Society for Women's Health Research

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Submitted electronically to: *WHWGRFI@nhlbi.nih.gov*

Gary H. Gibbons, MD
Director
National Heart, Lung, and Blood Institute
National Institutes of Health
Building 31
31 Center Drive
Bethesda, MD 20892

Re: Request for Information (RFI) NOT-HL-18-660: Understanding the Health of Women and the Role of Sex/Gender in Mechanisms of Heart, Lung, Blood, and Sleep Diseases and Disorders

Dear Dr. Gibbons:

The Society for Women's Health Research (SWHR) commends the National Heart, Lung, and Blood Institute (NHLBI) for forming the NHLBI Women's Health Working Group (WHWG) to pursue a better understanding of the health of women through behavioral and biomedical research. We support the NHLBI WHWG goals outlined in the October 23, 2018, Request for Information (RFI) Notice (NOT-HL-18-660) and are pleased to provide the following information on scientific gaps in understanding of how sex and gender differences in sleep disorders affect women across the lifespan.

SWHR is a nearly 30-year-old education and advocacy nonprofit dedicated to promoting research on biological differences in disease and improving women's health through science, policy, and education.
Because of SWHR's advocacy efforts, women are now routinely included in most major medical research studies, and NIH-funded scientists are required to consider sex as a biological variable in their research.

Quality sleep is essential for the health and well-being of all, but sleep needs vary across the lifespan and are impacted by sex and gender. For example, women and men may have the same sleep problems but present with different

symptoms, creating a potential need for sex-specific screening, diagnosis, and treatments.[1] In addition, women have more sleep disorders and sleep-related complaints than men.[2,3] However, much of what we know is based on studies in men or male animals, and research is only now delving into sex and gender differences in sleep. Therefore, prioritizing sleep health in women is critical. Currently, scientific gaps exist and could be better addressed by:

1) understanding risk factors and improving diagnoses in sleep disorders for women;
2) examining sex differences and gaps in treatments for sleep disorders; and
3) exploring how sleep impacts other diseases and conditions.

Understanding risk factors and improving diagnoses in sleep disorders for women

Female sex hormones play a role in the changing sleep needs of women across developmental milestones and are thought to be a factor in some sleep disorders such as insomnia and restless legs syndrome (RLS), which are more prevalent in women.[4,5] For example, sex differences in insomnia prevalence emerge around puberty and continue to widen throughout the lifespan.[3,4] Meanwhile, RLS is more prevalent in women than men because of an increased incidence during pregnancy. [6] However, it remains unclear *how* sex hormones may influence risk for insomnia and RLS. More research into sex differences in sleep disorder risk factors may lead to new therapeutic avenues for treatment.

Conversely, sleep disorders that are more common in men, such as obstructive sleep apnea (OSA), often go undiagnosed in women because women may present with "atypical" symptoms.[7] For example, approximately 90% of women with OSA are undiagnosed.[8] Because women's symptoms were not heavily researched in the past, OSA diagnostic tools may not be sufficiently sensitive in women because of their focus on symptoms more predominant in men.[9,10]

Similarly, narcolepsy was originally thought to be more prevalent in men, but studies now show no difference in prevalence between women and men.[11] However, women experience a diagnostic delay nearly double in length than men do.[12] It is imperative to recognize sex and gender differences in disease presentation in order to create better diagnostic and treatment options for women moving forward.

Examining sex differences and gaps in treatments for sleep disorders

Women and men may respond to treatments differently as well. A well-known example is the hypnotic medication, zolpidem, which is metabolized differently in women and men.[13,14] This ultimately led to the FDA lowering the recommended dosage for women.[15] Yet very little is known about sex differences in safety and efficacy for most therapies. There is a great need to carefully examine current and future sleep disorder therapies by sex to create a more tailored approach to treatment moving forward.

Women are particularly vulnerable to the effects of sleep disorders during pregnancy, when these disorders can develop, present, and exacerbate. However, we lack safe and effective treatment options for pregnant and lactating women. This leaves women and their health care providers to make decisions about treatment without the necessary information and may impact women's reproductive-related decisions. For women with narcolepsy, for example, data are lacking to assist them in deciding whether to take their medications while pregnant and

breastfeeding. As a result, studies show women with narcolepsy are generally older when they get pregnant and discontinue medications during pregnancy.[16,17]

In other diseases like RLS, many of the effective treatments are pharmacological. This poses a problem for pregnant women, as most medications have some teratogenic potential.[18] Meanwhile, non-pharmacological options, albeit safer, may not be as effective.[19] Research into alternative treatments options is greatly needed.

Exploring how sleep impacts other diseases and conditions

Poor sleep can have deleterious effects on both mental and physical health. Changes in sleep may also influence age-dependent diseases as well as susceptibility to chronic diseases such as obesity, diabetes, vascular disease, depression, neurological disease, and cancer.[20,21] Therefore, there is a need to study sex and gender differences in sleep disorders in the context of other diseases.

A prime example is Alzheimer's disease (AD). Sleep disturbances are common among those with Alzheimer's and may impact AD pathology as well.[22] Recent evidence suggests that disruption of slow-wave sleep increases levels of β-amyloid.[23] In addition, the prevalence of sleep disturbances and sleep disorders can increase with age. For example, sleep apnea increases in prevalence for women after menopause, and individuals with sleep apnea show cognitive decline at an earlier age than those without sleep apnea.[24] Interestingly, treatment of sleep apnea with continuous positive airway pressure may delay the onset of cognitive dysfunction.[24] Thus, sleep may represent a modifiable risk factor for AD. However, more research is needed to understand the relationship between sleep and AD risk and whether that risk differs between women and men.

Sociocultural factors specific to women also affect sleep and overall health. Women are often the primary caregivers for their families and may sacrifice sleep for social and familial obligations. Poor sleep quality increases risk for chronic illnesses. Women shift workers are particularly vulnerable, as they are at increased risk for breast cancer and endometrial cancer and have impaired reproductive health.[25-27] There is a need for more research to further our understanding of how these environmental factors, like shift work or caregiving, impact sleep and women's overall health.

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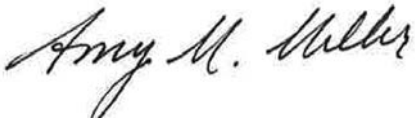
Thank you for this opportunity to comment on RFI NOT-HL-18-660 and for NHLBI's consideration of the information provided. We look forward to serving as a resource on sex and gender differences in women's health, which is leading to critical discoveries of how women and men differ in fundamental ways and how these differences affect disease risk, pathophysiology, symptoms, diagnostic sensitivity and specificity, and response to therapy. If you have questions,

please contact Sherie Lou Santos, Director of Science Policy, at 202-496-2006 or sherielou@swhr.org.

Sincerely,



Amy M. Miller, PhD
President and Chief Executive Officer
Society for Women's Health Research

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