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Women and Mental Health Across the Lifespan

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Director, NIH Office of Research on Women's Health
NIH Associate Director for Research on Women's Health

More than 1 in 4 women have a mental health disorder, compared to fewer than 1 in 5 men.[1] For several mental health disorders, the sex differences are stark: women have roughly double the lifetime risk for depression, anxiety, post-traumatic stress disorder, and eating disorders. Biological sex differences—including in genetics, gene expression, brain development and architecture, and hormones—may contribute to this greater prevalence of these disorders among women. Gendered power dynamics, early life experiences, and other social determinants of health also affect women's mental health and can interact in complex ways with biological sex differences.

In this issue of In Focus, *we highlight several areas of research on the biological and social drivers of women's mental health throughout the life course. The feature story describes how leading experts in the field are working to unravel the complex web of genetic, social, hormonal, and neurobiological influences on mental health disorders. The story highlights several important areas of research: the long-term consequences of early life adversity; the development and evolution of a community-engaged postpartum mental health intervention for low-income women; the complex relationship between menopause and mental health; and how decades of NIH-led research on neurobiological effects of female reproductive hormones led to novel medications for postpartum depression.*

For our Women in Science interview, we speak with Jill Goldstein, Ph.D., M.P.H., the founder and executive director of the Innovation Center on Sex Differences in Medicine at Massachusetts General Hospital (ICON-X), about her decades-long efforts to understand the early life antecedents of sex differences in brain- and heart-related disorders and to drive innovative solutions and industry partnerships that promote women's health through research on biological sex differences.

This issue also spotlights several recent ORWH events and research articles relevant to women's health. In addition, we are delighted to share several new NIH resources regarding women's health.

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

Women's Mental Health Throughout the Life Course

Women have a higher incidence and prevalence of mental health disorders than men, particularly of anxiety- and stress-related disorders.[2] They are twice as likely to develop depression—and their greater vulnerability to depression is found in both low- and high-income countries.[3] Conversely, men are at higher risk for schizophrenia, substance use, and antisocial and impulse disorders. Even when diagnosed with the same mental health disorder, men and women often differ in their clinical symptoms and prognosis, says Armin Raznahan, M.D., Ph.D., who serves as chief of the Section on Developmental Neurogenomics at the National Institute of Mental Health (NIMH).

Jill Goldstein, Ph.D., M.P.H., Massachusetts General Hospital, Harvard Medical School

These consistent and pervasive sex-based differences have been described as "among the most intriguing and stable findings in psychiatry;" however, their causes remain poorly understood.[4] "There is still a surprising lack of studies designed to investigate sex differences in mental health, as well as a lack of interest and knowledge on the industry side for translating the discoveries into therapies and diagnostic tools," says Jill Goldstein, Ph.D., M.P.H., professor of psychiatry and medicine at Harvard Medical School, founder and executive director of the Innovation Center on Sex Differences in Medicine (ICON-X) at Massachusetts General Hospital (MGH), and the Helen T. Moerschner Endowed MGH Research Institute Chair in Women's Health. "But," she adds, "understanding the causes of sex differences in diseases is critical for designing more precise and efficacious treatments for women *and* men."

Sex Differences and Genetic Susceptibility

Some of the most consistent sex differences in mental health are the male predominance in childhood neurodevelopmental disorders, and the female predominance in mood and anxiety disorders. These sex differences are large, emerge at highly consistent ages, and are found across diverse social contexts, suggesting that biological differences between the sexes (e.g., differences in genetics, gene expression, and hormones) play an important role in their development, says Dr. Raznahan. To understand how sex differences in gene expression might contribute to the development of mental health disorders, Dr. Raznahan studies individuals with sex chromosomal aneuploidies (i.e., who carry one or more extra or missing sex chromosomes).

Armin Raznahan, M.D., Ph.D., Chief, Section on Developmental Neurogenomics, NIMH

Humans typically have 23 pairs of chromosomes, or packages of genetic material, one set from each parent. Two chromosomes typically determine biological sex: biological males typically have one X and one Y chromosome, whereas biological females typically have two X chromosomes. Rarely, individuals can have an extra or missing sex chromosome or fail to inherit a second sex chromosome. For example, approximately 1 in 1,000 biological males carry an extra Y chromosome. Dr. Raznahan has found that XYY males have elevated rates of autism spectrum disorder and attention deficit hyperactive disorder (ADHD) compared to XY males, suggesting that genes on the Y chromosome increase the risk for these neurodevelopmental conditions.[5]

Studying individuals with sex chromosomal aneuploidies enables researchers to assess X and Y chromosome dosage effects more broadly, adds Dr. Raznahan. He has identified genes on the sex chromosomes as well as on other non-sex chromosomes (autosomes) that are differentially expressed based on the number of X and Y chromosomes an individual carries. This research has uncovered a set of sex chromosome genes, termed gametologs, whose expression is highly sensitive to sex chromosome dosage. Sex-based differences in gametolog expression appear to be highly stable throughout the body. By contrast, sex-based differences in autosomal gene expression appear to be tissue specific. Dr. Raznahan is now working to understand how these gene expression changes might affect neural pathways involved in the biology of sex-biased brain disorders such as depression and ADHD.

Early Life Adversity

Maternal Toxic Stress and Fetal Development

The seeds of vulnerability to various mental disorders are often set early in life. In utero and during infancy, the brain undergoes rapid maturation. Fetal exposure to severe or prolonged maternal (toxic) stress can induce enduring and potentially permanent alterations in brain architecture.[6] Depending on timing of the prenatal exposure, these effects can differ by sex.[7] "Maternal stress can stem from a wide range of circumstances, such as obstetric complications (e.g., preeclampsia), bacterial and viral infections, nutritional deprivation, oxygen deprivation, chronic social disadvantage, physical or sexual trauma, or death of a spouse," says Dr. Goldstein. This toxic stress disrupts the maternal hypothalamic-pituitary-adrenal (HPA) axis, a key neural and hormonal regulator of metabolic, immune, and autonomic system responses to stress. HPA dysregulation elevates maternal levels of stress hormones such as cortisol, which affect maternal immune responses, blood pressure, and vascular function, she says. It can also disrupt placental function and cross the placenta to dysregulate the fetal HPA circuitry, physiology, and vasculature. Animal research suggests that toxic maternal stress during pregnancy programs a "hyperactive" immune and HPA axis in their offspring that differs by sex —a stress response system that our research has shown heightens vulnerability to depression and cardiovascular disease, she adds.[8,9]

Tallie Z. Baram, M.D., Ph.D., University of California, Irvine

Toxic Stress During Infancy and Childhood

In addition to the effects of maternal stress on fetal brain development, new research highlights that emotional stress early in postnatal life may impact brain maturation, and thereby influence wellness and mental health during adulthood. Importantly, such early-life stress may affect the brains of males and females differently, says Tallie Z. Baram, M.D., Ph.D., professor of pediatrics, anatomy/neurobiology, neurology, and physiology/biophysics at the University of California, Irvine. Using powerful new viral-genetic techniques to assess specifically which brain cells are activated by early life stress, Dr. Baram has discovered several differences in how developing male and female brains sense and encode stress, as well as the sex-specific influences of stress on the brain and behavior. For example, in male mice, early life stress induces hyperactivity in a connection between the amygdala and the nucleus accumbens, that is, between a brain region involved in fear and response to threats and a brain region central to pleasure and reward.[10] These mice exhibit diminished reward-seeking behavior (e.g., preference for palatable food, responses to sex cues) relative to control mice. Chemogenetic block of this hyperactivity restored male mice's response to rewarding cues. Importantly, exposure to early life stress did not induce hyperactivity in this connection for female mice, nor did attenuating the connection alter female mice's adult behavior.[10] These types of findings imply important sex differences in the encoding and consequences of exposure to early life adversity and underscore the importance of investigating sex-specific effects in preclinical research.

The brain continues to develop rapidly throughout infancy and childhood, providing a continuing critical window of vulnerability to toxic stress. Two-thirds of adults living in the United States report exposure to severe or prolonged stress during childhood, such as growing up in poverty or being physically or sexually abused, and 1 in 6 report four or more such exposures.[11] Often referred to as adverse childhood experiences (ACEs), these exposures disrupt children's brain development and ability to regulate their emotions, dramatically increasing their risk for later mental health disorders.[11–13]

Women who experience two or more ACEs prior to puberty are more likely to experience perimenopausal depression and symptoms of cognitive dysfunction, such as memory and attention deficits, says Neill Epperson, M.D., professor and chair of psychiatry at the Ludean Family Center for Women's Health Research at the University of Colorado's School of Medicine.

Neill Epperson, M.D., University of Colorado

Research conducted by one of Dr. Epperson's mentees, Christina Metcalf, Ph.D., in conjunction with investigators for the Penn Ovarian Aging Study (Mary Sammel, Sc.D., and Ellen Freeman, Ph.D.) finds that increases in inflammation during

perimenopause may partially explain these women's greater cognitive impairments, suggesting that therapies that reduce inflammation may help alleviate their symptoms.[14] In addition, postmenopausal women who experienced more ACEs exhibit greater activation in the dorsolateral prefrontal cortex of the brain during memory tasks. This area of the prefrontal cortex plays a central role in working memory, behavioral inhibition, and abstract reasoning. This finding could indicate that these women's brains have to work "harder" to achieve the same level of performance as women not exposed to significant early life stress, explains Dr. Epperson. Notably, treatment with estradiol reduced this excess dorsolateral prefrontal cortex activation without affecting performance. Thus, estrogen replacement therapy may help alleviate some postmenopausal cognitive impairments among women who experienced high levels of toxic stress during early childhood, says Dr. Epperson. Overall, we still do not fully understand who benefits from hormone therapy (HT; formerly known as hormone replacement therapy or HRT) or the appropriate duration of HT when it comes to estradiol and progesterone's effects on the human brain, she adds.

These sentiments are echoed by Dr. Goldstein. The clinical guidelines on the timing, dose, duration, and route of administration for HT during menopause are "completely inadequate, sometimes misleading, and sometimes outright adverse to brain health," says Dr. Goldstein. "We are woefully ignorant regarding how to prescribe HT," which may be critically important to helping women maintain brain health as they age, she adds.

Women's Reproductive Life Cycle and Mental Health

Mitchell J. Prinstein, Ph.D.
American Psychological Association, University of North Carolina

Women's reproductive life cycle, which encompasses periods of rapid hormonal fluctuations (e.g., puberty, pregnancy and delivery, and menopause) contributes to women's enhanced health and mental health vulnerability. For example, the female predominance in anxiety, depression, and other stress-related disorders emerges during puberty, and an estimated 1 in 8 women who give birth experience postpartum depression making the postpartum period one of the highest risk periods for mental health disorders in women's lives.[2,3]

Puberty and Adolescence

Women's greater susceptibility for depression, anxiety, and other stress-related disorders emerges during adolescence,[2,3] in part because adolescence is a time of heightened interpersonal stress, particularly for girls, says Mitchell J. Prinstein, Ph.D., chief scientific officer for the American Psychological Association and John Van Seters Distinguished Professor of Psychology and Neuroscience at the University of North Carolina. The peer context becomes increasingly complex, because both boys and girls experience brain changes, such as increases in oxytocin and dopamine receptors, that increase their interest in social bonding and rewards and desire to avoid social punishments," explains Dr. Prinstein. One of the last areas of the brain to fully develop is the prefrontal cortex, an area of the brain critical for emotional regulation and behavior inhibition, "so you have a period of heightened social sensitivity but no real brake pedal," he adds. The interpersonal stakes can feel especially high for girls, who, from an early age, often face tremendous pressure to succeed socially. Perhaps as a result, girls are more likely than boys to critique other girls' bodies, relationships, and social positions and to use relational aggression as a form of social punishment, he notes. At the same time, girls' bodies are developing in ways that move them away from the current ideal female body image and that force them to confront the pressure and attention of being viewed as a sexual object.

Experiencing high levels of interpersonal stress during adolescence is linked with internalizing symptoms, self-injury, and suicide—but not all girls are at risk, says Dr. Prinstein. One critical factor is how girls perceive these interpersonal stressors. Perceiving stressors as threatening triggers changes in gene expression that increase inflammation and decrease antiviral responses. Dr. Prinstein characterizes this response as "our body prepares us to be kicked out of the herd, to conserve energy, to ward off bacterial infections, and to worry less about viral infections that might be transmitted to us from other people." These pro-inflammatory changes in gene expression may lead to increases in depression and anxiety.

Despite all the media attention on smartphones and social media usage among adolescents, the research does not suggest that these are their primary sources of stress, says Dr. Prinstein. Adolescents were already experiencing high levels of mental health disorders before the era of smartphones, and the longstanding and remarkably severe shortage of mental health care providers has exacerbated the problem, he explains. Social media impacts appear to be mixed and to depend on how adolescents use these platforms. Cyberhate, social comparisons, and unrealistic body images can certainly cause distress. At the same time, the ability to connect with others online can provide critical social support and a place of refuge for adolescents who belong to minoritized populations. When adolescents are asked about their biggest stressors, social media and loneliness are not at the top of the list. Instead, they point to academic pressures, climate change, political polarization, and their identities being disparaged, says Dr. Prinstein.

Perinatal Mood Disorders

Many women experience the "baby blues" after giving birth. These temporary feelings of moodiness, sadness, anxiety, and fatigue are typically mild and dissipate within a few days of delivery. But, for an estimated 1 in 8 women, more profound, debilitating, and enduring feelings of sadness, anger, guilt, apathy, or hopelessness occur, signifying the onset of postpartum depression (PPD). PPD is considered a major depressive episode, says Samantha Meltzer-Brody, M.D., M.P.H., Assad Meymandi Distinguished Professor and chair and director of the University of North Carolina, Chapel Hill Center for Women's Mood Disorders, and an internationally recognized physician-scientist and expert on perinatal mental health.

Perinatal mood disorders such as PPD are one of the most common complications of pregnancy and childbirth. These disorders can have devastating impacts on women's relationships, including their ability to bond with their babies, which can permanently impair their babies' neurodevelopment, says Dr. Meltzer-Brody. Perinatal mood disorders can lead to suicide, a leading preventable cause of maternal deaths in the United States.[15] Yet, despite the frequency and severity of PPD, more than half of the women with PPD never receive screening; many who are screened are never referred for mental health services; and fewer than 1 in 10 women with PPD receive adequate treatment.[16]

While more work is needed on screening and referrals, treatment options for PPD have greatly improved in recent years. The mainstay of PPD treatment has been selective serotonin reuptake inhibitors and other antidepressants commonly used for major depressive disorder. However, despite their widespread use, antidepressants are often inadequate for PPD, says Dr. Meltzer-Brody. They were not specifically designed for PPD, and typically require 4 to 6 weeks to take effect—a long time during a critical window for mother-baby attachment. Moreover, only about half of women with PPD respond to antidepressants. Fortunately, two new treatments that target postpartum hormonal changes, brexanolone and zuranolone, recently received Food and Drug Administration (FDA) approval.

Brexanolone

The development of the two new specific treatments for PPD, brexanolone and zuranolone, stemmed from decades of NIH-funded research into the neurobiological effects of female reproductive hormones. During pregnancy, estrogen and progesterone levels skyrocket, increasing 10- to 50-fold by the third trimester, only to plummet after birth. As progesterone levels fall, so do brain levels of its neuroactive metabolite, allopregnanolone.

In the 1980s, NIMH-led research showed that allopregnanolone helps blunt stress responses during pregnancy.[15] Building on this research, NIMH scientists Maria D. Majewska, Ph.D., and Steven M. Paul, M.D., discovered that allopregnanolone is a neuromodulator of γ-aminobutyric acid (GABA)—a major inhibitory neurotransmitter that helps regulate mood and stress responses. Specifically, allopregnanolone enhances GABA's binding to a subtype of GABA receptors known as $GABA_A$ receptors. Subsequent animal research showed that enhancing GABA's effects on $GABA_A$ receptors decreases anxiety and depressive symptoms, whereas damage to $GABA_A$ receptors induces anxiety.[17]

In 2008, a breakthrough series of NIMH-funded animal studies strongly suggested a role for allopregnanolone in PPD. Drs. Jamie Maguire and Istvan Mody bred mice to have disturbances in their $GABA_A$ receptors. These female mice exhibited normal behavior until giving birth, when they began to exhibit depressive symptoms and failed to engage in normal maternal caregiving.[18] Treating the mice with allopregnanolone reversed these symptoms and normalized maternal behavior.[18]

Maguire's and Mody's findings were first translated into human research in 2015, when Dr. Meltzer-Brody led an open label trial to test a 60-hour infusion of brexanolone—an infusible version of allopregnanolone—in women with PPD. The impact was rapid and dramatic. The first patient infused with brexanolone within 24 hours went from being withdrawn, not eating, and not interacting with her baby to smiling, talking, eating, and interacting with her baby. "We thought either that is one heck of a placebo or there is something there," recalls Dr. Meltzer-Brody. Subsequent positive Phase 2 and 3 clinical trials led the FDA to approve brexanolone for PPD in 2019.

Samantha Meltzer-Brody, M.D., M.P.H., University of North Carolina, Chapel Hill

Compared to standard antidepressants, brexanolone is remarkably effective for PPD (7 out of 10 women in the randomized trials experienced a significant improvement in their depressive symptoms). Unfortunately, it is also expensive and requires hospitalization for continuous monitoring. These requirements have limited women's ability to access brexanolone.

Recently, women's access to this class of drugs has improved. In 2023, the FDA approved an oral medication, zuranolone, which has a similar mechanism of action to brexanolone and also leads to a rapid improvement of depressive symptoms within days of starting treatment. The American College of Obstetricians and Gynecologists now recommends that clinicians consider zuranolone for depression that starts in the third trimester or within 4 weeks of delivery.[19]

Many unanswered questions about these treatments remain. These medications are given only temporarily; brexanolone for 60 hours and zuranolone for 2 weeks. So, why does temporary replacement of the effects of allopregnanolone lead to changes in depressive symptoms that persist for at least 30 days, while other antidepressants must be taken chronically? Why does the cessation of allopregnanolone treatment not re-trigger depression in vulnerable women? Preliminary research suggests that these treatments may improve depressive symptoms by reducing specific types of inflammation.[17] Dr. Meltzer-Brody and colleagues are continuing to study the downstream effects of these treatments to understand how they exert their longer-term effects.

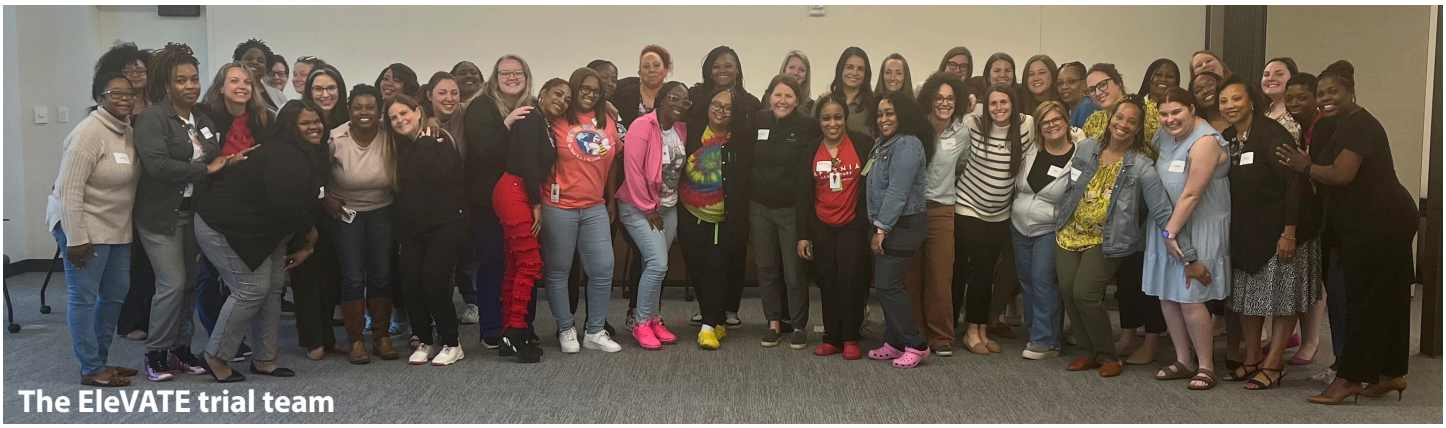
Although these new treatments have revolutionized care for PPD, they are not effective for everyone. "Like with breast cancer," says Dr. Meltzer-Brody, "many different kinds of PPD exist, and not all may be hormonally driven." For example, experiencing trauma, especially early in life, can alter the way the body responds to stress and cause epigenetic changes that affect which genes are turned on and off, explains Dr. Meltzer-Brody. She is involved in several ongoing NIMH-funded studies investigating possible genetic subtypes of PPD.

Ebony Carter, M.D., M.P.H., University of North Carolina, Chapel Hill

The single biggest risk factor for developing a mood disorder during pregnancy or after giving birth is a prior history of mental illness, says Ebony Carter, M.D., M.P.H., director for the Division of Maternal-Fetal Medicine at the University of North Carolina, Chapel Hill, who is studying whether maternal mental health interventions can improve pregnancy- and birth-related outcomes. For example, women who have experienced a mental health disorder in the past have a 1 in 3 risk of developing PPD.[20] Pregnancy serves as a major stress test, and caring for a new infant saps women's energy and time, which can exacerbate preexisting mental health problems, notes Dr. Carter. It is essential that clinicians screen for preexisting or prior mental health problems during pregnancy, she adds, because addressing mental health problems often becomes more difficult after the baby arrives. Dr. Carter saw the need to work with patients to develop a group prenatal curriculum for at-risk pregnant women. "My fellow clinicians and I knew that the answers for how to help historically marginalized women lay within their communities," says Dr. Carter. The women identified improving their mental health as a key unmet need. "Our conversations with patients and providers kept returning to the central importance of mental health as a root cause of maternal health disparities. Women cannot take necessary medications or otherwise care for themselves or their babies if they are depressed, barely functioning, and unable to get out of bed in the morning," she says.

In 2016, as Dr. Carter was formulating a group care curriculum, Missouri declined the Medicaid expansion. Mental health services were in short supply for everyone, but particularly inaccessible for low-income women. The women most likely to suffer from mental health problems during the perinatal period were the least likely to be screened, says Dr. Carter. Even when women were screened and found to be at risk for PPD, clinicians had no one available to refer them to for treatment. Women were being lost at every step of the journey, she says. They might not be screened, not be referred, not make the connection with the provider they were referred to, might not stay in care, and might not achieve remission while in care. Her team was not going to dramatically increase the number of mental health professionals available. Instead, they trained obstetricians, certified nurse practitioners, and family practitioners to become "mental health extenders" and to disseminate mental health techniques such as cognitive behavioral therapy through prenatal and postpartum group care. Women who participated in an observational pilot of this group care curriculum saw a significant reduction in preterm birth rates.

Dr. Carter is now testing this group care curriculum in the NIMH-funded Elevating Voices, Addressing Depression, Toxic Stress and Equity in Group Prenatal Care (EleVATE GC) randomized clinical trial at multiple sites across Missouri. Dr. Carter emphasizes that the intervention is for everyone: "Our belief is that if you improve health outcomes for those with the worst outcomes, you elevate outcomes for everyone. Our trial population includes Whites, Blacks, Asians, and Latinos. Thirty percent of our patients are Spanish speaking."



The EleVATE trial team

As the EleVATE trial progressed, Dr. Carter realized that the fundamental premise of the intervention might be incorrect: Rather than the intervention improving outcomes by providing additional support for patients, it might be improving outcomes by changing the clinicians' attitudes and behaviors toward their patients. A clinician might initially feel irritated with a patient who chronically misses or arrives late for appointments, she explains, but by participating in the group care intervention, realize that the patient has to catch three buses to get to the clinic and that their partner is unkind to them. Dr. Carter is now conducting implementation science research, supported by the National Institute on Minority Health and Health Disparities, on how different participating clinicians' experiences and behaviors within the EleVATE GC trial affect mental health outcomes.

Menopause

As with other periods of hormonal upheaval, the menopause transition represents another period of enhanced vulnerability to depression and other mood disorders. The menopause transition refers to the period from the onset of age-related menstrual changes (often known as perimenopause) through the 12 months after the cessation of menstruation.

Hadine Joffe, M.D., Harvard Medical School

This period is characterized by profound hormonal shifts in estrogen, progesterone, and other hormones involved in female reproductive function, which may trigger new and resurgent mental health disorders. Early in the menopause transition, the normal cyclic rise and fall of estrogen becomes erratic, explains Hadine Joffe, M.D., professor of psychiatry in the field of women's health at Harvard Medical School, and founder and director of the Women's Hormones and Aging Research Program, who studies how menopause affects women's risk for depressive symptoms and episodes of major depression. Even as menstrual cycle length remains relatively consistent, hormonal levels begin to vary greatly (e.g., estrogen may be very high one cycle, and then low the next). Later in perimenopause, as cycles begin to space out, both estrogen and progesterone levels are generally low.

For some women, these rapid hormonal oscillations darken their mood and increase depressive symptoms, says Dr. Joffe, whereas other women are relatively unaffected. Women whose estrogen levels are rising and falling rapidly and whose progesterone levels are low seem most at risk for mild depressive symptoms during perimenopause.[21] Low levels of progesterone being a risk factor suggests that, as for PPD, a decline in allopregnanolone may contribute to perimenopausal depressive symptoms. Dr. Joffe is now conducting a NIMH-funded study to determine mechanisms through which allopregnanolone therapy may be an effective approach to treat mild to moderate perimenopausal depression.

Although mild increases in depressive symptoms are common during the menopause transition, experiencing a major depressive episode is not, says Dr. Joffe. The women most at risk are those who have already experienced one or more major depressive episode. It is rare for women to have their first episode during perimenopause. In addition, her work on review of 12 prospective studies on depression during menopause found that women with early menopause (before age 45), women with surgically induced menopause, and women who experience particularly severe and disruptive vasomotor symptoms (colloquially known as "hot flashes") were particularly at risk for major depression.

HT can treat hot flashes and associated sleep disturbances, and may benefit women whose depressive symptoms stem from hot flashes and associated sleep disturbances.[22,23] However, HT should not be used as a replacement for standard antidepressants to treat an episode of major depression, because randomized controlled trials do not consistently find a benefit.[22] In line with the lack of apparent benefit, expert consensus guidelines currently recommend selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and psychotherapy as first-line treatments for depression during menopause. Dr. Joffe emphasizes that clinicians should screen women for life stressors and history of depression and other mental health problems; consider whether modifiable risk factors such as hot flashes might be contributing to women's depressive symptoms; and manage depression with evidence-based treatments such as cognitive behavioral therapy and antidepressants as they would during other phases of life.

Laura Rowland, Ph.D., NIMH

Depression is not the only mental health disorder that can develop or recur during the menopause transition. During this period, symptoms of psychosis can re-emerge, become exacerbated, and for some women, develop for the first time, says Laura Rowland, Ph.D., program chief of NIMH's Neuroscience of Mental Disorders and Aging Program. The reasons for this enhanced vulnerability to psychosis during the menopause transition are poorly understood; however, a decline in estrogen is widely believed to play a key role. Estrogen has long been thought to provide some degree of protection against psychosis, and to contribute to its greater prevalence and generally greater clinical severity among males.[24,25] Women with psychosis tend to have low estrogen levels, and premenopausal women often report worse symptoms during the low-estrogen phase of their menstrual cycles.[24,25] To stimulate research in this area, NIMH has open funding opportunities (PAR-23-097 and PAR-23-102) calling for applications that advance mechanistic and translation research on the onset and worsening of mood and psychotic disorders during perimenopause and the menopause transition.

For many years, women's menopausal symptoms have been dismissed. Greater recognition and understanding of menopausal biology represent

progress toward improving women's health. At the same time, researchers and clinicians must understand the causes of women's depressive and other mood symptoms and not assume that menopause is the sole or even primary cause, says Dr. Joffe. Midlife is often a period of major life events and transitions. Women may be engaged in more demanding responsibilities at work, providing care for children, aging parents, or both, and suffering from new or recent medical disorders. As with depression at other times of life, early life adversity and recent stressful events, such as unemployment, lack of social support, and financial strain, are important risk factors.

Menopause Among Racially or Ethnically Minoritized Women*

Of the more than 2 million American women entering menopause each year, approximately 500,000 are racially or ethnically minoritized (REM) women. A scoping review led by Tamara Lewis Johnson, M.P.H., M.B.A., program director for the Women's Mental Health Research Program at NIMH found that REM women experienced higher rates of depression during the menopause transition than non-Hispanic White women. One driver of these disparities may be REM women's greater experience of menopause symptoms. Most women experience hot flashes during the menopause transition, with a median duration of approximately 7 years. However, Black women report the longest duration of hot flashes, with a majority experiencing them for more than 10 years. Severe hot flashes disrupt sleep and are linked with worse mental health. Yet, despite their longer duration of symptoms, REM women are *less likely* to receive HT than non-Hispanic White women.

Tamara Lewis Johnson, M.P.H., M.B.A, NIMH

This scoping review identified several other notable research gaps regarding menopause in REM women. Few studies examined the effectiveness of mental health treatments specifically among REM women. Many studies failed to assess the influence of racial and ethnic status on mental health, or the intersecting influences of gender identity and sexual orientation. Given these significant research gaps, Ms. Lewis Johnson and her co-authors call for additional research on health care services delivery, prevention, and interventions among REM women. They also emphasize the need for intersectional research that examines how the interacting forces of racism, sexism, and other systems of oppression affect REM women.

Later Life

Women's elevated risks for anxiety and depression continue into late life, which increase their risks for Alzheimer's disease, strokes, and cardiovascular disease. Women represent more than two-thirds of people living with Alzheimer's disease worldwide, says Dr. Goldstein. Anxiety disorders, depression, and dementia frequently co-occur among older adults, particularly women, says Carmen Andreescu, M.D., professor of psychiatry, University of Pittsburgh. These three disorders are highly prevalent among women and feed on each other; treatment becomes more challenging when more than one of these disorders are present.

Environmental changes that occur with age, such as heightened financial stress and diminished social support, combine with the neurobiology of the postmenopausal aging brain can drive these sex and gender differences, explains Dr. Andreescu. Excessive worrying and rumination may be particularly damaging for the aging brain. "Worrying to death," says Dr. Andreescu, "is not a misnomer." Her research has shown that the more people worry, the older their brain looks, particularly the hippocampus, a key brain area involved in memory. More than half of older adults with severe anxiety or worry are not diagnosed or treated, she adds. Treating depression and anxiety early in life and preventing recurrence is essential, she stresses. Every new depressive episode is more difficult to treat and raises the risk for subsequent relapses.

Carmen Andreescu, M.D., University of Pittsburgh

Unfortunately, antidepressants are only effective about half of the time, and individuals often must cycle through multiple different medications before finding one that works. Thus, predicting individual response to antidepressants is an active area of research—one that must be approached with caution, because men and women may differ in the neural and biological markers that predict responses to antidepressants. For example, using a type of brain imaging known as functional magnetic resonance imaging (fMRI), Dr. Andreescu found that shifts in brain functional connectivity as early as the first day of starting an antidepressant can predict treatment effectiveness, but only in men.[26] Thus, using imaging and other biological factors to predict treatment effectiveness requires great care and attention to potential sex differences, she says.

* Racially and ethnically minoritized (REM) women refers to women historically marginalized by the majority (non-Hispanic White) due to race, ethnicity, or both and includes Black/African American, Hispanic/Latina/ex, Native/Indigenous, and Asian and Pacific Islander women.

Conclusion

Despite the many mental health challenges women face throughout the life course, "women's brain health has taken front and center stage in the last several years," says Dr. Goldstein, "in part due to the aging of the population and increasing awareness of how women's mental health affects economic health." Because of recent historic and substantial governmental funding focused on women's health, such as the White House Initiative on Women's Health Research and ARPA-H Sprint for Women's Health, "we are now at an inflection point in women's mental health research and clinical care," says Dr. Goldstein. In alignment with these initiatives, NIH has issued a new Notice of Special Interest (NOT-OD-24-079) to solicit research applications focused on conditions that solely, predominantly, or differently affect women, such as depression, anxiety disorders, and other stress-related disorders. The NIMH Women's Mental Health Program and other NIH institutes and centers continue to support and advance research on sex-based differences in brain anatomy, stress-response systems, the immune system, and hormones, as well as how these differences interact with gendered power dynamics to affect women's mental health throughout the life course.

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WOMEN IN SCIENCE

SCIENTIST SPOTLIGHT

An Interview with Dr. Jill M. Goldstein, Founder and Director of Innovation Center on Sex Differences in Medicine (ICON-✗), Massachusetts General Hospital (MGH); Helen T. Moerschner Endowed MGH Research Institute Chair in Women's Health; and Professor of Psychiatry and Medicine at Harvard Medical Schooll

Jill Goldstein, Ph.D., M.P.H., Massachusetts General Hospital, Harvard Medical School

For more than 35 years, Jill M. Goldstein, Ph.D., M.P.H., has studied sex differences in the human brain, psychiatric disorders, and associated comorbidities such as cardiovascular disease. Her interdisciplinary research laboratory at Massachusetts General Hospital employs multi-modal brain imaging, in-depth cognitive and clinical assessments, and advanced genetic/genomic and proteomic techniques to interrogate sex differences in physiology, neuroendocrinology, and immune, vascular, and metabolic functions. Her lab focuses on the comorbidity of depression, cardiovascular disease, and Alzheimer's disease—by applying a sex differences lens to understand their shared pathophysiology, beginning in fetal development, and develop sex-dependent therapeutics for precision medicine. In 2018, she launched the Innovation Center on Sex Differences in Medicine (ICON-✗) at Massachusetts General Hospital and sister institutions —a joint effort across departments, fields, methodologies, and technologies. The mission of ICON-✗ is not only to enhance discoveries of sex differences across medicine, but also to translate them into the development of sex-selective diagnostic tools and therapies.

What are your primary areas of research?

As a clinical neuroscientist, I have a longstanding interest in mapping out sex differences in the brain and the roles of steroid hormones, genes, and markers of immune function that contribute to sex differences in psychiatric disorders and common comorbidities, such as cardiovascular disease. For more than 35 years, I have been working with colleagues across Harvard's schools and departments and at other collaborative institutions to tackle issues of sex differences in medicine and women's health. Together, we have worked to integrate diverse fields of study, methods of analysis, and levels of study from basic to clinical. By understanding these sex differences, we can begin to develop sex-selective diagnostic tools and therapies.

There is a relative paucity of studies concerning sex effects in medicine, although this is changing. For example, we know relatively little about how sex differences in brain development contribute to pathology and affect treatment responses over the lifespan. In addition, clinical decisions are based on studies that have primarily involved males, and thus are often inappropriate for females. This problem is true even for disorders (like depression)

in which women predominate. Thus, clinicians and clinical guidelines do not incorporate the impact of sex in medicine.

My work has focused on four major areas: (1) the impact of sex on brain development and function, including on neuroanatomy and physiology, genetics/genomics, pre- and perinatal factors, steroid hormones, and markers of immune function, and its implications for psychiatric disorders; (2) how disruption of the healthy sexual differentiation of the brain during fetal development affects sex differences across the lifespan, including brain aging; (3) how fetal programming contributes to comorbid psychiatric and general medical disorders; and (4) understanding how sex affects the three common comorbidities of depression, cardiovascular disease, and Alzheimer's disease, and the development of targeted, sex-selective therapies for these conditions.

Which accomplishments are you proudest of?

I am especially proud of a few accomplishments. One of these is bringing methodologic rigor to the study of sex differences in the brain in the early 1990s, when it was unfashionable to even discuss sex differences in the brain. Another is my longtime commitment to mentoring and sponsoring the next generations of biomedical researchers who incorporate the impact of sex and gender into their work. We need to create the ambassadors for this thinking who will infuse science, clinical practice, and medical policies for future generations. I am also especially proud of my longstanding work to bring together scientists and clinicians across fields and methodologies to study sex differences in medicine and health with a focus on shared pathophysiology across the brain and body.

What are some of the biggest challenges you have faced?

As someone who committed their career to science, I have, of course, the ongoing stress of maintaining funding for my work. I have found that diversifying one's portfolio is key, as is forging collaborations.

Another challenge has been demonstrating to others the importance of sex in medicine and that women's health is not just about reproductive differences. The importance of sex continues to be debated today. Thus, during the many years I have been conducting this work, my colleagues' interest in this research and the availability of specific funding mechanisms have ebbed and flowed.

Finally, a key challenge that was true in the mid-1980s, when I began investigating sex differences, and that remains true to this day, is that some individuals confound the politics of gender with the reality and importance of the impact of the biology of sex on disorders of the brain and body. It is critical for us to understand the biologic substrate—and this understanding can only enhance our understanding of gender—rather than take an anti-intellectual political stance that the biology of sex does not matter, or that we cannot or should not study it. A failure to interrogate sex differences will only have negative consequences for the science and ultimately for the treatment of patients.

What led you to establish the Innovation Center on SeX Differences in Medicine (ICON-X) center??

In 2017, as I considered the next steps in my career, I reviewed the most important gaps and unmet needs in the women's health/sex differences space and pondered what vision I would propose to address them. Ultimately, I focused on two themes. First, I considered the issue of sex differences in the comorbidity of chronic diseases. These have very high prevalence worldwide and have no effective treatments, and women are at a distinct disadvantage for many of these comorbidities. Medicine has developed in silos that focus on a single organ or system, whereas a sex differences lens across the lifespan reveals shared pathophysiology across organ systems, and thus may provide targets for treating multiple diseases. The other issue I considered was the need to translate sex differences discoveries from preclinical animal studies to clinical trials involving humans to commercialization. At this time, even the so-called "FemTech" market, which was sorely needed, was primarily, if not solely, focused on reproductive medicine for women. Although numerous women's health research centers were conducting amazing discovery work, less emphasis was placed on translating these discoveries into diagnostic tools and therapies and on engaging industry in this process. I wanted to work on educating industry about the importance of sex effects in order to bring these discoveries through to commercialization.

Therefore, in 2018, I launched the Innovation Center on Sex Differences in Medicine or ICON-X at Massachusetts General Hospital (MGH), whose tagline is "when it comes to health, sex matters." Our mission is to enhance discoveries of sex differences in medicine and even more importantly, translate them into sex-selective diagnostic tools and therapies. We take a lifespan approach to understanding the impact of sex and believe that that will lead to our ability to prevent disease and intervene early with targeted treatments. An additional goal is to train the next generation to think differently about the role of sex and gender in medicine and to serve as ambassadors by introducing these concepts to their colleagues. Finally, we have been engaging potential industry partners to work with us on the animal studies to human/clinical trials to commercialization pipeline. We are very excited about this next stage for ICON-X, for our industry partners, and for the field in general. Given landmark increases in funding for women's health, this moment reflects a critical inflection point in the history of women's health research. We can now operationalize what many of us have believed for years: Given that every cell has a sex, there is nothing more basic for realizing precision medicine than the impact of sex.

What advice do you give to young scientists?

There are many lessons I have learned along the way during my career. First, an academic career trajectory is not a straight line—there are many detours along the way, and it is a marathon not a sprint. Second, as one of my former chairs used to say, the flip side of adversity is opportunity. Recognize opportunities when they arise and do not be afraid of going against the prevailing ideology. Third, academics is a business. We don't think of it that way, but it can be insightful to pull concepts and advice from the business world to help you be successful as an academic researcher. Finally, separate the personal from your work issues, and park your narcissism at the door.

INSTITUTIONAL SPOTLIGHT

Center for Women in Medicine in Science, a Community-Based Participatory Research Approach to Advancing Gender Equity

In 2021, NIH recognized the University of Minnesota with an NIH Prize for Enhancing Faculty Gender Diversity in Biomedical and Behavioral Science for its Center for Women in Medicine and Science (CWIMS). In 2015–2016 the University of Minnesota conducted an environmental scan to assess gender equity at its medical school. The resulting gender equity report suggested several institutional-level changes, including the creation of a center to support women in medicine and science. Inaugurated in 2018, CWIMS serves 27 medical school departments, including clinical and basic science departments, and more than 3,700 faculty members.

CWIMS employs a community-based participatory research framework to support effective and sustainable initiatives to foster gender equity, diversity, and inclusion. To oversee its efforts, CWIMS created a leadership group and four action groups consisting of medical school faculty. The four action groups focus on (1) recruitment and retention; (2) salary, resources, and leadership equity; (3) mentoring action group; and (4) strategic collaboration and communications.

From 2018 to 2021, CWIMS conducted a salary equity study, built an electronic metrics dashboard to track progress on gender equity, created a Distinguished Visiting Scholar mechanism to fund presentations by distinguished external women faculty, and received several grants for projects that reduce gender-based disparities in achieving promotion, tenure, and leadership. Additional efforts include nominating women to important boards and committees; creating a salary equity review committee to review and adjust faculty salaries; and developing the Early Pathways to Success Program, a peer mentoring and career development program for newly hired women faculty. Since the program's establishment, the medical school has seen increases in women and Black, indigenous, and other people of color (BIPOC) faculty, in women faculty advancing in rank, and in women search committee chairs.

ORWH thanks the University of Minnesota and CWIMS for their community-based, state-of-the-art gender equity research and initiatives. For more information regarding the NIH Prize for Enhancing Faculty Gender Diversity in Biomedical and Behavioral Science and other award-winning programs, please see the executive summary of "Effective Approaches to Fostering Faculty Gender Diversity, Equity, and Inclusion: Celebrating Progress," a virtual forum hosted by ORWH.

NEWS AND EVENTS

Too Few Articles with Women Corresponding Authors Are Being Published in Nature, Finds Research by the Publication

(Nature, 2024. DOI: 10.1038/d41586-024-00640-5)

Women were corresponding authors on only 17% of manuscripts submitted to Nature during a 5-month span in 2023–2024. Authors submitting original research to Nature during this period were asked to voluntarily disclose their gender. Of the 90% of the corresponding authors who disclosed this information, only 17% were women. In 2021, women made up 31.7% of all researchers globally, according to the United Nations Educational, Scientific and Cultural Organization (UNESCO). This underrepresentation of practicing women scientists among submissions may reflect the general underrepresentation of women among senior scientists. Nature's editors were equally likely to send manuscripts with women or men corresponding authors out for peer review. However, after being reviewed, manuscripts with women corresponding authors were accepted less often (46%) compared to manuscripts with men corresponding authors (55%). To address this issue, Nature will continue to collect data on gender identity and membership in other underrepresented groups. Its editors will also proactively connect with women researchers and other underrepresented groups to encourage them to submit manuscripts to the publication.

ORWH Hosts 60th Meeting of the Advisory Committee on Research on Women's Health

ORWH Deputy Director Vivian Ota Wang, Ph.D., FACMG, CGC, provided opening remarks at the 60th Annual Meeting of the NIH Advisory Committee on Research on Women's Health (ACRWH) in April 2024. ACRWH members voted to accept the NIH-Wide Strategic Plan for Research on the Health of Women 2024–2028. Following the opening remarks, ORWH

Director Janine A. Clayton, M.D., FARVO, presented the ORWH Director's Report. Her report reviewed several NIH staffing updates and some key programs on the health of women. Dr. Clayton emphasized the importance of studying sex as a biological variable and noted that over the past 20 years, deaths associated with excessive alcohol use have risen for both sexes, but women experienced greater increases in alcohol use problems and in alcohol-related suicides than men. Dr. Clayton shared that with several recent appointments, 13 NIH institutes and centers are now led by women directors. She highlighted the NIH Community Partnerships to Advance Society (ComPASS) program, which funded 25 community-led, health equity structural interventions and a ComPASS Coordination Center in 2023. The program anticipates funding up to five Health Equity Research Hubs in 2024. She also drew attention to a new Notice of Special Interest on Women's Health Research (NOT-OD-24-079), which calls for research applications on conditions that predominantly (e.g., depressive disorders, autoimmune diseases) or differentially (e.g., HIV, cardiovascular disease) affect women or are female-specific (e.g., uterine fibroids, endometriosis). Dr. Tara A. Schwetz, Ph.D., NIH deputy director of program coordination, planning, and strategic initiatives and NIH director of the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI), provided information about DPCPSI's mission and activities. NIH Director Monica M. Bertagnolli, M.D., presented highlights from the NIH Director's Report, and Carolyn Mazure, Ph.D., director, women's health research at Yale and chair of The White House Initiative on Women's Health Research, provided an update on the Initiative. A panel discussed the middle-life health of women and menopause, with presentations on bone health, Alzheimer's disease risk, and the impact of the timing of menopausal hormonal therapy on mortality and cardiovascular disease. The meeting agenda and video recording of the ACRWH meeting are available online.

ORWH Hosts 8th Annual Vivian Pinn Symposium

On May 15, 2024, ORWH hosted the 8th Annual Vivian W. Pinn Symposium, which focused on autoimmune diseases. Autoimmune diseases occur when the immune system mistakenly targets the body's healthy tissues; these diseases predominantly affect women. ORWH Director Janine A. Clayton, M.D., FARVO, opened the event by describing the establishment of the Office of Autoimmune Disease Research within ORWH (OADR-ORWH). In the first year since its establishment, OADR-ORWH funded 41 different grant applications concerning 17 different autoimmune conditions, including 6 EXposome in Autoimmune Disease Collaborating Teams PLANning Awards (EXACT-PLAN). The EXACT-PLAN Notice of Special Interest (NOT-OD-23-112) was developed by OADR-ORWH in partnership with the National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institute of Environmental Health Sciences, and other NIH institute, center, and office (ICO) partners. Following Dr. Clayton's opening remarks, Jane Buckner, M.D., president of the Benaroya Research Institute and affiliate professor at the Department of Medicine in the Division of Rheumatology at the University of Washington, gave the keynote address. Dr. Buckner described the central role of T cells in the pathogenesis of autoimmune diseases and highlighted recent research attempts to harness the power of a subtype of T cells, known as T regulatory cells (Tregs), to treat autoimmune diseases. Tregs recognize healthy tissue and inhibit the actions of other immune cells against this tissue; thus gene-editing approaches to target Tregs to tissues being attacked by the immune system in various autoimmune diseases may help develop highly targeted and effective cellular immunotherapies, analogous to some of chimeric antigen receptor T cell (CAR-T) therapies now being used to treat certain cancers. Additional presentations described research into the genetics of childhood-onset systemic lupus erythematosus, results of whole genome sequencing studies on genetic variants involved in autoimmune diseases, and the genetics of susceptibility to mycobacterial infections.

In a fireside chat with OADR-ORWH Director Victoria Shanmugam, MBBS, MRCP, FACR, CCD, David Fajgenbaum, M.D., M.B.A., M.Sc., associate professor of medicine, Division of Translational Medicine & Human Genetics, University of Pennsylvania, described his diagnosis with idiopathic multicentric Castleman disease, which led him to establish the Center for Cytokine Storm Treatment & Laboratory and the Castleman Disease Collaborative Network. Gail Kerr, M.D., FRCP, FACR, MACR, professor of medicine and chief of the Division of Rheumatology at the Washington D.C. Veterans Affairs Medical Center of Howard University Hospital, gave the capstone address, in which she described the creation of the Ethnic Minority Rheumatoid Arthritis Consortium to address the lack of racial and ethnic diversity in existing rheumatoid arthritis registries and her work with the Academy for Workforce Advancement to Enrich Rheumatology Diversity Program to address disparities in the rheumatology workforce. During closing remarks, the former director of ORWH, Vivian W. Pinn, M.D. reflected on ORWH's longstanding efforts to promote research on autoimmune diseases.

The full video recording of the symposium is available online.

Executive Order to Expand Investment in Women's Health Research

On March 18, 2024, President Joe Biden signed a new Executive Order (EO) on Advancing Women's Health Research and Innovation. This EO announces new actions to prioritize investments in women's health research. ORWH Director Janine Austin Clayton, M.D., FARVO, and Deputy Director Vivian Ota Wang, Ph.D., were honored to attend the historic signing, along with NIH Director Monica Bertagnolli, M.D.,

and Deputy Director for Program Coordination, Planning, and Strategic Initiatives Tara A. Schwetz, Ph.D. "Accelerating women's health research is vital because data show that sex and gender affect health at all levels," says Dr. Clayton. "President Biden's historic Executive Order will ensure that women's health is prioritized across the federal research portfolio and further ORWH's mission of transforming knowledge into impact to improve the health of all women." The EO focuses on actions in support and advancement of five key goals: (1) prioritize and increase investments in women's health research; (2) foster innovation and discovery in women's health; (3) expand and leverage data collection and analysis related to women's health; (4) strengthen coordination, infrastructure, and training to support women's health research; and (5) improve women's health across the lifespan.

STAFF UPDATES

In March 2024, ORWH appointed **Elizabeth Barr, Ph.D.**, to serve as associate director for the ORWH Interdisciplinary Research section. Dr. Barr joined ORWH in 2019 as a research program officer in the ORWH Clinical Research Section, where she focused on advancing intersectional health research on gender as a social and structural variable. She also managed the ORWH interprofessional online education program and has served as a leader for advancing research for women with HIV. She has expertise in gender and women's studies, interdisciplinary research, community-led HIV research, and reproductive justice. Dr. Barr completed her Ph.D. at the University of Wisconsin, Madison in rhetoric, politics, and culture and her M.S. at Towson University in women's and gender studies. Prior to joining ORWH, Dr. Barr served on the faculties of Towson University and the University of Maryland, Baltimore County, and led interdisciplinary, cross-sector projects to increase women's engagement in clinical research.

Luz Blanco, Ph.D., joined ORWH as a health scientist administrator in the Office of Autoimmune Disease Research (OADR-ORWH) in February 2024. Dr. Blanco is an accomplished research scientist with more than 30 years of experience in the fields of immunology and microbiology. She received her bachelor's degree in biochemistry with a minor in immunology at the Pontifical Catholic University of Chile in 1987 and completed her Ph.D. in microbiology at the University of Chile. Prior to joining ORWH, Dr. Blanco served as a staff scientist for the Systemic Autoimmunity Branch at the National Institute of Arthritis and Musculoskeletal and Skin Diseases, where she studied the innate immune system's role in autoimmunity and inflammation. Dr. Blanco's research concerns how innate immune cells, particularly neutrophils, participate in autoimmune and inflammatory diseases. She has also studied potential therapeutic agents for systemic lupus erythematosus and the mitochondrial dysfunction associated with this autoimmune disease.

Carolyn Bondar, Ph.D., joined ORWH as a program officer in the Careers Section in February 2024. She completed her doctorate in pharmacology and biochemistry and molecular biology at Baylor College of Medicine. She received postdoctoral training at the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital. Prior to joining ORWH, Dr. Bondar served as a health program specialist at the National Institute of Neurological Disorders and Stroke, where she supported the Blueprint Neurotherapeutics Network and the HEAL Pain Therapeutics Development Program in the Division of Translational Research. Throughout her career, she has engaged in numerous diversity, equity, inclusion, and accessibility initiatives and advocated for accessibility for scientists with disabilities.

Artificial Intelligence Based Deep Learning Models Reveal Behaviorally Relevant Sex Differences in Human Functional Brain Organization

(Original research by Ryali C., Zhang Y., et al., 2024. PNAS. DOI: 10.1073/pnas.2310012121)

Research has identified several sex-based differences in brain structure. For example, females generally have more gray matter but less white matter than males. Females also have more connectivity between brain hemispheres, whereas males have more connectivity within hemispheres. Despite these known structural differences, sex differences in functional brain organization have remained unclear. To study how sex relates to functional brain organization, Drs. Srikanth Ryali and Yuan Zhang and colleagues trained an end-to-end spatiotemporal deep neural network (stDNN) on resting state fMRI (rsfMRI) data from 1,000 young adults in the NIH-funded Human Connectome Project. Their stDNN model directly learned latent brain dynamics from raw rsfMRI data, rather than relying on precomputed functional connectivity between brain regions, as previous deep neural network models have done.

Following training, the stDNN model correctly classified MRIs by sex more than 90% of the time. The model's classifications were robust across multiple sessions within the same individuals and in three independent research samples, and greatly exceeded the performance of previous AI-based models. Further analyses examining the differences underlying these classifications revealed that the default mode network, striatum, and limbic network (especially the orbitofrontal cortex) exhibited large and consistent sex-based differences. The default mode network helps integrate self-relevant information and monitor the internal mental landscape. It plays a critical role in introspection and retrieval of autobiographical memories. Sex-based differences in this network may therefore influence how females and males recall past experiences, form self-concepts, and engage in perspective-taking. The striatum and limbic networks are involved in habit formation, reinforcement learning, reward sensitivity, and correction of behaviors in response to changing incentives. The authors note that these functional brain differences may relate to sex-based differences in internalizing versus externalizing problems and risk for psychiatric disorders, such as anxiety, attention deficit disorder, and depression.

Black Women in the United States Are Murdered at Three Times the Rate of Their White Counterparts

(Original research by Waller B.Y., et al., 2024. Lancet. DOI: 10.1016/S0140-6736(23)02279-1)

Homicide is a leading cause of death among women younger than age 44 in the United States, and Black women have long been disproportionately affected. To examine whether Black-White disparities in homicide rates had shifted in recent years, Dr. Bernadine Y. Waller and colleagues reviewed data on causes of death among women aged 25–44 in 30 states. From 1999 to 2020, Black women continued to be murdered at more than three times the rate of their White counterparts. Apart from a brief dip in homicide rates for Black women during the early 2010s, this disparity remained steady during this period. Black-White disparities were greatest in the Midwest, where Black women were murdered at more than seven times the rate of their White counterparts. For all women, the risk of being murdered by a firearm more than doubled during this period.

Dr. Waller and colleagues note that structural racism—including poverty, residential segregation, and reduced home ownership and educational attainment in Black communities—likely contribute to Black women's disproportionate risk for being murdered.[1] Intimate partner violence is also a major contributor to murders among young women in the United States, with more than half experiencing intimate partner violence prior to being killed.[2] Black women may be disproportionately impacted by violence. In addition, tensions and distrust between the police and the Black community may prevent Black women from seeking help from law enforcement despite fearing for their lives.[3] The authors propose that addressing structural racism, improving neighborhood safety, increasing mixed income affordable housing, and reducing access to firearms may help reduce homicide rates.

Xist Ribonucleoproteins Contribute to Females' Greater Risk for Autoimmunity

(Original research by Dou, et al., 2024. Cell. DOI: 10.1016/j.cell.2023.12.037)

As many as 50 million Americans have an autoimmune condition, and nearly 4 out of 5 of those affected are women.[4] Some autoimmune diseases have an extreme female predominance. For example, systemic lupus erythematosus (SLE) affects 9 times as many women as men, and Sjögren's disease affects 19 times as many women as men.

Although hormonal differences may play a role in this female predominance, the dosage of the X chromosome also appears to be a major factor. Biological sex is determined by the X and Y sex chromosomes: Females carry two X chromosomes, while males carry one X chromosome and one Y chromosome. Notably, males with Klinefelter syndrome, a sex chromosomal abnormality, who carry two X chromosomes and one Y chromosomes are male in appearance and hormonal levels but have an elevated risk—equivalent to that of females—for autoimmune disease.

Now, new research led by Dr. Diana Remy Dou demonstrates a potential mechanism for how X chromosome dosage increases risk for autoimmunity. Females selectively silence one of their two X chromosomes in every cell. In each cell, one of the two X chromosomes will express Xist long non-coding RNA, which then binds to proteins to coat and inactivate the chromosome. To study the impact of the Xist-protein complex, Dr. Dou created transgenic male mice that express Xist, using a mouse strain known to be susceptible to autoimmunity. Like the female mice of this strain, the transgenic males expressing Xist were susceptible to chemically induced autoimmunity. The males also exhibited female-like changes in B cell and T cell gene expression related to immune activity and regulation. Dr. Dou then showed that humans with autoimmune diseases carry antibodies to several components of Xist-protein complex. Many of these human antibodies were also found in the transgenic mice with chemically induced autoimmunity. Together, these studies show that the Xist-protein complex contributes to women's elevated risk for autoimmunity. Previous research may have missed the impact of Xist because of its reliance on male cell lines as the reference standard, notes senior author, Dr. Howard Y. Chang. Further investigation of Xist's contribution to autoimmunity may help clarify the complex chain of immune changes leading to autoimmunity and illuminate targets for improved therapies.

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NOTEWORTHY

Menopause Roundtable

On May 16, 2024, ORWH and the Office of Disease Prevention (ODP) co-hosted the first in a series of roundtables focused on important women's health topics. As part of the White House Initiative on Women's Health Research, these roundtables will direct attention to priority topics within the Department of Health and Human Services and to disseminate information on federally supported research concerning female-specific health conditions (e.g., endometriosis) and diseases and conditions that predominantly affect women (e.g., autoimmune diseases) or that present or progress differently in women (e.g., cardiovascular disease, depression). The inaugural event, "Future Directions in Menopause Research: Optimizing Midlife Health of Women Roundtable," focused on the science of menopause and NIH-supported work in this area. Following introductory remarks by ORWH Director Janine Austin Clayton, M.D., FARVO, NIH Director Monica M. Bertagnolli, M.D., and ODP Director David M. Murray, Ph.D., a panel of experts on women's health in midlife discussed how NIH and the research community can advance innovative research concerning this critical period in women's lives.

ORWH Publishes the 2024-2028 NIH-Wide Strategic Plan on Research on the Health of Women

In May 2024, ORWH published the 2024-2028 NIH-Wide Strategic Plan on Research on the Health of Women. This comprehensive roadmap reflects ORWH's charge to address the unique health needs and challenges women face throughout the life course and to support and promote the advancement of women in biomedical careers. The plan articulates five strategic goals: research, data science and management, training and education, basic and translational science, and community engagement. Six cross-cutting themes are emphasized in pursuit of these goals: comorbidity and multimorbidity, interdisciplinary collaboration, precision medicine, inclusion of women and girls in clinical studies, sex and gender differences research, and preventive care and services. Several principles guided the plan's development, including the need to consider complex intersections of multiple factors affecting the health of women, as well as the critical importance of including diverse populations of women in clinical research and integrating perspectives from a diverse workforce of scientists. The plan underscores NIH's continuing

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commitment to advance research that enables all women to receive evidence-based prevention and treatment that is tailored to their unique needs and circumstances.

Health of Women of U3 Populations Data Book

In May 2024, ORWH published the fifth edition of the Health of Women of U3 Populations Data Book, which focuses specifically on the health of women of underrepresented populations (U3), with particular attention on how systems, policies, and socially determined categories and environments interact to produce health disparities. Despite advances in addressing these health disparities, many challenges remain. Women from U3 populations continue to have elevated rates of maternal mortality and morbidity; women continue to die at greater rates than men with similar conditions such as cardiovascular disease; and many women lack sufficient access to high-quality health care. The data book draws on data from the 2020 Census to provide details on health disparities and inequities using an intersectional lens. The findings are organized by different types of social determinants of health (e.g., sociocultural environment, behaviors). The Health of Women of U3 Populations Data Book is available online.

NIH Publishes Fact Sheets on Women's Health Research

In May 2024, NIH published a new collection of fact sheets that outline the state of the science for women's health on autoimmune diseases, cancer, cardiovascular disease, dementia, HIV, maternal morbidity and mortality, menopause, mental health, substance use disorder, and violence against women and trauma. The NIH Fact Sheets on Women's Health review how sex and gender differences and female-specific considerations may contribute to these conditions and list important scientific gaps and opportunities for further study within each research domain. The fact sheets also highlight funding for women's health research in Fiscal Year 2023 for each topic. The fact sheets are available via the ORWH website.

UPCOMING EVENTS

Diverse Voices: Nutrition and Health Disparities
July 25, 2024 | 3 –4 p.m. EDT

Specialized Centers of Research Excellence (SCORE) on Sex Differences 2024 Annual Meeting Keynote Address
September 30, 2024 | 9 –10 a.m. EDT

Building Interdisciplinary Research Careers in Women's Health (BIRCWH) 2024 Annual Meeting
October 1, 2024 | 10 a.m.–4 p.m. EDT

FUNDING OPPORTUNITIES

Administrative Supplements for the Study of the Diverse Aspects of Uterine Serous Carcinoma (Clinical Trial Not Allowed) (NOT-CA-24-044)
Applications due by July 02, 2024

Mood and Psychosis Symptoms During the Menopause Transition (R01 Clinical Trial Optional PAR-23-097; R21 Clinical Trial Optional PAR-23-102)
Applications due by January 8, 2025

Research Opportunities Centering the Health of Women Across the HIV Research Continuum (NOT-OD-24-119)
Applications due by January 08, 2026

Women's Health Research (NOT-OD-24-079)
Applications due by November 5, 2027

For up-to-date information, visit www.nih.gov/women.

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