



WOMEN'S HEALTH *In Focus* AT NIH

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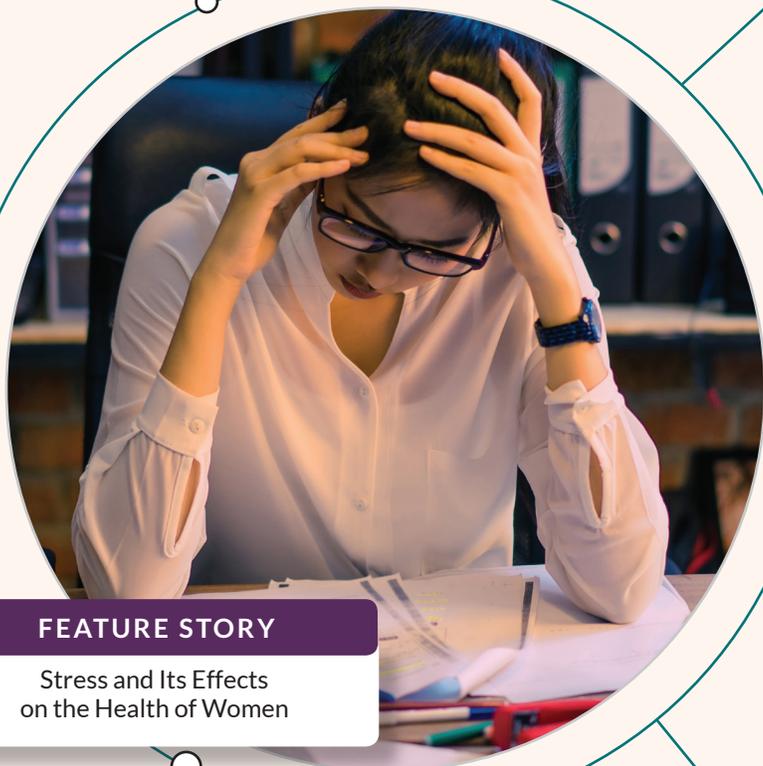
DIRECTOR'S CORNER



SCIENTIST SPOTLIGHT

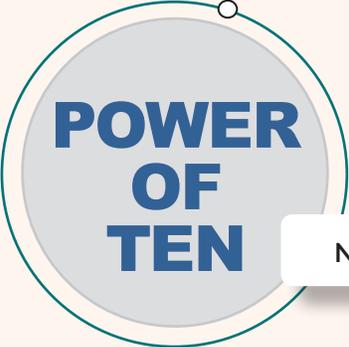


CLINICAL RESEARCH



FEATURE STORY

Stress and Its Effects on the Health of Women



NOTEWORTHY



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Stress and Its Effects on the Health of Women

“I’m stressed out!”

We hear this phrase all the time and understand that stress contributes to irritability, restlessness, anger, and social withdrawal. When we feel particularly overwhelmed, we know that stress can lead to memory and concentration problems, sleep disturbances, and headaches. Stress can also contribute to more serious health conditions,^{1,2} such as obesity, high blood pressure, diabetes, anxiety disorders, emotional disorders, and even unhealthy aging and dementia. Up to 43% of American adults suffer from adverse health effects as a result of stress,³ and one calculation showed that stress costs American industry about \$300 billion annually.⁴ In this article, we will describe common stressors; characterize sex- and gender-specific responses to stressors; discuss some of the health risks of those responses, including those particular to women and men; and suggest some ways to mitigate the effects of stress to prevent their adverse impact on health.

What Is Stress?

“Stress” is a common term used to describe the body’s natural reaction to perceived threats, also known as stressors.⁵ This reaction to stressors is part of the fight-or-flight response, which helps animals survive by temporarily increasing bodily energy, preparing the body to contend with injury, increasing attentiveness, and decreasing activity of other biological functions that are not essential in dangerous situations, such as digestion and reproduction. For most modern humans, stress results less often from physical danger and more frequently from other types of threats, such as concerns about work, money, or family; racism, gender inequality, and microaggressions; and regular daily hassles.

Physiologically, the hypothalamic–pituitary–adrenal (HPA) axis regulates our stress response. When we perceive a threat, our hypothalamus signals the pituitary and adrenal glands through nerve and hormone signals, resulting in the release of hormones, including adrenaline and cortisol.⁶ These hormones increase heart rate and blood pressure, enhance the brain’s use of glucose, and prepare the body to repair damaged tissue.⁶ Normally, after the threat passes, this response ceases; the body quickly returns to baseline hormone levels; and blood pressure and heart rate return to the non-threat state.



C. Neill Epperson

“Many people may think this is crazy to say, but stress is good. Our stress response keeps us alive,” says C. Neill Epperson, M.D., Chair of the Department of Psychiatry at the University of Colorado School of Medicine and former principal investigator of the [Specialized Centers of Research Excellence \(SCOR\) on Sex Differences](#) at the University of Pennsylvania. “Although society today has pathologized stress, not all levels and types of stress are bad for you. You want a little shot of cortisol when you need to pay attention. If you’re facing real

danger or simply gearing up for an exam or job interview, activation of the HPA axis keeps you alert,” she says. Dr. Epperson further explains that although activation of the HPA axis is an important process, prolonged, uncontrolled, excessive, or frequent life-threatening stress can cause physiologic damage, resulting in too great or too small a cortisol response to stress, both of which are maladaptive.

Dysfunction in the stress response can result in poor concentration, negative affect, professional burnout, and mental and physical health problems. “We need to help

Almost 4 years ago, NIH enacted the [Policy on Sex as a Biological Variable \(SABV\)](#), requiring investigators with NIH support to factor the influence of biological sex into research design, analysis, and reporting in vertebrate animal and human studies. Long before implementation of this policy, a few insightful scientists, biomedical leaders, and publication editors realized the limitations of research that focuses on animals and cells of one sex.

In 1991, Michael Lauer, M.D., now Deputy Director for Extramural Research at NIH, published data disaggregated by sex and reported sex-specific findings from the [Framingham Heart Study](#). Marianne Legato, M.D., Ph.D., published *The Female Heart*, a book on aspects of heart disease particular to women, in 1991; founded two scientific journals (*The Journal of Gender-Specific Medicine* in 1997 and *Gender Medicine* in 2004); established two organizations (the *Partnership for Gender-Specific Medicine* at Columbia University in 2006 and *The Foundation for Gender-Specific Medicine* in 2008); and advocated for the inclusion of women in clinical trials. Virginia Miller, Ph.D., has spent 25 years researching sex-specific vascular functions, and ORWH funds her research through NIH’s [Specialized](#)

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people identify when stress is likely to be harmful but also when stress presents an opportunity to learn a new skill or new coping strategy,” Dr. Epperson says. “People who work in constant high-stress environments, like doctors, nurses, and teachers, or acute high-stress situations, like soldiers, police officers, and firefighters, could benefit from being proactive with respect to their stress management.” (See *Evidence-Based Stress Management Strategies*, below.) She adds, “It is also important to be vigilant regarding signs of burnout or enduring post-traumatic stress and to seek professional help before these conditions adversely affect psychological and physical health.”

Sex and Gender Differences in the Response to Stress

The stress response differs from person to person, for a variety of reasons, including genetics and factors associated with life experience. Sex- and gender-specific characteristics also have profound effects on the stress response. The adrenal gland is larger in female animals and humans, and females typically have higher levels of cortisol, both at baseline and when under stress.^{7,8} Studies with humans and animals have shown that compared with males, females have an increased response to fear and stress because of sex-specific sensitivities, differences in neural organization, and the interaction of gonadal hormones with stress mechanisms.^{6,7} The body’s most potent estrogen, 17 β -estradiol, enhances HPA reactivity, whereas testosterone inhibits it, typically resulting in less cortisol secretion in men in response to stress.^{6,7} Neuroimaging studies have shown additional differences in stress-induced changes in cerebral blood flow between men and women.⁹

Societal gender roles often result in women facing different chronic stressors than men, including sexism, work-home balance, domestic violence, and at-home caregiving. Research shows that women’s reactions to stressors indicate that they tend to perceive them as being more threatening than men perceive them.¹⁰ Men and women have differential responses depending on the type of stressor.⁷ For instance, men tend to respond more to stressors involving achievement pressure, whereas women may find interpersonal conflict more stressful.⁷ Men are also less likely than women to be aware of the impact of stress on their health and less likely to seek treatment for it.¹¹

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[Centers of Research Excellence \(SCORE\) on Sex Differences](#) and [Building Interdisciplinary Research Careers in Women’s Health \(BIRCWH\)](#) programs.

In 2012, the [Endocrine Society](#) encouraged researchers to identify the sex of experimental animals and cells to ensure proper interpretation of results and reproducibility. The American Society for Microbiology and the journals *Endocrinology*, *Stroke*, and the *Journal of Neuroscience Research* soon followed suit.

The NIH Office of Research on Women’s Health (ORWH) thanks these early adopters of the SABV ethos.

We hope you enjoy and learn from this issue of *Women’s Health in Focus* at NIH. Please share it with colleagues and encourage others to subscribe.



Janine Austin Clayton, M.D.
Director, NIH Office of Research on Women’s Health
NIH Associate Director for Research on Women’s Health



Sex-specific differences in the stress response and vulnerabilities to stress exposure change over the life course.⁶ “Animal studies and some human studies have shown that the health impact of stress begins *in utero*,” says Dr. Epperson. “Maternal psychosocial stress, hypoxia, significant illness in the mother, and other maternal stresses can result in adverse health effects on the child, and these have different effects on males and females.” Many studies have shown that stresses *in utero* adversely affect the health of male offspring to a greater degree than they affect female offspring. Dr. Epperson explains that immunologic, metabolic, epigenetic, and hormonal factors may contribute to these observed sex differences, though the mechanisms most likely are multifactorial and depend on the type and timing of prenatal stress exposure.

Young children have similar stress responses and associated health risks until puberty. Thereafter, according to Dr. Epperson, adolescent girls and women have an increased risk for depression, anxiety, and post-traumatic stress disorder (PTSD). “Though androgens dampen the stress response in males, it is not clear that sex differences in HPA axis response to stress are primary contributors to sex differences in affective disorders,” she says. “Would a female given a high dose of testosterone have a similar cortisol response to stress, or is this a male-specific response? We don’t know.”

These differences continue with age. Both men and women become more responsive to stress as they age, but this change is more dramatic in women. When faced with stress from cognitive challenges, postmenopausal women respond with higher cortisol levels than younger women, younger men, and age-matched men.⁶

Dr. Epperson is quick to caution against assuming that greater stress reactivity in female animals and humans is unhealthy or abnormal. “Females react with higher levels of cortisol to stressors, but that doesn’t mean the male response is ideal. It’s just what’s expected for the male organism,” she says. “It doesn’t follow that we should treat women to dampen their HPA stress responses to match those of men, as if males were model organisms for optimal health.”

How Can Stress Affect Health?

Stress, particularly chronic stress or dysfunction in stress-related physiologic systems or neurocircuitry, can affect mental health and is associated with panic disorder, major depression, anxiety disorder, PTSD, addiction, some psychotic behaviors, and other psychiatric illnesses.^{6,7,12} Many of these stress-associated disorders are more prevalent in women than in men.

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Stress can also have adverse effects on physical health, both in worsening existing conditions and in the development of new illnesses. Minor symptoms such as tension headaches, chest pain, shortness of breath, fatigue, and muscle tension might occur in both men and women during stressful periods. Stress can cause insomnia and result in poor-quality sleep, which are linked to many health problems. Stress can also result in gastrointestinal/digestive problems, such as stomachache, nausea, and heartburn. “Stress eating” is unhealthy, often results in consumption of junk food, and contributes to obesity. Stress can affect reproductive and sexual health, as well. Though it can increase sex drive in both men and women, more often it decreases sex drive. Stress can lead to impotence and low sperm production in men. Other research has linked stress and stress responsivity to delayed conception, changes in hypothalamic–pituitary–ovarian axis function, risk of perimenopausal hot flashes, and the likelihood of mood disorders during menopause.

Stress is also associated with more serious physical health conditions. Chronic stress can increase the risk of type 2 diabetes.¹² Moreover, stress hormones tighten blood vessels, which can raise blood pressure.¹² These hormones can cause cardiovascular inflammation, which can lead to or complicate cardiovascular problems, heart attack, and atherosclerosis.¹² Studies have shown that chronic stress increases the risk of Alzheimer’s disease—which, like many stress-related conditions, is more prevalent in women than in men.¹³ Though many factors may contribute to this sex difference in prevalence, researchers have highlighted potentially important links between corticotropin releasing factor and glucocorticoid signaling and female-biased increases in molecules associated with Alzheimer’s disease pathogenesis.¹³ Stress can also weaken the immune system, cause a state of chronic inflammation, and make individuals more vulnerable to infection and other conditions.¹²



Paige Green

Although apocryphal anecdotes link stress to cancer, the scientific evidence that stress causes cancer is minimal.¹⁴ “This history of connecting stress and cancer has a sordid and tenuous reputation. We can’t say that stress causes cancer,” says Paige Green, Ph.D., M.P.H., FABMR, of the [National Cancer Institute \(NCI\)](#). Although animal studies have associated some stress exposures to cancer development or accelerated progression,¹⁵ “making that connection in humans is difficult,” Dr. Green says. “In cancer research, we study neuroendocrine hormones like epinephrine and norepinephrine and how they regulate the tumor microenvironment. We sometimes find that an increase of these stress-associated hormones can cause

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Evidence-Based Stress Management Strategies

- Eat healthful foods. Avoid sugar and processed food.
- Exercise regularly.
- Get plenty of sleep.
- Minimize alcohol and caffeine use.
- Do not use tobacco or illicit drugs.
- Practice good time management.
- Practice safe sex.
- Maintain a healthy weight.
- Increase positive thinking, e.g., gratitude.
- Foster rewarding friendships and family relationships.
- Take time for hobbies.
- Volunteer in the community.
- Practice [relaxation techniques](#), such as yoga and meditation.
- Seek [professional help](#).

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tumor growth and metastasis, causing the cancer to spread.” Stronger evidence suggests that stress can lead individuals to engage in unhealthy behaviors, such as overeating, tobacco use, and excess alcohol consumption, which can increase the risk of cancer.¹⁴ Distress can also reduce the quality of life in patients with cancer, and some evidence suggests it can lead to poorer clinical outcomes.¹⁴

Mindfulness-Based Therapies and Other Techniques Can Mitigate Stress and Improve Health



Rezvan Ameli

Although a healthy adaptive response to life stressors is needed, limiting exposure to chronic stressors and managing daily stress with a few simple practices and mindfulness techniques can improve overall health and serve as a powerful preventive measure. (See *Evidence-Based Stress Management Strategies*.)

NIH supports biomedical research on mindfulness-based therapies (MBTs), which can modulate cognition, emotion, and self-perception; function as stand-alone or adjunct treatments for a wide range of psychiatric and other conditions; and promote wellness. Rezvan Ameli, Ph.D., of the [National Institute of Mental Health \(NIMH\)](#) explains that research has demonstrated the efficacy of MBTs for populations ranging from preschool age to the elderly; in multiple settings, including schools, hospitals, correctional facilities, and other institutions; and for various physical and psychiatric conditions, including pain conditions, immune disorders, cardiovascular conditions, addictions, anxiety, and depression. One MBT, mindfulness-based stress reduction, involves a standardized regimen of mind-body therapies—including meditation, patient education, and group support—and can effectively treat stress, anxiety, depression, and pain.¹⁶

Dr. Ameli explains that although research has shown that MBTs are effective for everyone, “they are utilized more by women than by men, which is true for other mind-body practices, such as yoga and tai chi, in the United States. Meta-analyses show that 80% of participants in mindfulness-based classes are women, and the [National Center for Complementary and Integrative Health \(NCCIH\)](#) reports similar findings for complementary treatment modalities like yoga.” Social norms of what is considered appropriate behavior for men and women may, in part, explain these trends.

Dr. Ameli says, “Research on mindfulness has grown, and there are over 500 ongoing research efforts funded wholly or in part by NIH.” She adds, “Day-to-day stress is inevitable, but

mindfulness helps change our relationship with stress. We can learn to *respond* to stress rather than *react* to it.”

Stress and the Health of Women

[Advancing Science for the Health of Women: The Trans-NIH Strategic Plan for Women's Health Research](#) articulates a multidimensional framework for biomedical research and encourages investigators and clinicians to consider the many factors that influence the health of women. Social and environmental stressors are powerful determinants of mental and physical health, warranting a concerted effort by researchers, clinicians, and public health policymakers. We will likely continue to hear cries of “I’m stressed out,” but with a better understanding of the influence of sex and gender on life stressors and their effects on health—as well as more widespread use of mindfulness and other wellness practices—we can improve the health of women.

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NIH Studies Investigate Stress, Its Mitigation, Its Health Effects, and the Influence of Sex and Gender



Margaret Bevans, Ph.D., RN, FAAN, Associate Director for Clinical Research, Captain, U.S. Public Health Service

The feature story of this issue of *In Focus* highlights that women experience many chronic stressors across their life course. Women respond to these stressors differently than men, and stress often has distinct health effects on women in both the types and the prevalence of stress-related health consequences they experience. For instance, stress-associated disorders like depression occur more frequently in women than in men. The multidimensional framework for biomedical research described in *The*

Trans-NIH Strategic Plan for Women's Health Research illustrates how considering sex as a biological variable and its interaction with physical and mental stressors is critical to advancing science to improve the health of women.

Many NIH-supported studies have investigated and continue to explore stress, including sex- and gender-specific health effects related to stress, such as how:

- [Psychological stress affects cellular aging](#);
- [Increasing stress resilience and improving treatment for post-traumatic stress disorder affects outcomes](#);
- [Stress can decrease the likelihood of conception](#);
- [Stress during pregnancy increases a child's risk of depression in adolescence](#);

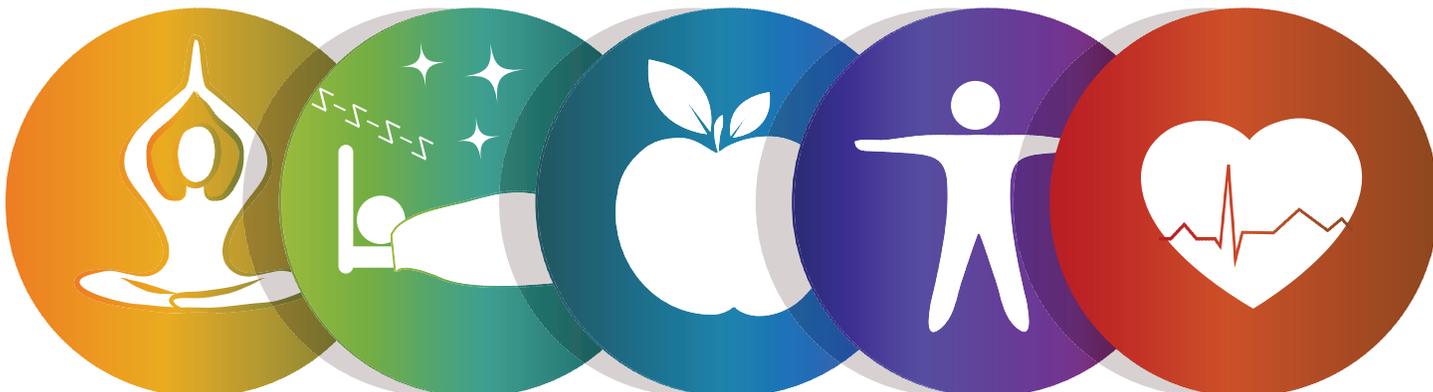
- [Maternal and familial stress and adversity may have health effects on children and perpetuate racial health disparities](#);
- [Stress affects family caregivers](#) (see also [Women's Health in Focus, issue 2.1, pages 8-9](#)); and
- [Stress may be connected to sexual and gender minority status and HIV comorbidities](#).

NIH has also invested in research on evidence-based methods of mitigating stress to improve well-being and prevent disease, notably [studying stress in female animals to deepen the basic science understanding of stress](#). The [National Center for Complementary and Integrative Health](#) (NCCIH) currently supports several ongoing stress mitigation studies, including investigations on the effects of grapeseed polyphenol extract and resveratrol on cognitive and psychological resilience during times of stress, on tai chi as a depression treatment for older patients, on the effects of a mind-body stress management program on outcomes of a workplace weight-loss program, and on a mindfulness-meditation program for treating mental health conditions in post-life-support patients.¹

The studies listed above represent a small sample of NIH's research initiatives on stress. With greater attention to sex and gender, NIH hopes to realize greater progress in neuroscientific, behavioral, and treatment research on stress and its effects on the health of women.

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Perimenopause Is Associated with Increased Fat Mass and Decreased Lean Body Mass

(Original article by [Greendale et al. 2019](#). [JCI Insight 4: e124865](#).)

The menopause transition—or perimenopause—has well-known symptoms, such as irregular menstruation and hot flashes, and culminates in the complete cessation of menstruation. Recent research correlates perimenopause with dramatic, unfavorable changes in body composition involving loss of lean body mass and a doubling of the rate of increase of fat mass with no detectable changes in average body weight. These changes begin with the onset of the menopause transition, slow around the time of a woman's final menstrual period, and stop about 2–3 years after menopause.

In a study cofunded by ORWH, Gail Greendale, M.D., and colleagues analyzed dual-energy X-ray absorptiometry body composition data from 1,246 participants in the longitudinal Study of Women's Health Across the Nation (SWAN). The researchers found no significant differences between the body composition changes of perimenopausal Black women and those of perimenopausal White women. However, Japanese women experienced neither gains in fat mass nor losses in lean mass during the menopause transition, and perimenopausal Chinese women experienced decreases in fat mass, increases in lean mass, and overall weight loss. Women who experienced their final menstrual period later in life had less pronounced body composition changes. Hormone therapy did not affect body composition trajectories.

These findings may affect research and clinical practice related to obesity and its health consequences in perimenopausal and postmenopausal women. Although numerous studies indicate that body mass index (BMI) can be a robust indicator of disease risk, other research

shows that BMI is a less reliable indicator in older women. As the menopausal transition results in no changes in weight or BMI in most populations, measures of fat and lean body mass, which can variably contribute to different health risks, may be better predictive clinical indicators than BMI for perimenopausal and postmenopausal women.

U.S.-Born Black Women Have a Higher Risk of an Aggressive Breast Cancer Subtype

(Original article by [Sung et al. 2019](#). [Cancer](#). doi: [10.1002/cncr.32293](#).)

A recent study by Hyuna Sung, Ph.D., and colleagues that was funded by the American Cancer Society finds that Black women born in the United States have a much higher risk of developing the triple-negative subtype of breast cancer than Black women residing in the United States who were born in certain regions of Africa or the Caribbean. Black women are twice as likely as White women to develop triple-negative breast cancer, an aggressive form of cancer characterized by breast tumors with no expression of three proteins related to other subtypes of cancer: estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2.

Sung and colleagues used statistical methods to analyze data from the National Program of Cancer Registries and U.S. Cancer Statistics on over 65,000 Black women diagnosed with invasive breast cancer from 2010 to 2015 in the United States. This analysis compared data from women born in the United States with those from women residing in the United States but born in East Africa, West Africa, or the Caribbean. The latter three groups, particularly those born in East Africa, had a much lower prevalence of triple-negative breast cancer. The researchers explain that these differences in risk may stem from both genetic and nongenetic factors and recommend that researchers consider

not only race but country or region of origin, as well as the diversity of the Black population in the United States, when studying breast cancer in women of African descent.

Antidepressant Drug Development May Benefit from Clinical Trials That Factor in Sex Differences

(Review article by [Kokras et al. 2019](#). [Br. J. Pharmacol.](#) doi: [10.1111/bph.14710](#).)

Researchers have yet to develop an effective antidepressant medication that manipulates the hypothalamic-pituitary-adrenal (HPA) axis, which evidence suggests is a promising pharmacotherapeutic target for patients with depression and other psychopathologies. A recent review article by Nikolaos Kokras, M.D., Ph.D., Christina Dalla, Ph.D., and colleagues suggests that attempts to develop such a drug have failed because clinical trials of candidate compounds have not considered sex-specific factors related to depression, HPA function, and drug response.

In the article, the authors review a wide body of scientific literature characterizing these sex-related considerations. For instance, depression is more prevalent in women and manifests differently in women and men in many respects (e.g., depressed women have higher levels of cortisol than women without depression, but men with and without depression may have similar cortisol levels). Additionally, both human and animal studies have identified numerous sex-specific biochemical mechanisms in the stress response and the HPA axis.

A further complication in previous studies of antidepressants is that the sex of the animals used in preclinical models often did not match the sex of clinical trial participants. Many HPA-targeting antidepressants were tested preclinically in male animals and later studied in

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clinical trials with mostly—and sometimes even exclusively—women. The authors posit that as a result, these clinical trials were not appropriately designed to test the efficacy of antidepressants targeting the HPA axis.

However, drugs targeting the HPA axis may yet prove effective in treating depression in some patients. Although, as the reviewers point out, the one-drug-fits-all approach to developing antidepressants has proved ineffective, some evidence suggests that men may be more responsive to HPA axis interventions than women. Thus, future clinical trials could demonstrate the efficacy of sex-targeted strategies, such as a hypothetical HPA axis-targeting antidepressant for men. Considering sex in the design and analysis of future studies on HPA axis interventions will help to advance this body of research. Across all categories of disease and body systems, improving the health of women and men benefits tremendously from the incorporation of [sex as a biological variable](#) throughout the biomedical research continuum, including preclinical, translational, and clinical investigations.

Suicide Rates Increase in Girls, Narrowing Historical Male–Female Suicide Gap Among Youth

(Original article by [Ruch et al. 2019. JAMA Netw. Open. 3: e193886.](#))

A statistical analysis of U.S. mortality data has found that since 2007, suicide rates among girls have increased faster than those of boys, who historically die by suicide with much greater frequency. Donna A. Ruch, Ph.D., and colleagues analyzed data on the 85,051 instances of suicide from 1975 to 2016 by youths ages 10–19. Of these deaths, 80.1% were boys or young men, and 19.9% were girls or young women.

After a downward trend in rates of youth suicide until 2007, rates



increased overall, and this increase was significantly higher for girls compared with boys—12.7% versus 7.1% for ages 10–14 and 7.9% versus 3.5% for ages 15–19, respectively. The investigators show that the gap between girls and boys—what statisticians refer to as the incidence rate ratio or IRR—narrowed significantly among several demographic groups, including ages 10–14, ages 15–19, non-Hispanic Whites ages 10–14, and non-Hispanic other races ages 15–19. The study also detected significant changes in male-to-female trends in the method of suicide over the study period. Among youths ages 15–19 who killed themselves with a firearm, the male-to-female IRR increased significantly; that is, boys became increasingly likely, relative to girls, to use a firearm to kill themselves. However, the male-to-female IRR decreased for youths ages 10–19 whose method of suicide was hanging or suffocation. No significant changes were detected in the male-to-female IRR for suicide by poisoning.

In light of these trends and because suicide is the second-leading cause of death in this age group, the researchers recommend additional research to investigate sex-specific factors related to suicide. Such research could inform effective prevention efforts and other interventions to decrease suicide rates among the young.

New Article Series in JAMA Examines Health Issues Particular to Women

(Editorial article by [Crandall and Livingston. 2019. JAMA. 321: 1676.](#))

A recent issue of *JAMA: The Journal of the American Medical Association* introduced a new article series titled “JAMA Clinical Insights: Women’s Health.” The new series and associated podcasts discuss health issues and diseases that are particular to or more common in women over the lifespan. The series will also consider conditions, such as emphysema and osteoporosis, that manifest and progress differently in women and men.

The impetus behind the new series lies in the biomedical research community’s increasing attention to the effects of sex and gender on health, health research, and clinical practice. The JAMA editorial that introduced the series mentioned efforts by NIH/ORWH and the U.S. Food and Drug Administration’s Office of Women’s Health in raising awareness of medical considerations related to sex and gender.

In the first article in this series, “[Treatment of Nonmetastatic Breast Cancer](#),” Kathryn J. Ruddy, M.D., M.P.H., and Patricia A. Ganz, M.D., describe current treatment practices for different subtypes of breast cancer. A [subsequent article in the series](#) by George F. Sawaya, M.D., and colleagues discusses cervical cancer screening.

FEATURED RESEARCH AND PERSPECTIVES

Is Professional Burnout Prevalent Among Women Physicians?

(Original article by [Templeton et al. 2019. NAM Perspect. doi.org/10.31478/201905a.](#))

In a recent discussion paper, Kim Templeton, M.D., and colleagues examine the problem of physician burnout, which involves work-related “emotional exhaustion ... cynicism, and feelings of diminished personal efficacy.” Some evidence suggests that physician burnout is more common among women, though the authors question the assessment tools used to arrive at that conclusion, as well as the different ways burnout may manifest in men and women. The article identifies several factors contributing to physician burnout that affect women disproportionately, such as difficulty achieving work–life balance, workplace bias and discrimination, sexual harassment, having little autonomy, lack of control over workload, and impostor syndrome. The authors suggest several strategies for preventing physician burnout and retaining women physicians, a particular priority in light of predicted physician shortages. These strategies include appointing responsible leaders who address disparities, level the playing field, address sexual harassment, and create an equitable workplace; fostering the careers of women in hiring decisions, with mentorship programs, and through leadership development initiatives; encouraging self-care and wellness; and developing institutional and individual strategies for preventing burnout.

The Lancet Publishes Article Series on “Gender Equality, Norms, and Health”

(Original Articles by [Gender Equality, Norms, and Health Steering Committee. 2019. Lancet. 393: 2440–2454, 2455–2468, 2522–2534, 2535–2549, 2550–2562.](#))

The United Nations’ [2030 Agenda for Sustainable Development](#) incorporates a number of global health care goals and calls for increased attention to social determinants of health, including gender. In response, *The Lancet* and its Gender Equality, Norms, and Health Steering Committee, led by Gary Darmstadt, M.D., recently published a series of five articles focusing on how gender norms and inequalities influence human health. The article series explores how health care systems, policies, and research can mitigate the unhealthful consequences of these social influences.

In “[Gender Inequality and Restrictive Gender Norms](#),” committee members describe how gender identity emerges through the intersection of biological sex and social factors. Normative influences—such as social power, social experience,

and restrictive gender norms—can function to restrict access to care, affect the likelihood of exposures to various health risks and behaviors, and deflect the results of biomedical research.

The next article in the series, “[Gender Norms and Health: Insights from Global Survey Data](#),” describes the difficulty of measuring the effect of gender norms on health. The investigators use survey data pertaining to the attitudes of men and women toward premarital sex, proportions of young women who work outside the home, and similar measures as proxies for societal gender norms. The authors then use statistical methods to demonstrate how numerous factors—such as early-life gender-normative influences, gender nonconformity, and social context—can affect health over the life course.

The third article, “[Improving Health with Programmatic, Legal, and Policy Approaches to Reduce Gender Inequality and Change Restrictive Gender Norms](#),” examines the nascent research area of testing solutions to gender-based inequalities in health. The article identifies four factors for positive change: “(1) multisectoral action, (2) multilevel, multistakeholder involvement, (3) diversified programming, and (4) social participation and empowerment.”

In “[Disrupting Gender Norms in Health Systems](#),” committee members describe how health systems perpetuate gender inequalities. The researchers suggest strategies for identifying and disrupting systemic bias. For instance, evidence suggests that increased representation of women physicians and institutional support and respect for women nurses improve outcomes, quality of care, provider responsiveness, and other measures.

The final article in the series, “[Gender Equality and Gender Norms: Framing the Opportunities for Health](#),” characterizes remaining barriers to gender equality in health and describes policy changes that governments, corporations, and health, civil, and academic organizations could make for more gender-equitable health care, workplaces, and research.

Survey Suggests Changes in University Culture Result from Equity Initiative

(Original article by [Ovseiko et al. 2019. Interdisc. Sci. Rev. 44: 166–191.](#))

A recent analysis of survey data collected from faculty members, as well as other professional and support staff, in medical and social sciences at the University of Oxford found that men had more positive perceptions of university culture than women. Study results also showed that medical staff of both sexes had a more positive perception than social

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science staff. Pavel V. Ovseiko, DPhil, and colleagues analyzed approximately 5,000 responses to a validated faculty survey to reach these conclusions. The survey included questions on 12 dimensions of university culture, such as self-efficacy in career advancement, relationships/inclusion/trust, gender and minority equity, and work-life integration. The researchers attribute the more positive responses of the women in the

medical field to the success of the Athena SWAN program. Launched in the United Kingdom in 2005, Athena SWAN promotes women in the sciences, rates and accredits scientific institutions based on equity benchmarks, and determines academic departments' eligibility to receive funding from the U.K.'s National Institute for Health Research. For more information on Athena SWAN, see [In Focus, issue 2.1, page 15](#).

SCIENTIST SPOTLIGHT

Ashley Kopec, Ph.D., is an Assistant Professor in the Department of Neuroscience and Experimental Therapeutics at Albany Medical College. Her research examines how adolescent experiences, such as drug use and social stress, influence central nervous system development and behavior. Her National Institute on Drug Abuse (NIDA)-supported postdoctoral research identified sex-specific developmental mechanisms in the central nervous system of rats, and her National Institute of Mental Health (NIMH)-supported thesis characterized memory formation in a marine mollusk. Dr. Kopec earned her doctorate in neural science from New York University in 2015 and her baccalaureate from Carroll University in 2009.

What are the barriers to women in science?

Unconscious bias is real. When names are submitted for awards, speaking opportunities, or leadership positions, women tend to be under-represented. Peer-reviewed manuscripts and grants are judged more harshly for women. It means that succeeding in science is just a little bit harder.

What is the biggest challenge you have faced as a woman in science?

A decisive woman who stands her ground is considered bossy or inflexible, whereas the same traits in a man mark him as a leader who commands respect. As a stubborn, outspoken young woman, I found this perception difficult to manage. I had to learn to advocate for myself effectively. Thomas Carew, Ph.D., and Staci Bilbo, Ph.D., my research mentors, taught me to assert myself respectfully and thoughtfully. In the research field, the burden of communicating diplomatically often falls on women and other under-represented persons, but learning to do so makes one a better colleague, mentor, and listener. The scientific community needs to address these biases, and having women in leadership positions may be the best solution.

How has mentorship shaped your career?

Mentorship is a huge part of science, and it doesn't get the attention it deserves. A career in science can make life hard. Experiments fail. Reviews can be harsh. Grants don't get



Ashley Kopec

funded. My mentors didn't fix my mistakes or shield me from challenges but helped me grow, problem-solve, and gain perspective. Good mentorship balances freedom and individuality with support and resources.

Could you briefly explain your postdoctoral research?

My colleagues and I studied the role of microglia (i.e., immune cells in the central nervous system) in adolescent brain development. The nucleus accumbens region of the brain's reward circuitry, which develops during adolescence, is important for social behaviors in both male and female rats. We found that microglia refine, or "prune," the connections between neurons in the nucleus accumbens and showed that they do so in a sex-specific manner throughout adolescence and at different times in males and females. Synaptic pruning regulated play behavior in all rats, but the mechanism behind this process was different in males and females.

Why is it important to consider sex-specific characteristics?

It is important to consider sex as a variable in biological outcomes and equally important to consider sex as a variable in experimental design. My research shows that males and females have different developmental trajectories, making it crucial to study both sexes throughout all stages of a developmental process. Researchers must also consider whether traditional experimental protocols, originally designed to assess male behaviors, are informative in females. Neuroscience will face this challenge in the coming years: How do we experimentally interrogate biology in a way that does each sex justice?

A Personal Journey – Ping Zhang

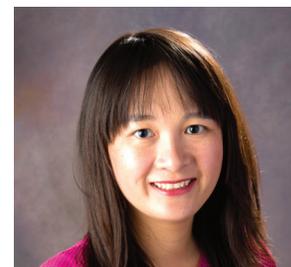
Ping Zhang, Ph.D., joined the National Cancer Institute's (NCI) Structural Biophysics Laboratory as a Stadtman Tenure-Track Investigator in August 2016. Her doctoral research under Michael Rossmann, Ph.D., at Purdue University resolved the structures of poliovirus receptor complexes with X-ray crystallography and cryoelectron microscopy (cryo-EM). She completed her postdoctoral work on protein kinases under Susan Taylor, Ph.D., at the University of California, San Diego. Through her research, she hopes to reveal the molecular mechanisms of kinase signaling complexes linked to human cancers and other diseases.

Dr. Zhang lectured on “Structural Studies of Kinase Complexes and Working in Academia as a Woman of Color” at the July 17 meeting of the Women of Color Committee of the [NIH Working Group on Women in Biomedical Careers](#). She described her research using single-particle cryo-EM and X-ray crystallography to characterize the fundamental

mechanisms of kinase signaling complexes. Establishing the structural and mechanistic basis of multicomponent biological complexes may suggest new therapeutic targets. Dr. Zhang concluded her presentation by describing some of the challenges

of working in the life sciences—such as the discouraging number of academic positions relative to the number of students earning doctorates in the biomedical sciences, salary gaps among different scientific disciplines, achieving work-life balance, and securing child care.

Throughout her professional journey, Dr. Zhang has been inspired by prominent women scientists from different disciplines who succeeded in the face of significant challenges. These scientists include chemist and physicist Marie Curie, M.S., architect Huiyin Lin, experimental physicist Chien-Shiung Wu, Ph.D., research mathematician Katherine Johnson, and astronaut Ellen Ochoa, Ph.D.



Ping Zhang

INSTITUTIONAL SPOTLIGHT

Data2X

[Data2X](#) is a nonprofit advocacy group affiliated with the United Nations Foundation that collects and distributes “gender data” to policymakers, educators, researchers, health professionals, and others. Gender data, as defined by the United Nations Statistics Division, are “collected and presented by sex as a primary and overall classification.” The founders of Data2X believe that robust gender data can help to improve the lives of women and girls worldwide.

Even today, datasets that accurately reflect sex and gender distinctions are the exceptions. In many datasets, important information about women and girls may be missing, incomplete, or inaccurate. Those gaps in the data may exist because of limited research resources or because of data collection methods that fail to account for sociocultural factors, resulting in biased data.

Data2X supports data collection methods that minimize bias, reflect sex and gender issues, and accurately represent the diversity of women and men. Assuming that good decisions stem only from good data, Data2X strives to provide the best possible gender data to leaders in government, business, economics, health, and other sectors to inform sex- and gender-equitable practices and policies.

Much of the work of Data2X involves drawing attention to gaps in data when it comes to sex and gender and supporting research efforts to fill those gaps. Data2X also educates policymakers and other stakeholders on the

need for sex- and gender-equitable data and convenes gender and data experts to increase and improve gender data production, dissemination, and use. After its founding in 2012, the early efforts of Data2X focused on identifying the most egregious sex-and-gender gaps in data pertaining to health, education, economic opportunity, political participation, and human security and on forming partnerships with other organizations to address these gaps. In 2014, Data2X published “[Mapping Gender Data Gaps](#),” detailing the organization’s early findings and recommendations. Since then, Data2X has also mapped the availability of gender data in 15 African nations and published the results in “[Bridging the Gap](#).” The group maintains online [gender data resources](#) pertaining to women’s employment, financial inclusion, civil registration, vital statistics, and political involvement. Data2X also experiments with new data collection methodologies, new data sources, and big-data techniques to improve gender data further.

Although Data2X studies a broader field of inquiry than NIH, the two organizations often act from a common impulse. Data2X’s advocacy of improved collection and use of gender data is consistent with NIH’s [Policy on Sex as a Biological Variable](#) and its [Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research](#). Through these efforts and policies, both organizations strive to produce more inclusive, sex- and gender-equitable data to improve the health and well-being of all.

500 Women Scientists Organization Launches “Request a Woman Scientist” Webpage

The grassroots organization 500 Women Scientists recently started a searchable online platform called [Request a Woman Scientist](#). Through this webpage, journalists, educators, students, researchers, and others can search for and make requests of women scientists listed in the organization’s database. These scientists have been vetted by experts and represent multiple scientific disciplines. The name 500 Women Scientists has become a misnomer, as the database now comprises more than 8,500 professional scientists. The organization launched the webpage in reaction to the disproportionate representation of men scientists in news media, at academic and professional conferences, and in leadership positions. Reports indicate that the Request a Woman Scientist platform has been accessed over 100,000 times and that of the 1,200 listed scientists surveyed, 11% indicated that they had been

contacted through the database for news interviews, academic panels, and opportunities for peer review.

Director of Women’s Health Research at Yale Discusses Inclusion of Women in Health Research

A [recent article for Yale News](#) features an interview with Women’s Health Research at Yale Director Carolyn M. Mazure, Ph.D., in which she discusses her advocacy of the inclusion of women in health research. Dr. Mazure believes that health science has reached a turning point at which the field could fully incorporate the study of women and the role of sex and gender on human health into all aspects of biomedical research—not just reproductive health. She also discusses the 20-year history of Women’s Health Research at Yale, the need for an interdisciplinary approach to health care and research, the [NIH Policy on Sex as a Biological Variable](#), and seed grants available to researchers through Women’s Health Research at Yale.

NOTEWORTHY

10 Women Lead NIH Institutes and Centers

NIH recently realized a historic first: 10 women leading NIH Institutes and Centers. The 10 Directors share insights, advice, and anecdotes on serving in biomedical leadership positions, succeeding as a woman in the sciences, and striving for greater diversity in the sciences in two NIH online features: the [Pearls of Wisdom](#) video series, produced by ORWH, and a recent [blog post](#) from NLM Director Patricia Flatley Brennan, RN, Ph.D., FAAN, FACMI. ORWH congratulates recent appointees Noni Byrnes, Ph.D., of CSR and Helene Langevin, M.D., of NCCIH and looks forward to their continuing contributions to the work of NIH.



Top, from left, Diana Bianchi, Director, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD); Patricia Flatley Brennan, Director, National Library of Medicine (NLM); Ann Cashion, former Acting Director (retired Sept. 30, 2019), National Institute of Nursing Research (NINR); Nora D. Volkow, Director, National Institute on Drug Abuse (NIDA); Martha J. Somerman, Director, National Institute of Dental and Craniofacial Research (NIDCR).

Bottom, from left, Linda S. Birnbaum, former Director (retired Oct. 3, 2019), National Institute of Environmental Health Sciences (NIEHS); Noni Byrnes, Director, Center for Scientific Review (CSR); Helene Langevin, Director, National Center for Complementary and Integrative Health (NCCIH); Andrea T. Norris, Director, Center for Information Technology (CIT); Judith A. Cooper, former Acting Director (now Deputy Director), National Institute on Deafness and Other Communication Disorders (NIDCD).

NIH Director Will Speak Only at Gender-Inclusive Panels and Conferences

This summer, NIH Director Francis S. Collins, M.D., Ph.D., announced that it was “[Time to End the Manel Tradition](#)” and that he would decline to speak at conferences and professional meetings with “manels,” or majority-male panels. In his statement, Dr. Collins reiterated NIH’s commitment to changing the culture of the biomedical research community to foster a more inclusive and diverse workforce. Dr. Collins, by his example and through his online statement, challenged other scientific leaders to work toward stopping the biases preventing women and others from contributing the full extent of their talents to the biomedical research enterprise.

NIH Releases Biennial Report

In late October, NIH will release the *Report of the Advisory Committee on Research on Women’s Health: Fiscal Years 2017–2018*. Members of the Advisory Committee on Research on Women’s Health (ACRWH) submit this report biennially to the NIH Director for dissemination to the U.S. Congress and the public. The report summarizes the programs, initiatives, and activities of NIH Institutes, Centers, and Offices, including ORWH. Additional reporting addresses implementation of the 21st Century Cures Act ([Public Law 114–255](#)), budgetary expenditures over fiscal years 2017 and 2018 for NIH research on the health of women, and adherence to NIH policies on [the inclusion of women and minorities in clinical research](#), [sex as a biological variable](#), and [inclusion across the lifespan](#).

NIH Continues to Address Sexual Harassment

NIH does not tolerate sexual harassment in its facilities, on NIH-funded projects, at awardee organizations, or in any form or place. NIH’s continuing efforts to combat sexual harassment include a [website](#) that details relevant NIH policies and answers [frequently asked questions](#), an [online platform](#) and email address (GranteeHarassment@od.nih.gov) where grantees can report incidents of sexual harassment, the [NIH Workplace Climate and Harassment Survey](#) of NIH employees and contractors, oversight by the [U.S. Department of Health and Human Services \(HHS\) Office for Civil Rights \(OCR\)](#), and the formation of the [Advisory Committee to the Director \(ACD\) Working Group on Changing the Culture to End Sexual Harassment](#).

This ACD working group met for the first time in February, heard from a wide range of experts, and made several recommendations to the NIH Director. The group’s interim recommendations included (1) establishing an ethos of transparency and accountability to demonstrate NIH’s commitment to stopping harassment and future inappropriate workplace behavior, (2) clarifying expectations to institutions

and investigators to ensure a safe workplace, (3) providing clear channels of communication to NIH, and (4) listening to victims of sexual harassment and incorporating their perspectives into future actions.

ORWH Director Janine A. Clayton, M.D., spoke of these and other NIH initiatives to address sexual harassment at Academy Health’s [Annual Research Meeting](#) in June. Dr. Clayton highlighted the findings and recommendations of [Sexual Harassment of Women](#), a report from the National Academies of Sciences, Engineering, and Medicine (NAEM), particularly the report’s first recommendation—to increase diversity in the scientific workforce and leadership. Dr. Clayton also explained how sexual harassment is antithetical to NIH’s goal of promoting “training and careers to develop a well-trained, diverse, and robust workforce to advance science for the health of women,” as articulated in the [Trans-NIH Strategic Plan for Women’s Health Research](#).

Incidence Rates of Aggressive Subtypes of Uterine Cancer Increase

(Original article by [Clarke et al. 2019. J. Clin. Oncol. 37: 1895–1908.](#))

Findings from a recent National Cancer Institute (NCI) study indicate that incidence rates of aggressive histologic subtypes of uterine cancer rose from 2000 to 2015 among U.S. women ages 30–79. These increases were particularly high among non-Hispanic Black women, who also experience poorer rates of survival than women of other races and ethnicities. This research was reported in the *Journal of Clinical Oncology* by Megan Clarke, Ph.D., of NCI’s Division of Cancer Epidemiology and Genetics and colleagues, who analyzed statistics from NCI’s Surveillance, Epidemiology, and End Results (SEER) database to evaluate hysterectomy-corrected uterine cancer trends by race, ethnicity, geographic region, and subtype. The researchers indicated that obesity constituted the strongest risk factor for endometrioid subtypes of uterine cancer. However, other risk factors contributed to the increased incidences and warrant additional research. More information on this study is available [here](#).

New NIH Statistics Webpage Makes Inclusion Data Publicly Available

NIH recently launched the [Research, Condition, and Disease Categorization \(RCDC\) Inclusion Statistics Report webpage](#), enabling users to access inclusion data on sex, gender, race, and ethnicity categorized by research type, disease, or condition. For over 20 years, NIH has required researchers to include women, racial/ethnic minorities, and children in their studies (unless there is a valid reason for not doing so

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on scientific or ethical grounds). Data presented at the April 10 meeting of the [NIH Advisory Committee on Research on Women's Health](#) showed that in fiscal year 2018, over 52% of participants in NIH-supported clinical research were women, about 29% were members of racial minority groups, and 9% were ethnic minorities. Making these inclusion data publicly available constitutes an important step toward increasing the transparency and accountability of the research NIH supports and could inform research, policy, and clinical practice as to how best to generalize findings across populations or to apply those findings only to specific populations. More information on the RCDC Inclusion Statistics Report webpage is available [here](#).

ORWH Launches New "In the Spotlight" Webpage

ORWH recently added a new [In the Spotlight](#) section to its website. This webpage features breaking news relevant to ORWH initiatives, the health of women, biomedical careers, related funding opportunities, and more. In the Spotlight enables ORWH to communicate with researchers, clinicians, policymakers, stakeholders, and the general public in between publication of issues of *In Focus*. New articles are posted several times a month.

Women's Health Issues Focuses on the Influence of Sex and Gender in Veterans Affairs Research

(Original article by [Bevans and Clayton. 2019. Women's Health Issues 29 Supplement 1: S9-S11.](#))

A recent supplementary edition of *Women's Health Issues*, supported by the U.S. Department of Veterans Affairs (VA) Cooperative Studies Program, features research reports and commentaries on the growing number of women veterans and their unique health needs. ORWH Associate Director for Clinical Research Margaret Bevans, Ph.D., RN, FAAN, and ORWH Director Janine A. Clayton, M.D., contributed a commentary, titled "Integrating the Influence of Sex and Gender in Research: Keeping Women Veterans in Focus." Drs. Bevans and Clayton posit that quality medical care for women veterans stems from an integrated consideration of military-related health needs and of the influence of sex and gender on health. The authors discuss how combat stress and exposure affect women differently than men and how women veterans can have different health concerns than civilian women, including increased risk for some medical conditions. Drs. Bevans and Clayton describe how recent policies demonstrate the VA's commitment to delivering quality, sex- and gender-appropriate health care to women veterans and point to consistencies between VA and NIH research initiatives, practices, and policies, including the NIH policies on [sex as a biological variable](#) and [the inclusion of women in clinical](#)

[research](#), which function to ensure that biomedical research remains relevant to all populations of women and men, including veterans and civilians.

National Institute on Drug Abuse Director Nora Volkow Receives Awards

Nora Volkow, M.D., Director of the National Institute on Drug Abuse (NIDA), recently received two scientific awards. She was awarded the [Presidential Award from the American Society of Addiction Medicine](#) for "outstanding dedication and service in addressing addiction issues or promoting education, training or awareness of the specialty of addiction medicine." Dr. Volkow also received the "Keeper of the Flame" award from the [American College of Academic Addiction Medicine](#) for advocating for "physician specialists to serve as clinical experts, faculty, researchers, and system change agents." ORWH congratulates Dr. Volkow and thanks her for her contributions to addiction science and public health.

Outdated Gender Stereotypes Influence Experimental Design

(Original article by [Shansky. 2019. Science 364: 825-826.](#))

A recent perspective article by Rebecca M. Shansky, Ph.D., describes persistent biases in the field of neuroscience stemming from sex-related assumptions and stereotypes long rejected by science. So-called scientific theories of the sexes from the 19th century describe the female brain as sensitive and emotional—a result of reproductive physiology—and the male brain as more rational and implicitly superior. Dr. Shansky argues that the influence of these assumptions continues to influence experimental design. Neuroscience studies often use male animals instead of females, the assumption being that circulating estrogens skew test results. However, both testosterone and estrogen are neuromodulators with the potential to induce hormone-related variability in a cohort of lab animals.

Dr. Shansky refers to both the praise and criticism of the [NIH Policy on Sex as a Biological Variable \(SABV\)](#) and analyzes a common but flawed approach to SABV in neuroscientific research. Neuroscientists will sometimes conduct an experiment first with male animals and then with female animals. This supposed compromise perpetuates the assumption that the male brain represents the norm and that the female brain is a deviation from it. The article also identifies the fallacy of using behavioral tests validated with male rodents to model depression and post-traumatic stress disorder, illnesses twice as common in women as they are in men. Dr. Shansky concludes by asserting that neuroscientific progress will improve when the field accepts male and female brains as equally informative.

Priscilla Logan-Waller



Priscilla Logan-Waller joined ORWH as a program analyst in June 2019. She works closely with ORWH leadership to develop and execute annual operating budgets and provides administrative support to both leadership and staff. Ms. Logan-Waller also serves as a contracting

officer's representative (COR) for the ORWH communications contract. She has 28 years of Federal service experience in administrative operations, including human resources, acquisitions, travel, budgets, records management, and emergency management. She previously worked at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) for 14 years. Ms. Logan-Waller earned an associate degree from Montgomery College and a baccalaureate from the University of Maryland University College in sociology and behavioral and social sciences.

Elonna Ekweani



Elonna Ekweani, J.D., is a public health analyst at ORWH. She previously served as a public health analyst in the NIH Office of Science Policy (OSP), where she promoted the safe and effective conduct of clinical and health care research in areas such as data privacy, protections for human research participants, and

clinical trials stewardship. Ms. Ekweani was the point of contact between NIH and the Food and Drug Administration and the U.S. Department of Health and Human Services (HHS) Office of the General Counsel for review of guidance documents on clinical trials reporting. She earned her law degree from the University of Maryland Francis King Carey School of Law and a baccalaureate in sociology from The George Washington University.

UPCOMING EVENTS

49th Meeting of the NIH Advisory Committee on Research on Women's Health

October 23, 2019

9:00 a.m.–5:00 p.m. (Eastern Time)

NIH Main Campus

Natcher Conference Center

Meeting available on [videocast](#).

Building Interdisciplinary Research Careers in Women's Health Annual Meeting

December 11, 2019

9:00 a.m.–5:00 p.m. (Eastern Time)

NIH Main Campus

Natcher Conference Center

For up-to-date information, [visit www.nih.gov/women](http://www.nih.gov/women).

FUNDING OPPORTUNITIES

The ORWH website now lists over 40 [funding opportunity announcements \(FOAs\)](#) funded in part by ORWH and/or related to women's health research, sex as a biological variable, sex and gender in health and disease, or women in biomedical careers. We list a few of these FOAs below:

- [The Intersection of Sex and Gender Influences on Health and Disease \(R01 Clinical Trial Optional\)](#)
- [Factors Underlying Differences in Female and Male Presentation for Dental, Oral, and Craniofacial Diseases and Conditions \(R01\)](#)

- [Research Supplements to Promote Re-Entry into Biomedical and Behavioral Research Careers \(Admin Supp\)](#)
- [Addressing the Challenges of the Opioid Epidemic in Minority Health and Health Disparities Research in the U.S. \(R21 Clinical Trial Optional\)](#)

Application deadlines vary. See the individual FOAs for more details.

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