Female Sex and Gender in Lung/Sleep Health and Disease

Increased Understanding of Basic Biological, Pathophysiological, and Behavioral Mechanisms Leading to Better Health for Female Patients with Lung Disease

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Abstract

Female sex/gender is an undercharacterized variable in studies related to lung development and disease. Notwithstanding, many aspects of lung and sleep biology and pathobiology are impacted by female sex and female reproductive transitions. These may manifest as differential gene expression or peculiar organ development. Some conditions are more prevalent in women, such as asthma and insomnia, or, in the case of lymphangioleiomyomatosis, are seen almost exclusively in women. In other diseases, presentation differs, such as the higher frequency of exacerbations experienced by women with chronic obstructive pulmonary disease or greater cardiac morbidity among women with sleep-disordered breathing. Recent advances in -omics and behavioral science provide an opportunity to specifically address sex-based differences and explore research needs and opportunities that will elucidate biochemical pathways, thus enabling more targeted/personalized therapies. To explore the status of and opportunities for research in this area, the NHLBI, in partnership with the NIH Office of Research on Women's Health and the Office of Rare Diseases Research, convened a workshop of investigators in Bethesda, Maryland on September 18 and 19, 2017. At the workshop, the participants reviewed the current understanding of the biological, behavioral, and clinical implications of female sex and gender on lung and sleep health and disease, and formulated recommendations that address research gaps, with a view to achieving better health outcomes through more precise management of female patients with nonneoplastic lung disease. This report summarizes those discussions.

Keywords: sex/gender; lung disorders; sleep disorders

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Introduction to the Role of Female Sex and Gender in Lung/Sleep Health and Disease

The NIH is committed to improving the health of all individuals. Central to this mission is supporting research that informs prevention and treatment strategies for both men and women. The role of sex and gender in scientific discovery, disease detection, diagnosis, and treatment is often underappreciated. To this end, the NHLBI, in partnership with the NIH Office of Research on Women's Health and the Office of Rare Diseases Research, convened a 2-day workshop of investigators in Bethesda, Maryland in September 2017. At the workshop, the participants, chosen based on their expertise in women's health as it applies to various aspects of lung and sleep medicine, reviewed the current understanding of the biological, behavioral, and clinical implications of female sex and gender on lung and sleep health and disease. Topics were chosen by the NHLBI and workshop chairs. Experts presented data with subsequent discussion. After the workshop, electronic discussions continued with participants formulating recommendations that address research gaps, with a view to achieving better health outcomes through more precise management of female patients with nonneoplastic lung disease.

Central to these discussions at the outset was to be precise regarding the difference between the terms "sex" and "gender." Whereas "sex" refers to biological differences between females and males, including chromosomes, sex organs, and endogenous hormonal profiles, "gender" refers to socially constructed and enacted roles and behaviors, which occur in a historical and cultural context and vary not only across societies and over time, but may also impact individuals differently across the lifespan. Gender encompasses factors, such as social support, environmental exposures, and work roles (i.e., shift work exposure causing circadian misalignment is prevalent in women). Ultimately, health is influenced by the interactions between both sex and gender. However, including women and diverse populations in research is not just a matter of enrolling women and diverse populations in clinical studies, but requires changing current paradigms of how research is designed. Researchers must consider the impact that their experimental design has on the sex hormonal profile and accurately analyze data focusing on the impact of sex, not only of the individual being studied, but also of the cell used in an *in vitro* experiment. Treating all adults as equivalent, drawing conclusions devoid of sex, gender, age, race, and environment, is imprecise, and focusing research only on one sex or gender to the exclusion of the other is no longer acceptable (1). Exploring the potential influences of both sex and gender on lung and sleep research is the focus of this report.

Biological Domains through Which Sex and Gender Impact Health and Disease

Sex Hormones in Lung Development and Disease

Inherent sex differences in human lung structure and function are apparent even *in utero*, and manifest throughout the lifespan (2). Sex differences in lung structure/function at puberty, pregnancy, menopause, and in aging suggest additional modulatory roles of sex steroids (estrogen, progesterone, testosterone) and/or their metabolites. Relationships between sex steroids and lung structure/function are underscored by sex differences in susceptibility to and incidence and severity of, for example, asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, lung cancers, and pulmonary hypertension. A greater female-to-male ratio, or worse outcomes in women, emphasize the need to understand the relative roles of intrinsic sex differences versus the roles of sex steroids *per se* (particularly female sex steroids) in disease pathophysiology. Appreciation of how sex steroids or their metabolites exert their action, both as gonadally derived hormones and locally produced, may be important. Furthermore, it is necessary to understand the likely substantial cellular, tissue, or even species heterogeneity in basic sex steroid and receptor signaling pathways, as well as interactions between sex steroids. Understanding the role of sex steroid signaling in the lung could contribute to development of novel biomarkers and therapeutic strategies to target lung diseases (3).

Tobacco Use, Sex/Gender, and Lung Disease

Tobacco use is the leading cause of preventable morbidity and mortality in the United States, resulting in roughly 500,000 deaths yearly (4). The disease risks from smoking by women, including lung disease, have risen sharply over the last 50 years, and are now equal to those for men (5). Historically, males have initiated tobacco substance abuse at earlier ages and in higher proportions than females (6), although current smoking prevalence for teenage boys and girls is roughly similar (7). Unfortunately, the age of smoking initiation for most adults who smoke is before 18 years of age (7). Limited reports suggest that early tobacco initiation may be associated with delayed puberty in both girls and boys (8, 9). The U.S. Food and Drug Administration has outlined a strategy to reduce tobacco-related disease, which includes minimizing the abuse liability of cigarettes, and investigating whether "less harmful" tobacco/nicotine products can support this public health goal (10). It is critical to understand whether this approach would be equally effective for women and men. The U.S. Food and Drug Administration is also supporting research evaluating whether reduced-nicotine cigarettes translate to reductions in smoking behavior. It is more difficult for women to quit smoking, and women's smoking behavior is less tied to nicotine content and nicotine-related reinforcement. Continued research designed to investigate sex and gender differences in response to

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reduced-nicotine-content cigarettes is critical. The prevalence of e-cigarette use continues to increase, especially among adolescents. There is much conflicting data about whether e-cigarettes contribute to smoking cessation behavior, and it is unknown whether there are sex differences in these relationships or in their health impact. Animal models of tobacco exposure have just begun to explore some of these issues.

Circadian Rhythms, Sex/Gender, and Lung Disease

Circadian rhythms are endogenous variations in physiology resulting from feedback loops that produce rhythms in gene expression with a cycle length of approximately 24 hours (11). The suprachiasmatic nucleus, a master pacemaker in the hypothalamus, receives light/dark information, synchronizes this system to the 24-hour solar day, and then transmits timing information to the rest of the body via autonomic and endocrine signals. Cells, tissues, and organs of the body also receive circadian timing information from feeding and other behaviors. When synchronized and optimally timed, the circadian system allows the body to anticipate and prepare for regular physiologic challenges (11). However, access to artificial light, irregular sleep schedules, travel across time zones, shift work, and other aspects of modern 24/7 society can desynchronize these rhythms, resulting in suboptimal functioning in the short term and, over the longer term, increase the risk of cardiovascular disease, diabetes, cancer, depression, and reproductive complications, among other conditions affecting women. Sex differences in key features of the human circadian system may result in differential susceptibility to circadian misalignment, circadian rhythm sleep disorders, and circadian-coupled pathophysiology disease risk in men and women (12). In fact, in a clinical study where sleep–wake cycle was purposefully disrupted, women experienced more cognitive impairment than men, suggesting that women may be more susceptible to the effects of shift work and jet lag (13). Nearly half of protein-coding genes show circadian expression, and there is major overlap of those genes with disease-associated genes and molecular targets of medications. These discoveries may be leveraged to identify circadian-dependent molecular signatures and mechanisms of disease pathophysiology to improve the prevention and management of diseases affecting women's health across the lifespan (14).

Microbiome, Sex/Gender, and Lung Disease

The human microbiome, a complex system comprised of bacteria, viruses, fungi, and archaea that inhabit various niches, plays a role in a number of diseases, including cardiovascular disease, diabetes, obesity, and cancer. Several reasons point to a potential influence of sex and gender on the microbiome. Differences in anatomy, environmental exposures, hormones, and medications may alter both the types of microbes present at a given body site and their functions. Cross-talk between the host and microbes may occur via effects of sex hormones on bacterial growth and signaling, as well as through bacterial metabolism of sex hormones. The microbiome may also differ over the lifespan and across reproductive phases, such as puberty, pregnancy, and menopause. There may also be sex differences in the microbial community structure and function in the gut, where most microbiome studies have so far been focused. The microbiome of the lung is less-well understood. Investigators are exploring the role of the lung microbiome in diseases, such as asthma, cystic fibrosis (CF), and COPD, but very little has been reported about the influence of sex and gender. A study of patients with CF found that exacerbations increased during the menstrual cycle in correspondence of higher estradiol levels, and women taking oral contraceptives had fewer exacerbations (15). In a mouse asthma model of vitamin D supplementation, investigators reported that the lung microbiome differed in male and female mice (16).

Animal and Cellular Models of Lung Disease and Sex/Gender

Understanding of the biology and pathobiology of lung disease has been greatly enhanced by the availability of animal models of lung diseases (17). However, many variables in mouse experimental models, including sex, can confound comparisons among papers published from different groups, but often go unreported. It is critical that investigators provide detailed reporting of their model(s). This is of particular importance when modeling lifespan stages (puberty, adulthood, old age) in animal models. Asthma is a prime example where discrepancies exist in the literature (18). Due to differences in lung structure, the inflammatory response, and airway hyperresponsiveness to allergens in mouse versus human lungs, developing animal models that attempt to more closely resemble different human asthma endotypes is warranted (19). There is a need to better model and understand the effect of female sex and obesity on allergic lung inflammation, as well as premenstrual exacerbations, *de novo* asthma postmenopause, and severe steroid-resistant asthma (20, 21). Animal models have also been widely used to study tobacco smoke exposure (22, 23), but there is a scarcity of experimental data on sex differences. Evidence suggests that increased small airway wall remodeling is observed in female compared with male mice (24, 25). Data on airspace enlargement are less conclusive, with reports that cigarette smoke–induced emphysema occurs more readily in female compared with male mice, whereas other studies did not observe differences between sexes (26, 27). Clearly, further studies are warranted to assess sex differences in animal models of COPD. These same principles are relevant to cell lines where sex, age, time of collection, and culture conditions must also be carefully considered and detailed (28). The products of the X and Y genes include functions beyond those related to development of sex hormones. Differential gene expression by sex has been noted in many tissues, and may have marked impact on biology. However, a review of articles published in 2013 in the *American Journal of Physiology–Cell Physiology*, which requires sex of cell lines to be reported, demonstrated 20% of cell lines used to be of male origin, 5% female, and the other 75% still unreported (29). To further illustrate, of the most commonly used lung epithelial cell lines reported in that journal, both are of male origin. Yet male sex has also been associated with reduced alveolar epithelial sodium transport capacity (30) and impaired regenerative capacity after injury (31), demonstrating the importance of accounting for cell sex in respiratory research

Role for Female Sex and Gender in Specific Lung/Sleep Diseases

Asthma

Asthma is caused by complex heterogeneous pathological processes that affect the airways (32). In females, asthma is influenced by the rise during puberty, and then fluctuating levels, of sex hormones. Early-onset menarche resulting in greater cumulative estrogen and progesterone increases the risk of asthma (33). Asthma incidence and hazard rate increases in women on hormone replacement therapy, and asthma worsens perimenstrually in 30–40% of females. Puberty also marks the point in which women develop higher adiposity and a greater ratio of leptin to adiponectin, adipokines implicated in asthma. These hormonal changes, together with differences in airway size (i.e., dysanapsis [34]), contribute to the higher asthma prevalence in women. Clinically, women have more frequent and severe asthma symptoms, poorer quality of life, greater healthcare utilization, greater likelihood of hospitalization, and a higher mortality rate (35). The Severe Asthma Research Program showed that asthma is worse in boys than in girls and in women than in men. Androgens are generally associated with higher lung function in asthma; in a large Norwegian population study, lower FEV_1 was associated with lower testosterone (36). Similar findings were observed in a large Australian cohort (37). Inhaled dehydroepiandrosterone (DHEA) improves asthma symptoms (38). Testosterone can promote airway smooth muscle relaxation. DHEA inhibits human airway smooth muscle and fibroblast proliferation, and is a bronchodilator in guinea pigs (39). In the Severe Asthma Research Program cohort, endocrine substudies revealed differences in levels of DHEA and testosterone associated with the severe asthma phenotype. Surprisingly, both males and females with severe asthma improve in adolescence, but asthma severity increases among women in adulthood. These facts underscore the need to better understand asthma in females, taking into account not only the cellular and tissue-specific alterations, but also the interplay of the complex hormonal milieu and the impact of sex/gender (40).

CF

CF is an autosomal recessive disease that results in progressive airway obstruction and is characterized by chronic inflammation and infection of the lungs. Although equally prevalent in males and females, females exhibit a decreased life span due to complications of more severe lung disease. The United States CF Foundation patient registry showed a sex disparity with regard to median life expectancy, which was found to be nearly 3 years shorter in females (41). Females with CF after puberty also have a higher rate of pulmonary exacerbations (42). Furthermore, *Pseudomonas aeruginosa* is acquired by females with CF earlier in life, and is associated with a more rapid decline in lung function (43). Interestingly, although females with CF receive lung transplantation at a younger age than males, the post-transplantation survival is equal between sexes regardless of the sex of the donor lung (44). Discrepancies in adherence, access to care, size of the airways, and activity or exercise levels may account for some of the differences. Existing data also implicate sex hormone–mediated effects on CF lung disease. One hypothesis is that 17β-estradiol contributes to worse female outcomes through modulation of bacterial morphology, airway epithelial ion channels, inflammation, and neutrophil functions. 17β-estradiol induces a mucoid conversion of *P. aeruginosa in vitro*, and higher levels of 17β-estradiol are associated with increased exacerbations in CF (15). 17β-estradiol affects uridine triphosphate–induced chloride secretion on airway epithelium, resulting in a further decreased air surface liquid layer in females (45). 17β-Estradiol induces marked impairment in *P. aeruginosa*–killing capacity by neutrophils, correlating with an exaggerated inflammatory response (46). The effects of other sex hormones, including progestin and androgen, have not been thoroughly evaluated in CF. These data show that CF may provide a model disease to understand differences in male and female outcomes in a lung disease. The robust national registry supported by the CF Foundation can track the influence of sex hormones across the lifespan, and a large subset of lung transplant data allows for analysis of the impact of transplant sex mismatch.

COPD

COPD is a complex condition, characterized by progressive and largely irreversible airflow limitation (47). Although COPD affects both men and women, COPD prevalence is increasing more rapidly in women, particularly in younger women (48). In the United States, COPD-related hospitalizations and deaths in women now also surpass those in men (48). Women also predominate the roughly 25% of nonsmokers with COPD (49). Sex-specific susceptibility to COPD is poorly understood; however, published data suggest that women are more susceptible to tobacco smoke (48). Women with COPD also face challenges related to their interface with the healthcare system. Women are more likely to be misdiagnosed (50), and survey data also suggest that women are more likely to perceive a delay in diagnosis, attributing it to lack of availability of providers and poor insurance (51). Although individuals with COPD tend to have lower socioeconomic status than those without COPD, income for women with COPD tends to be even lower than that for men. It is not known exactly what impact this has on the ability to obtain appropriate care and other clinical outcomes. Multiple studies outside of COPD demonstrate that women in general are less likely to be adherent to medication, which could also impact disease presentation and management (52). Although socioeconomic factors certainly could influence adherence, differences appear to persist even after adjusting for socioeconomic factors (53).

Women report more dyspnea than men despite similar lung function testing and fewer pack years of smoking (54). Factors that may contribute include greater prevalence of anxiety and depression and increased frequency of COPD exacerbations in women (54, 55). Differences for COPD risk and manifestations are likely multifactorial: smaller lung size in women, estrogen impacts on xenobiotic metabolism of cigarette smoke, and environmental exposures may also contribute. In addition, the perimenopausal period represents a time of significant lung function decline in women. Molecular analyses suggest sex differences in inflammatory burden. Sex-specific genetic and epigenetic associations, gene-by-smoking interactions, and X chromosome associations all contribute to

the differential impact in women. These findings present an opportunity for the development of sex-specific therapeutics.

Multiple studies suggest that it is more difficult for women to quit smoking, but data from the Lung Health Study also suggest that smoking cessation results in greater lung function improvement for women (56). Additional data from the Lung Health Study also suggest greater FEV_1 response to inhaled ipratropium for women, possibly due to greater M3 relative to M2 receptor expression in women (57), and a pooled analysis of indacaterol/glycopyrronium studies reported greater quality-of-life improvements in women (58). Taken together, the compendium of evidence suggests that gender-specific approaches to COPD are imperative. As gender is clearly multidimensional, systems-based analytic approaches may also allow us to refine early diagnosis, therapeutics, and primary prevention to account for these differences (59).

Pulmonary Fibrosis

Interstitial lung diseases are a heterogeneous group of disorders that are increasing in prevalence. The most common of these diseases, idiopathic pulmonary fibrosis (IPF), displays evidence of sexual dimorphism (60). Men are affected by IPF more than women, and female sex is predictive of better outcomes in IPF, including outcomes with surgical lung biopsy, lung transplantation over the age of 65 years, and overall survival (61–63). However, women are more burdened by the symptoms of IPF compared with men, and have worse health-related quality of life (64). There have been a few animal models of pulmonary fibrosis that have sought to understand this sexual dimorphism, mostly pointing toward the adverse effect of testosterone (65). However, confirmatory studies in humans are absent. Interestingly, in one population-based case–control study, the adverse effect of smoking on development of severe pulmonary fibrosis was amplified by male gender (66). The other main group of ILDs that display sexual dimorphism in regard to prevalence and natural history are the autoimmune-related interstitial lung diseases. Young women are most commonly affected by this condition, yet men who get this disease generally have a worse natural history compared with women (67).

Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) is a destructive, progressive lung disease that can lead to respiratory failure in young women. LAM is caused by inactivating mutations in the tuberous sclerosis complex (TSC) genes, TSC1 and TSC2, leading to activation of mTORC1 (68). For reasons that are incompletely understood, but possibly associated with estrogen pathways, LAM affects women almost exclusively, with one of the strongest gender predispositions of all human diseases, except for diseases of the genital organs (69, 70). LAM progresses more rapidly in premenopausal women, further supporting a key role of hormonal factors. It is believed that LAM cells originate outside the lungs, although the precise site of origin is not established; the uterus, pericytes, and neural crest are candidates. Both cell-autonomous effects of hormones on cell proliferation and metabolism, and non–cell-autonomous effects on lymphangiogenesis and the destruction of lung parenchyma are likely to contribute to LAM pathogenesis. Recent data show that targeting estrogen receptors may be efficacious in the treatment of LAM (71).

Pulmonary Hypertension

Pulmonary arterial hypertension (PAH), a progressive cardiopulmonary disease that involves remodeling and vasoconstriction of vessels in the lung, is a sexually dimorphic disease more common in women (72). Despite female preponderance of disease development, female patients with PAH exhibit better survival than males (73, 74). This puzzling observation has been termed the "estrogen paradox" of PAH. An additional estrogen paradox in PAH research centers on the fact that estrogens have been shown to be protective in several animal models of PAH, an observation that is opposed to the clinical finding of female susceptibility to disease development (72). On the other hand, animal studies exist in which estrogens (in particular, 16α-hydroxyestrone) have been linked to disease development (72). The reasons for the discrepancy are unclear, but it is likely that differences in experimental models used, differences in estrogen delivery, and/or differences in the age of experimental animals contribute to these findings. The underlying etiology of PAH/pulmonary hypertension (PH), the presence of genetic alterations (e.g., mutations in the *BMPR2* gene) and the stage of the disease (early vs. late) may determine whether estrogens are beneficial or harmful in PAH. In humans with established PAH, it is clear that sex affects success of some PAH-directed therapies, in addition to survival (75, 76). A fairly uniform body of evidence suggests that 17β-estradiol has important direct and indirect effects on right ventricular (RV) function, which allow for better RV adaptation to the PAH-induced increase in RV afterload (72). The etiology of the observed sex-based difference in treatment responses is presently unknown.

Sleep-disordered Breathing

Sleep-disordered breathing (SDB) is a serious medical condition characterized by recurrent episodes of airway closure and reopening during sleep, typically resulting in intermittent hypoxia, elevated sympathetic tone, oxidative stress, as well as fragmented and poor sleep quality (77). Sleep apnea is associated with an array of disease risks and outcomes common in women, including hypertension, myocardial infarction, heart failure, stroke, diabetes, cancer, depression, dementia, and quality-of-life measures (77). Women tend to report different sleep apnea symptoms than men, more commonly noting insomnia, fatigue, and/or depressive symptoms, rather than the more traditional symptoms of chronic snoring and gasping for air during sleep (78). Sleep questionnaires are not routinely designed and validated taking sex differences in SDB clinical presentation into consideration. Women are less likely than men to seek medical attention for concerns about SDB, and medical professionals less likely to recognize women's symptoms of SDB, leaving the large majority of women with SDB undiagnosed and untreated (78, 79). There is a critical need to improve the identification of patient-reported symptoms and physiological risk factors of SDB in women to reduce the number of undiagnosed cases.

The severity of SDB generally differs in women compared with men, including a lower apnea–hypopnea index, shorter duration of individual apnea/hypopnea events, less oxygen desaturation, and greater occurrence of airflow limitation accompanied by microarousals from sleep (79). Although sleep apnea is overall less prevalent in women, susceptibility increases with overweight/obesity, and during

particular life stages, including pregnancy and menopause (78). Research is needed to more completely understand mechanisms underlying sex differences in the etiology of SDB, including upper airway anatomy, neuromuscular function, sex hormone effects on ventilatory control, and genetic susceptibility. For example, sex-specific differences have been identified in the sleep-state–dependent hypoxic ventilatory response (80). *RAI1* and obstructive sleep apnea–related quantitative trait locus in men, but not women, suggest that different biologic pathways may be involved in the etiology of SDB in men compared with women (81).

Although epidemiologic findings point to middle-aged men as most vulnerable to sleep apnea–related mortality and coronary heart disease, recent findings point to an array of SDB-associated cardiometabolic risks in women (79), with even greater susceptibility to elevated hs-troponin levels, increased left ventricular mass, incident heart failure, impaired endothelial function, and brain white matter loss (79, 82–84). Emerging experimental intermittent hypoxia models support a link between estradiol and SDB-triggered cardiopulmonary dysfunction (85). In addition, associations of SDB with cardiovascular and metabolic outcomes in pregnancy, such as pre-eclampsia and gestational diabetes, have been consistently described (86, 87), both conditions anticipating cardiovascular and metabolic disease later in life. Maternal SDB is linked to adverse neonatal outcomes that are associated with long-term morbidity in the offspring, such as preterm birth and possibly growth restriction (86). The effect of SDB exposure (e.g., oxidative stress, inflammation, sympathetic drive) on mechanisms of placental function and *in utero* development are not well understood. A better understanding of SDB-triggered mechanisms of pathobiology in women is needed to identify intermediate markers and therapeutic targets to mitigate SDB risk to women's health. SDB is frequently comorbid with insomnia, depression, fatigue, asthma, and chronic pain, and may contribute to the etiology, severity, and the ability to effectively treat these conditions (78, 79). In summary, SDB is a risk factor for many conditions affecting women, and needs to be considered as an important variable in research studies, and evaluated as a key factor in the health of women.

Conclusions and Future Perspectives

One of the most important issues on which biomedical researchers and social scientists can collaborate is defining the mechanisms by which the environment modifies the phenotype, central to which is the interplay between sex and gender. This report highlights variations in disease prevalence, presentation, and progression that may be mediated by biological or social factors, or both. Personalized medicine will not advance without inclusion of the roles of sex/gender in biology and pathobiology (88). A key goal of the workshop was to develop a list of future recommendations to advance our understanding of the roles of sex and gender in sleep and lung diseases, as outlined in Table 1. Although multiple recommendations were developed, top priorities that could be implemented within the next few years include, first, the need for guidelines standardizing reporting of sex for cellular and animal models. Second, the participants recommend that

Table 1. Workshop Recommendations

Key recommendations:

- Establish guidelines/standardization encompassing sex for reporting of cellular and animal models for *in vitro* experiments
- Develop multidisciplinary platforms, with the inclusion of endocrinologists, for understanding sex steroid expression and signaling in both basic and clinical research
- Encourage the reporting of sex-stratified analyses when possible (as supplemental tables), to allow future meta-analyses of sex differences
- Train pulmonary researchers in big data methods that accommodate systems biology and network modeling of sex and gender and their impact on lung diseases and sleep disorders

Additional recommendations:

Basic research
- Include female animals and take into account the estrous cycle of the female mice in all modeling of lung/sleep disorders
- Microbiome studies should incorporate sex as a variable and address causal pathways by which sex/gender influences the structure and function of the microbiome, including metabolomics and transcriptomics
- Develop a multi-institutional "biobank" specific to exploration of women's lung and sleep health and promote sex-specific analysis of genome-wide association studies in various populations

Clinical research
- Perform preclinical and clinical trials to determine how hormonally based therapies can be used to benefit women with lung diseases and sleep disorders
- Understand the impact of gender on symptoms of disease and therapeutic choices
- Understand the impact of sex and gender on side-effect sensitivities to therapies, including pharmacologic and nonpharmacologic (e.g., oxygen, pulmonary rehabilitation) options, and drug metabolism
- Study the effects of modifying factors, such as age, menopausal state, and nutrition, on sex hormone signaling in pulmonary diseases and sleep disorders
- Clarify how gender disparities in comorbidities of lung diseases/sleep disorders may impact disease progression and prognosis
- Clarify the impact of hormone contraceptive therapy and hormone replacement therapy on lung diseases/sleep disorders
- Study in detail sex hormones, ratios, and metabolites other than estrogens
- Study of how sex/gender may mechanistically alter drug responses

Training
- Train pulmonary care providers in the biological, environmental, and psychosocial aspects of gender as it relates to lung disease/sleep disorders
- Train pulmonary care providers about sex differences in lung biology and pathobiology/sleep disorders, and their manifestations across the life course, including susceptibility, presentation, and severity of disease
- Train pulmonary care providers in the chromosomal and endocrinological differences that may drive health effects in lung diseases/sleep disorders

multidisciplinary platforms, particularly including endocrinologists, be developed to encourage broader understanding regarding the role of sex steroids in the mechanisms of health and disease. The workshop itself brought together individuals with a wide variety of research focus and expertise. These types of collaborative efforts will be crucial to expanding our understanding the role of sex and gender. A third recommendation is that clinical trials report sex-stratified analyses when possible to allow for future meta-analyses, which would be fairly easy to implement. Fourth, we must leverage new scientific advancements, including gene editing and epigenetic modifications. We now know that genetic expression is moderated through epigenetics, not confined to the methylation of DNA only. Some examples of epigenetic phenomena/action include X chromosome inactivation, sex-specific gene expression in tissues during development, the creation of the sex-specific setting for disease later in life, and the establishment of the machinery for the heredity of epigenetic modifications. Societal trends, where chromosomal and hormonal sex are mismatched, may also represent an opportunity to clarify the role of sex versus gender in health and disease. Finally, we must enhance the training for future researchers in big data methods that accommodate systems biology and network modeling of sex and gender and their impact on sleep and lung disease. ■

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