health and the Environment, 1 Shields Avenue, Davis, CA 95616. E-mail: kepinkerton@ucdavis.edu

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Other respiratory conditions that impact women nearly exclusively include pulmonary hypertension (1), catamenial diseases (2), and pregnancy-associated asthma exacerbation (3). Although rare, bloody pleural effusions can occur with endometriosis or with ectopic endometrium in the chest during the menstrual cycle (2). There are more respiratory disorders common to women, such as autoimmune lung disease (especially lupus), than men (1).

The development and progression of certain common respiratory diseases has been found to differ by sex. One such disease is chronic obstructive pulmonary disease (COPD), which is now the third leading cause of death in the United States (4). Although COPD was traditionally a disease of men, COPD prevalence and mortality has rapidly risen more in women than men in the last few years (5): in 2009, women accounted for 53% of COPD deaths in the United States (6). The increased prevalence of COPD in women is believed due to changing smoking patterns and women taking on more traditional male occupations. However, growing evidence supports significant sex-based differences in the disease (7). For example, of never-smokers who develop COPD, women are 1.5 times more likely to be diagnosed than men (8). When differences in age, smoking status, income, ethnicity, and education are taken into account, women are 37% more likely to have COPD than men (8). Women are also twice as likely to have COPD with the chronic bronchitis form rather than the emphysema form as men (8). New research on sex differences in COPD development is focusing on hormonal signaling and the immune system proteome (9, 10).

Importance of Diagnosis

All people, regardless of sex, deserve a timely and correct diagnosis. As more knowledge is gained about sex-specific symptoms of respiratory disease, it is hoped that the rate of misdiagnosis, such as occurred in the LAM story described above, will decrease. Underdiagnosis for COPD can be a risk for women, perhaps because COPD has been associated with men for so long. One North American study found that physicians presented with a clinical vignette suggestive of COPD were significantly less likely to diagnose COPD when the patient was described as female compared with male (11). A similar study found that differences in the rates of diagnosis disappeared when spirometry data were presented (12), underscoring the importance of obtaining spirometry in patients with symptoms suggestive of COPD. Currently, only approximately one-third of patients with a diagnosis of COPD in the United States have undergone confirmatory spirometry (13).

Correct diagnosis and treatment is important to improve quality of life. Women with COPD report a lower frequency of phlegm production than men (14) but similar or higher frequency of cough and more severe dyspnea (15). Increased rates of COPD exacerbations have also been documented in women in large clinical trials (15–17); however, it is unknown whether the increased rates are due to differences in reporting thresholds or disease biology. COPD-related deaths in the United States among women outnumber those of men (18). Yet, the recent Toward a Revolution in COPD Health (TORCH) study found that women had lower all-cause mortality, but, after adjusting for baseline variables, the difference was no longer statistically significant (15). Respiratory-related deaths in the TORCH study were the most frequent cause of death, and the causes of death were similarly distributed across both sexes.

Biologic Plausibility: Sex-based Differences?

Basic differences in anatomy and physiology between men and women no doubt influence both the course of respiratory disease and response to treatment. A metaanalysis of 11 longitudinal studies suggests that women experienced a greater rate of lung function decline than men when adjusted for the amount of tobacco smoked (19). In the Lung Health Study, lung function decline in women who continued to smoke was more rapid than in men (20). One hypothesis posits that the relatively smaller size of women's lungs means that each cigarette smoked represents a higher "dose." Women may also metabolize several components of tobacco smoke differently than men, which could translate into relatively higher and more prolonged exposure to toxic substances (21).

An important clinical question going forward with many respiratory diseases is whether men and women should be treated differently. Currently approved COPD treatments, such as bronchodilators and inhaled corticosteroid/bronchodilator combinations, appear to be equally effective in women and men. Nonetheless, smoking cessation products may differ in effectiveness based on sex. Researchers have recently shown that dopamine activation during smoking differs in women and men (22), with men being more responsive to nicotine and women more responsive to the taste and sensory effects of smoking. This may be why the use of nicotine patches to quit smoking is more effective in men than women, whereas other non–nicotine-based pharmacologic therapies, including bupropion and varenicline, appear to be equally effective. Further research is needed to delineate optimal, sex-specific treatment approaches.

Women may be protected from certain age-related biological processes by producing lower levels of reactive oxidant species, important drivers of pathology in age-related pulmonary disease (23), and by having a slower rate of telomere shortening and longer telomeres than men (24–26). One popular hypothesis is that the action of estrogen on an estrogen response element present in telomerase reverse transcriptase stimulates telomerase activity and the addition of telomere repeats to the ends of chromosomes (23). Women's susceptibility to pulmonary diseases varies with age due to the variation of their level of estrogen. The development and progression of the age-related diseases is dependent on mechanisms associated with cellular senescence that may be triggered by telomere shortening, which in women occurs at a slower rate than in men.

Further research is needed to explore the variables impacting women's susceptibility to age-related lung diseases, including addressing the following: (*1*) the role of telomere length: Do longer telomeres help women develop less pulmonary fibrosis than men? Does telomere shortening versus cigarette smoking affect the susceptibility of women to COPD? and (*2*) Is the susceptibility of women to pulmonary disease, such as COPD, influenced by women reacting differently to treatment of age-related pulmonary diseases than men?

Life Stage and Respiratory Susceptibility?

Sex variation in respiratory disease may also arise from early life exposures that occur in a broad window of time extending from lung growth and maturation during the fetal period through young adulthood (27–29). Many stressors can impact lung development and lung disease, including indoor and outdoor air pollution, stress (both anxiety and that associated with socioeconomic status), access to health care, genetics and epigenetics, and diet.

Evaluations of the impact of environmental factors on respiratory disease often overlook everyday chemicals. These ubiquitous chemicals can impact respiratory health in unexpected ways (30). The lung has hormone receptors that have been implicated in disease (31). Furthermore, the lung plays a significant role in xenobiotic metabolism, and many of these systems mature in the postnatal period. The lung has two primary routes of exposure to injurious compounds: via inhalation and via cardiac output and blood circulation.

Chemicals that can be metabolized and impact the respiratory tract differentially by sex and age include products of combustion, such as naphthalene (32, 33), smoke (34), vehicle exhaust–related air pollution (35), and the ubiquitous component of plastics, bisphenol A (BPA) (36). Early-life exposure to BPA is linked to both allergic sensitization and decrements in lung function, including wheeze, in children (30, 37, 38) and alterations in fetal lung maturation in experimental animals (39). More information is needed on how early exposure to ubiquitous chemicals like BPA affects the pulmonary health of women later in life.

These studies underscore several key points regarding environmental exposures and sex differences in lung disease: (*1*) there is a shifting steady state as the lung and individual grows and develops, (*2*) exposures can have both toxic and conditioning effects on the lung where exposure does not exhibit a phenotype at time of exposure but displays a phenotype when subsequently challenged, (*3*) the lag between exposure and health outcome can be substantial (even multigenerational), and (*4*) interactions between exposures as well as cumulative effects from many exposures can be present. Because these effects may differ by sex, it is critically important to include both sexes in research (40).

Sociocultural Context of Women's Respiratory Disease

Women and Household Air Pollution

Women lead different lives than men. That intuitively obvious statement carries with it a sense of disparity in opportunity, whether one lives in New York City or in the most remote village on the planet. It may also indicate a health disparity based on differences in risk related to the roles of women in the household and within society. Of course, the greatest source of health disparity for either sex is the level of household income. In the context of respiratory diseases, one global environmental exposure that has particular relevance for women is household air pollution (HAP) that results from indoor burning of solid fuels (biomass and coal) for cooking and heating. HAP exposure is associated with approximately 4 million deaths each year, predominantly from COPD, cardiovascular diseases, acute pneumonia in children under age 5 years, and lung cancer (41, 42). The vast majority of HAP-related deaths and disabilities occur in low- and middle-income countries among those households living in severe poverty (43).

Women and children have the highest exposure to HAP due to their domestic roles (43). Households typically have limited access to fuels, so wood, charcoal, animal dung, coal, or crop residues are used for cooking using either open fires or traditional unvented stoves. These cooking fires have low combustion efficiencies resulting in excess emissions, such as black carbon or "soot," into the households, blackening the interior walls. The daily breathing of filthy air that exceeds World Health Organization air quality standards by 10- to 100-fold has obvious health risks, as noted above. Women often have the domestic responsibility for cooking and for childcare, and are thus, along with children, particularly exposed to very unhealthy air to breathe. Women and children are also at risk for two related injuries: (*1*) burns and scalds; and (*2*) sex-based violence, as women and children are often tasked with fuel gathering, miles from the safety of their villages and communities (44).

The good news is that cleaner cooking solutions, such as highly efficient cookstoves or effective ventilation of stoves by well-maintained chimneys, can significantly reduce household exposures and save children from dying of acute pneumonia, as shown in a recently reported randomized controlled trial from Guatemala (45). There is also an increasing global awareness of the challenge ahead and the need to improve and implement cleaner cooking solutions that are accepted by households and communities in the very different social and cultural settings around the world. The scale of the problem is daunting, with a need to reach hundreds of millions of households and to find the best solutions and the best mechanisms to implement such strategies. The consensus-based research priorities to reduce the global burden of diseases from HAP and its burden on women and children are clear and many relate to the reduction of adverse respiratory outcomes (46). The United States government and the United Nations Foundation formed a public private partnership in 2010 called the Global Alliance for Clean Cookstoves that offers a platform to support research and implementation of clean cooking solutions, as noted in their mission statement to "save lives, improve livelihoods, empower women, and protect the environment." Additional information can be found at http://cleancookstoves.org/.

Lack of Accessible Health Care for Diagnosis and Treatment: Kenyan Women and Tuberculosis/HIV

Variability in diagnostic and treatment efficacy for tuberculosis (TB) in Kenya has been noted among HIV-positive and -negative pregnant women. Reduction of TB transmission, morbidity, and mortality relies largely on intensified case finding, with early initiation of adequate treatment. Screening and diagnosis remains a challenge in resource-limited settings, especially among women due to pregnancy, poverty, and low levels of empowerment. Diagnosing TB among pregnant women remains a challenge in Kenya. Kosgei and colleagues (47) found TB symptom screening questionnaires to be less useful than chest X-rays to identify TB suspects in both symptomatic and asymptomatic women. Physiological changes associated with pregnancy, as well as women living with HIV, may mask the symptoms of TB. These findings emphasize sex imbalances in resource-limited settings mostly biased toward women mainly due to socioeconomic and biologic factors, thus calling for a need to include sex in the core of TB management.

Sexual Minority Women and Respiratory Disease

Even in high-income countries, disparities in respiratory risk and disease are documented among certain subpopulations of women, such as sexual minority women (SMW). Although some SMW identify with a lesbian or bisexual identity, other women who have sex with women participate in same-sex relationships without identifying as "lesbian" or "bisexual." Strikingly, smoking rates among SMW are dramatically and significantly higher (at least double in most cases [48–51]) than among heterosexual peers and vary between SMW subgroups (48, 52, 53). Nonsmoking SMW are also significantly more likely to exhibit physiological evidence of secondhand smoke exposure (48). National and state-based data sets show that SMW are significantly more likely to be diagnosed with asthma (54–58), and preliminary work shows that smoking SMW report high rates of asthma among their or their partner's children (59).

These disparities arise from a multifactorial etiology. SMW experience minority stress or stress associated with being part of a stigmatized minority (60). To cope, some SMW may adapt maladaptive behaviors, like smoking. In the case of asthma, minority stress likely also plays a direct role in disease pathophysiology (54, 55). The tobacco industry actively targets sexual minorities, such as through ads in sexual minority media (61). SMW often have limited access to health care due to a lack of health insurance and financial barriers (55, 58, 62). In large part, these disparities stem from inequities in employer-sponsored health insurance for same-sex couples (63, 64). Deficiencies in cultural competency among providers further impede the delivery of quality care to SMW. Substantial proportions of SMW worry that there are not enough providers trained to work with sexual minorities, fear being treated differently if they disclose their sexual orientation, and express concern that their provider assumes them to be heterosexual (65, 66). This discomfort can manifest in high rates of health care avoidance: one state survey found that approximately one-third of sexual minority individuals report not seeking health services because of their sexual orientation (65, 66).

Going forward, it will be critical to more accurately describe respiratory disparities among SMW, which necessitates including sexual orientation demographics—at a minimum, identity and behavior—in public health surveillance systems, such as the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database. In addition, further research is needed to evaluate within-group differences in respiratory risk and disease based on factors such as sexual orientation, geographic region, and race/ethnicity (52). Importantly, tobacco prevention and cessation programs targeted to SMW must be validated and implemented.

Women's Use of Complementary and Alternative Medicine

Chronic illness is a leading cause of morbidity and mortality worldwide (67), affecting nearly one in two people in the United States (68). Patients and families often manage chronic illness largely outside of the health care system, focusing on their personal concepts of health as they experience it (69), relying on idiosyncratic concepts of health (69), and selecting nonstandardized forms of treatment. For example, although asthma is more prevalent among women (70), the latter are more likely than men to experience uncontrolled asthma (71) due, in part, to lower rates of adherence to prescription controller therapies (72). It is not the case that women fail to get involved in managing their disease; rather, they may be more likely to attempt management in ways that do not make use of standardized medicine.

Lung disease and respiratory symptoms rank in the top 15 most common conditions for which complementary and alternative medicine (CAM) is used (73). CAM includes "diverse medical and health care systems, practices, and products that are not generally considered to be part of conventional medicine" (74). CAM is used by more women than men (42.8 vs. 33.5%, respectively), and when prayer and megavitamins are included in responses, women of color have the highest rate of CAM use (73). Providers infrequently inquire about CAM (75, 76), and patients may not disclose, even if asked, for fear of disrupting the therapeutic alliance (75, 77). In these circumstances, if patients and providers could openly discuss and reconcile these differences to the satisfaction of both parties (shared decision making), then women's asthma medication adherence (78, 79) and satisfaction with care (80) may be improved.

Conclusions

Sex-based disparities in respiratory disease are apparent and highly diverse in nature. These disparities range from physiological differences (e.g., body size, ventilator patterns, and hormonal levels) to different environmental exposures (household air pollution in low- and middle-income countries, enhanced TB in women with HIV infection in resource-limited settings, increased asthma and COPD in developed countries) around the world. The year 2000 marked the first time that more women than men died from COPD. This trend is expected to continue and highlights the urgent need to better understand the potential mechanisms by which women are more susceptible to certain respiratory diseases than men. Disparities within disparities among women, such as those experienced by SMW, as well as tradition-based CAM, also deserve further research and understanding. We are optimistic with the recent National Institutes of Health mandate to include both sexes in animal research and make sex equality a priority in research. Different mechanisms underlying disease susceptibility in women and men may be uncovered more readily as future research addresses sex-based disparities in symptoms and diseases of the respiratory system. ■

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