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NIH Supports Research on Autoimmune Diseases in Women

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Autoimmune diseases (ADs) occur when the immune system fails to discriminate between self vs. non-self and mistakenly attacks the body's healthy cells, tissues, or organs. An estimated 8% of the U.S. population has an AD, and more than three-quarters of these individuals are women. In some ADs, such as lupus and Sjögren's syndrome, the female predominance is extreme. In addition, some ADs are more prevalent among different racial, ethnic, and age groups. For many ADs, the reasons underlying the observed sex and other group differences are not well understood. Despite their prevalence and resulting large burden of disease, many ADs are understudied, have limited treatment options, and no known cures.

In this issue of In Focus*, we review several promising areas of research on ADs. Our feature story describes sex differences and future research directions for several common ADs that primarily affect women, including rheumatoid arthritis, multiple sclerosis, autoimmune thyroid diseases, primary biliary cholangitis, Sjögren's syndrome, antiphospholipid syndrome, and lupus. NIH researchers discuss the potential contributions of genetics, hormones, and environmental and lifestyle factors to the development of these ADs.*

This issue's Spotlight Article describes the establishment of the new Office of Autoimmune Disease Research within ORWH (OADR-ORWH) and its goals and support for AD research. In 2022, the National Academies of Sciences, Engineering, and Medicine (NASEM) published the report, Enhancing NIH Research on Autoimmune Disease*. Following publication of this report, Congress allocated funds to ORWH to establish the OADR-ORWH. This new office will complement efforts across NIH and other organizations to study ADs, address gaps in our understanding of these complex conditions, and improve treatments.*

This issue also highlights important upcoming ORWH events.

If you find this issue of In Focus *interesting and informative, please share it with your colleagues. You can subscribe by clicking the link on the front or back cover.*

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

NIH Supports Research on Autoimmune Diseases in Women

Autoimmune diseases (ADs) are conditions in which the immune system attacks healthy body cells. ADs often cause significant loss of physical and psychosocial function, represent a significant basis of chronic disability and lost productivity, reduce quality of life, and can be fatal. Medical experts use varied and evolving criteria to categorize ADs and—depending on definition—have identified between 80 and 150 ADs, including rheumatoid arthritis, multiple sclerosis, celiac disease, and type 1 diabetes. Individuals with one AD often develop other autoimmune conditions and have an increased risk for other diseases, including cancer and cardiovascular disease. Estimates from 2005 indicate that ADs affect between 14.7 million and 23.5 million people in the United States, and the current number of people with AD is likely much larger because of population growth and trends of increasing AD prevalence.[1] Although difficult to estimate, the personal and overall economic costs of ADs—from the costs of acute care, drugs, hospitalizations, and long-term caregiving to lost wages and productivity—are substantial. Currently, there are no cures for ADs, but many treatments can mitigate symptoms, delay or arrest disease progression, or increase periods of remission.

Anyone can develop an AD, but ADs tend to have greater prevalence and severity among specific subpopulations. Conservative estimates indicate that greater than 75% of individuals with an AD are women.[2] Female-to-male prevalence ratios can reach 9:1, or even higher for some ADs, and ADs are among the top 10 leading causes of death in women.[1]

"Using mouse models and human clinical samples, we consistently show that adult females of reproductive ages mount greater immune responses than males," says Sabra Klein, Ph.D., an NIH-funded vaccine researcher; Associate Professor of Molecular Microbiology and Immunology, Biochemistry, and Molecular Biology at the Johns Hopkins Bloomberg School of Public Health; and member of the NIH Advisory Committee on Research on Women's Health. "Greater immunity among females is a double-edged sword. These immune responses protect against infection and improve the effectiveness of vaccines, but an excessive immune response can contribute to tissue damage and disease," Dr. Klein says.

Sabra Klein, Ph.D., Johns Hopkins Bloomberg School of Public Health

In addition, some ADs are more prevalent among different racial, ethnic, and age groups. For example, although 90% of people with lupus are women, the disease is two to three times more prevalent among Black, Latina, Asian, Native American, Alaska Native, and Pacific Islander women than among White women.[3]

Lindsey Criswell, M.D., M.P.H., D.Sc., Director of the National Institute of Arthritis and Musculoskeletal Diseases (NIAMS), adds, "In some ADs, like lupus and Sjögren's syndrome, the female predominance is extreme, but we still don't fully understand why. Some research efforts have demonstrated that hormonal sex differences play a role, but sex hormones do not fully explain these differences in AD prevalence." Investigators have also explored the involvement of sex chromosomes and associated genes in AD prevalence, as Dr. Criswell explains: "Women have two copies of the X chromosome—men only one. Normally, in women, one copy is silenced in cells and tissues. However, sometimes that silencing is not complete. Having two active copies of the same gene can increase the risk for AD." Researchers have identified many genes

associated with susceptibility to AD, and interestingly, in some cases, distinct ADs with different symptoms and clinical characteristics share the same genetic variants.[1]

Environmental and lifestyle factors—sometimes called the "exposome"—may also contribute to AD etiology. Researchers have linked several types of exposure to the development of ADs, including pesticides, solvents, some infectious agents, endocrine-disrupting chemicals, respirable particulates and fibers, cigarette smoking, and diet. "Many autoimmunity talks and papers conclude with the fact that the cause of the female bias is multifaceted and involves genetics, hormones, and environmental influences," says Dr. Klein. "With the growing interest in our changing environment, there is room to better define the environmental causes of ADs, which could lend itself to intersectional analyses of sex and gender to address exposures."

Although the many types of AD affect different organ systems and manifest in varied symptoms, researchers have identified several commonalities among these diseases. Most ADs involve proinflammatory immune responses. In many cases, clinicians can detect associated autoantibodies or other biomarkers in serum, tissues, or other samples.[1] Further, in spite of their different clinical presentations, many ADs may share immune pathways and other biological mechanisms that lead to immune-mediated damage.[1] As such, research on the development, progression, and treatment of one AD could inform our understanding of another AD. Thus, NIH has established the Office of Autoimmune Disease Research within ORWH (OADR-ORWH) as a way of encouraging collaboration and cross-cutting innovation among AD researchers. Public Law 117-328—enacted by the U.S. Congress after the publication of *Enhancing NIH Research on Autoimmune Disease* by the National Academies of Sciences, Engineering, and Medicine (NASEM)—instructed NIH to establish this new office. (*For more information on the establishment of OADR-ORWH, please see "NIH Establishes the Office of Autoimmune Disease Research Within ORWH."*

The 2022 NASEM report provides an overview of 11 ADs that collectively represent the spectrum of ADs. This article describes a subset of those 11 ADs that predominantly affect women, with a focus on associated differences in prevalence and severity among sex, gender, racial, ethnic, and age groups; current diagnostic and treatment practices; and opportunities for future research.

Rheumatoid Arthritis

Arthritis is a general term describing dozens of conditions causing joint swelling, stiffness, and pain. Rheumatoid arthritis (RA) is an autoimmune disease that causes inflammation and damage to the joints, commonly to the hands, wrists, or knees. RA can also cause fatigue and weight loss and inflammation of the skin, lungs, and cardiovascular systems. Many patients with RA experience cyclical periods of symptom flares and remission. More women than men develop RA, with prevalence ratios varying from 3:1 to 3:2, depending on age.[4] Rates of RA are higher among Black and Latinx populations than in White populations.[1] The inflammation associated with RA can lead to atherosclerosis, which in turn can lead to strokes, myocardial infarction, and other health problems.[1] The pain and stiffness can result in a loss of function, decreased quality of life, and an increased risk of depression.[1] RA has a large social and economic impacts and results in large health care costs and lost wages and productivity.

Genetic factors may predispose certain individuals to RA, but various environmental factors including smoking also play a role. RA more commonly affects women. The lifetime risk of developing RA is 3.6 percent for women and 1.7 percent for men.[5] Risk factors for RA include cigarette smoking, other inhaled exposures, and periodontal disease. Early age at menopause has also been reported to be associated with higher RA risk,[6,7] and breast feeding has been associated with a lower RA risk.

Physicians diagnose RA by evaluating symptoms, conducting physical examinations, and testing blood for rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPA).[8] Images of the joints via radiography and ultrasound can indicate the extent of joint involvement, and inflammatory markers can detect disease activity.[9] Like all ADs, RA has no cure. However, multiple therapeutic regimens can control disease activity and achieve sustained remission, including traditional disease-modifying anti-rheumatic drugs, biologic drugs such as monoclonal antibodies, and targeted small molecule therapies.

Ongoing and future research on RA is needed to continue to understand the pathogenesis of disease, develop new therapies, and improve outcomes for patients with RA. (For more information on NIAMS research related to AD, see *NIAMS* and *AD Research*).

Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune disorder of the central nervous system (CNS) in which the immune system damages the myelin sheath around the axons of neurons (see *In Focus 6.3* for more information). This damage can lead to degeneration of the nerve fibers and poor nerve signaling to the muscles, and therefore loss of muscular function and coordination. Other symptoms include numbness, tremor, impaired balance and walking, vision problems, bowel and bladder problems, and fatigue. Approximately 85% of patients diagnosed with MS experience a pattern of relapse and remission, but about 15% have primary progressive MS with few or no periods of remission.[1]

NIAMS and AD Research

Many ADs, such as RA, systemic lupus erythematosus (SLE), and psoriasis, fall within the NIAMS mission areas, and the institute makes significant investments in associated research. Below, **NIAMS Director Lindsey Criswell, M.D., M.P.H., D.Sc.**, comments on NIAMS efforts in AD research, including participation in the AMP® AIM (Accelerating Medicines Partnership® in Autoimmune and Immune-Mediated Diseases) and AMP® RA/SLE (AMP® Rheumatoid Arthritis and Systemic Lupus Erythematosus) programs.

Lindsey Criswell, M.D., M.P.H., D.Sc., NIAMS Director

The AMP® programs are public–private partnerships that follow a highly successful team science model for research. NIAMS was involved in one of the first AMP projects, AMP® RA/SLE, which focused on RA and lupus. AMP research has helped to characterize some of the mechanisms underlying those diseases.

Later, AMP® AIM expanded AD research to include Sjögren's syndrome, psoriasis, and psoriatic arthritis. Now, we can look across a broader set of ADs to identify common pathways and mechanisms as well as pathways unique to those individual autoimmune conditions. In addition, we can leverage new tools that have been developed to enable us to more deeply understand ADs. For example, we can look at individual cells and reconstruct how they form neighborhoods within AD-affected tissues. We can also use bioinformatics tools, tools for studying the exposome, and software to analyze and integrate multiple large data sets. By bringing together a diverse group of investigators with support from NIH, industry partners, and nonprofit organizations, we have created a team science network that has enabled unprecedented progress related to AD and other diseases. In addition, NIAMS has invested significantly in centers of research—programs, typically at individual institutions, that bring together a diverse group of investigators to work on related projects. Often these centers fund core resources, which many researchers can leverage for a variety of projects. Many of these centers focus on ADs such as lupus, scleroderma, and psoriasis.

NIAMS also invests in individual investigator awards—for example, the classic NIH R01 grant. Much of this type of NIAMS funding supports research on AD, ranging from basic science research focused on the immune system to population-level studies that investigate why certain populations have an increased burden or severity of disease.

The cause of MS is not known, but there is a strong familial component, and genetic studies have implicated multiple different pathways in the disease. Environmental exposures also seem to play a major role in predisposition to MS. These exposures include viral infections, geographic factors, sunlight and vitamin D, and smoking.

MS, like most ADs, has a female predominance, with women approximately 2.8 times more likely to develop MS than men.[1] Researchers have identified racial and ethnic differences in MS prevalence in a cohort of U.S. patients, with the highest incidence among Black individuals.[10] Because the mean age of onset is 30,[1] MS represents a major cause of disability among young adults, resulting in high economic costs to both individuals and society as a whole.

Clinical diagnosis of MS remains challenging and generally involves a physical examination, a review of the patient's medical history, imaging of the brain to detect lesions, and assays of immunoglobulin G (IgG) levels in the cerebrospinal fluid and blood. Several agents have been shown to have efficacy as disease modifying therapy (DMT) in MS, and observational studies suggest that use of DMT is associated with lower long-term risk of MS disease progression.[11]

Ongoing research in MS is needed to further understand how genetics and other risk factors contribute to disease etiology, refine diagnostic testing and develop new biomarkers, develop new therapeutic agents, and investigate how best to treat MS particularly in women whose disease activity may vary in response to hormonal fluctuations over the lifespan. Research on these and other questions could help improve long-term MS outcomes.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) also called lupus is an AD that causes inflammation in multiple organs. Patients experience disease flares interspersed with periods of remission. SLE is associated with arthritis, skin and facial rash, kidney disease, blood disorders, pain, reduced function, fatigue, neurocognitive symptoms, musculoskeletal symptoms, weakness, hair loss, and other symptoms. SLE can be debilitating and often leads to poor quality of life. Without treatment the disease can be fatal, but with treatment, many patients with SLE will live a normal lifespan.[12]

The causes of SLE remain unclear, however, genetic factors, infections, hormonal fluctuations, and environment exposures

may contribute to the development or worsening of SLE. As many as 90% of individuals with SLE are women, particularly young women and women of color.[1] "Individuals of non-European ancestry have a significantly increased risk of developing lupus, for reasons that we don't fully understand," says Dr. Criswell. "It likely has to do with environment, socioeconomic factors, as well as interactions between genes and environment over time."

SLE may present clinically in many ways, which can sometimes cause delays in diagnosis and therefore effect prognosis. Diagnostic criteria developed to help clinicians diagnose SLE include both clinical features and laboratory tests. One of the most common findings in SLE is the presence of autoantibodies, and studies have shown that autoantibodies may predate clinical manifestations of SLE by several years.[13]

Treatment in SLE is typically tailored to the patient and their particular disease manifestations. Hydroxychloroquine has been shown to reduce the risk of relapse and to improve patient survival in SLE and is therefore recommended in most cases. Additional immunosuppressive therapy is guided by severity of disease and organ manifestations. Patients should also be monitored for complications including cardiovascular disease and osteoporosis.

Women with SLE often find that their disease activity varies over their lifespan. Hormonal factors can play a role in disease flares. The disease may flare in pregnancy, and presence of some autoantibodies can cause complications during pregnancy, necessitating close monitoring and sometimes causing pre-term delivery.[1] Organ damage in SLE is associated with higher health care–resource utilization and health care costs before and after SLE diagnosis.

Ongoing research has started to characterize the molecular mechanisms that contribute to different forms of SLE and to suggest new therapies. For example, investigators are exploring the use of monoclonal antibodies to block abnormal molecular and cellular pathways, an intervention targeting the interferon pathway, and medications that can block antigens from binding to cells or that can mark damaging immune and inflammatory cells for destruction. Additional research is needed to identify new diagnostic biomarkers; develop better disease treatments; improve understanding of differences in disease prevalence among racial, ethnic, sex, and age groups; and further characterize organ involvement in SLE.[1]

Antiphospholipid Syndrome

Antiphospholipid syndrome (APS) is an autoimmune condition in which antiphospholipid antibodies damage body tissue through vascular thrombosis, as well as lead to non-thrombotic manifestations including pregnancy complications, heart valve thickening, and cutaneous manifestations.

The etiology of APS is not well understood. APS is more prevalent among women, and White individuals have greater risk than other races and ethnicities, with Black individuals at the lowest risk.[1]

APS may occur in conjunction with other ADs including SLE and scleroderma. Sometimes the first presentation of APS is a pregnancy-related complication. Viral infections may be a trigger for APS, and notably, COVID-19 infection has been shown to trigger development of antiphospholipid antibodies.

A diagnosis of APS is made based on clinical manifestations and laboratory testing for antiphospholipid antibodies but can be complicated by fluctuating levels of antibodies.

The current understanding of APS remains limited, and more research is needed to characterize the sources of antibodies that trigger APS, the interplay of vascular and immune cells in APS, and hormonal factors that contribute to disease manifestations.

Sjögren's Syndrome

Sjögren's syndrome, is a chronic AD causing inflammation of the salivary and tear-producing glands as well as other organs. Symptoms include dry mouth and eyes; ocular damage; dental caries and loss of teeth; trouble talking, chewing, and swallowing; fatigue; and systemic effects. Sjögren's syndrome may occur in isolation or in conjunction with another AD, for example autoimmune thyroid disease, RA, SLE, systemic sclerosis, or autoimmune liver disease. Patients with Sjögren's syndrome are at risk for other comorbidities including cardiovascular disease, lymphoma, and depression.

Sjögren's syndrome is more prevalent among women and girls with female-to-male ratios of 6:1 in U.S. adults, 14:1 in adults worldwide, and 5:1 in children worldwide.[1] Researchers have also identified racial and ethnic differences in prevalence (i.e., 77% of diagnosed cases are among White patients, 14% Asian, 6% Hispanic, and 1.4% Black).[14]

Diagnosis of Sjögren's syndrome involves physical examination, tests of tear flow, autoantibody testing, and sometimes tissue biopsy of the minor salivary glands. Some viral infections can mimic symptoms of Sjögren's syndrome, including hepatitis C and HIV, and these diagnoses must be excluded before a diagnosis of Sjögren's syndrome can be made.

Treatment of Sjögren's syndrome involves both mitigation of symptoms and specific therapy for systemic disease. The treatment selected depends on the clinical manifestations and tissues and organs affected. Some of the antibodies associated with Sjögren's syndrome can cross the placenta, creating issues with development of the fetal heart. Patients with these antibodies require close monitoring during pregnancy.

Ongoing research is investigating potential new disease-modifying therapies for Sjögren's syndrome. More research is needed to identify biomarkers of disease progression, the economic impact of Sjögren's syndrome, and the effect of Sjögren's syndrome on pregnancy.

Primary Biliary Cholangitis

Primary biliary cholangitis (PBC, previously known as primary biliary cirrhosis) is an immune-mediated chronic disease that damages the bile ducts in the liver. It is a rare disease, but women represent 90% of diagnosed cases of PBC.[1]

The disease has an initially indolent course, with slowly progressive symptoms of fatigue, itchy skin, and cholestasis (i.e., low bile secretion into the digestive tract). Later symptoms may include dry eyes and mouth; pain in the abdomen, joints, muscles, or bones; swollen feet, ankles, and spleen; vitamin deficiencies; night blindness; jaundice; hyperpigmentation of the skin; high cholesterol; and osteoporosis.

Over time, PBC can cause cirrhosis or liver failure, which may necessitate a liver transplant. Familial clustering of PBC has been reported, suggesting genetic susceptibility, but the etiology remains poorly understood. Environmental factors may be at play because disease prevalence exhibits geographic variations.

Diagnosis of PBC is often delayed; many individuals are asymptomatic at first, and about half remain so at diagnosis. Diagnoses often involve assays indicating a reduced flow of bile, tests determining the presence of antimitochondrial antibodies, and a histology report showing inflammation in the bile ducts.[1] Treatment options are currently limited and usually involve chelating agents. More research is needed to develop new therapies for PBC, and to identify genetic and immunologic pathways driving the disease.[1] Thorough studies on the incidence, prevalence, and natural history of the disease are also needed.

Autoimmune Thyroid Diseases

Autoimmune thyroid diseases, including Graves' disease and Hashimoto's thyroiditis, are among the most common ADs and are leading causes of hyperthyroidism and hypothyroidism, respectively.

Graves' disease, characterized by an enlarged thyroid gland and an excess of thyroid hormones, can present with heart rate and blood pressure, weight loss, anxiety, sweating, sleep disturbances, and eye problems (e.g., Graves' ophthalmopathy).

Hashimoto's thyroiditis can result in an underactive thyroid, fatigue, and decreased tolerance to cold. Autoimmune thyroid diseases are associated with depression, other autoimmune problems, and increased risks for thyroid cancer, mortality, dementia, cardiovascular disease, and osteoporosis. Women with autoimmune thyroid disease are more likely than healthy women to experience pregnancy problems or infertility.[1]

Autoimmune thyroid diseases generally develop in mid to late adulthood, and 95% of cases occur in women. Hashimoto's thyroiditis has a higher prevalence in White women than in Black women. Among active-duty military personnel, Graves' disease has higher prevalence among Black, Asian, Pacific Islander, and Latinx populations than among White populations. Possible risk factors for autoimmune thyroid disease include genetics, smoking, iodine insufficiency, selenium deficiency, exposure to some toxins, and infectious agents such as hepatitis C. Information on the economic impact of autoimmune thyroid disease remains limited.[1]

Diagnosis of autoimmune thyroid diseases involves lab testing for thyroid hormone, thyroid-stimulating hormone, and autoantibodies.[15] Treatment for Graves' disease may involve antithyroid medications, thyroid ablation with radioactive iodine, and thyroidectomy, but many of these interventions can result in toxicity, side effects, increased risks for other diseases, and other adverse consequences.[1] A monoclonal antibody treatment for Graves' ophthalmopathy received FDA approval in 2020. Clinicians treat patients with Hashimoto's thyroiditis with synthetic levothyroxine, a form of thyroid hormone replacement, although people with normal or near-normal thyroid function may require no treatment in the early stages of the disease.[16]

Ongoing research into autoimmune thyroid disease is investigating the mechanisms of disease development as well as potential new therapies.

NIH and AD Research

As the world's largest supporter of biomedical research, NIH is dedicated to improving understanding of autoimmune diseases (see *Researching a Rare Autoimmune Condition: Relapsing Polychondritis* for an example). NIH continues to support scientific investigation into AD to build the knowledge base for these debilitating conditions and to develop new diagnostics, treatments, and potentially, cures. In 2020 alone, NIH spent more than $1 billion on AD research. Half of NIH's 27 institutes, centers, and offices (ICOs) provide most of the support to extramural, investigator-initiated AD research, and 11 of these ICOs support intramural AD research programs as well.[1]

Because many ADs affect multiple organs and systems, often, several medical disciplines as well as the corresponding ICOs participate in research efforts. For instance, Sjögren's syndrome is a multisystemic AD that can have respiratory and kidney manifestations, mucosal and ocular abnormalities, arthritis, neuropathy, lymphoma, and other symptoms and comorbidities. As Sjögren's syndrome affects so many organ systems, multiple NIH institutes (e.g., National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institute of Allergy and Infectious Diseases, National Eye

Institute, National Institute of Neurological Disorders and Stroke, National Heart, Lung, and Blood Institute, National Cancer Institute, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institute of Dental and Craniofacial Research) provide grants and other support for research on this condition.

The new OADR-ORWH will collaborate with the AD-focused biomedical research community within and outside of NIH, provide funding, catalyze available resources, and offer other support to researchers. OADR-ORWH will analyze the autoimmune disease research portfolio and use these data in collaboration with NIH institutes and centers (ICs) to catalyze autoimmune disease research. Input from the community as well as NIH ICs will inform the NIH-wide strategic research planning process, focusing on identifying emerging areas of innovation and opportunities for collaborative, synergistic research across ICs.

As Dr. Criswell says, "OADR-ORWH will allow us to leverage activities across NIH, to be more efficient with our investments in AD research, and to learn from one another to accelerate the pace of research. We are confident that if we coordinate AD research across the institutes and centers, we will learn more and learn it more quickly than if we worked separately."

Researching a Rare Autoimmune Condition: Relapsing Polychondritis

Before joining NIAMS as a staff clinician and most recently as clinical associate professor in the Division of Rheumatology, Allergy and Clinical Immunology at the University of Maryland School of Medicine in Baltimore, **Marcela Ferrada, M.D.**, was a critical-care infectious disease physician. After being diagnosed with relapsing polychondritis (RPC)—a rare, systemic, inflammatory condition that affects the cartilage in the ear, nose, airway, and many other organs—Dr. Ferrada completed a fellowship in rheumatology at NIAMS and was also a Lawrence Shulman Scholar, to better understand and research her condition. Below, she discusses her ongoing and planned research on RPC.

Marcela Ferrada, M.D.

I am now investigating the possible mechanisms leading to inflammatory processes in RPC with my current principal investigator, Peter Grayson, M.D., M.Sc. We have created the first prospective cohort of patients with this disease. Many patients with RPC are initially diagnosed with fibromyalgia and later develop more severe RPC symptoms. Although some of the literature conflicts with our findings, we have found that RPC is more common in females, and women with RPC tend to have greater systemic involvement than men. Our hypothesis, based on clinical observations, is that mitochondrial function maybe a main culprit in RPC inflammatory processes. We hope to pursue research in this area in the future.

Many ADs are considered rare, but I suspect that many cases remain undiagnosed. The new OADR-ORWH could help raise awareness of these so-called rare diseases, particularly among clinicians who may not have been trained to recognize and diagnose them. OADR-ORWH could also support research toward finding biomarkers that can help clinicians make definitive diagnoses of RPC and other ADs. Finding a biomarker will be a key element to help improve the life of many patients suffering from autoimmune diseases.

AD research and treatment require a holistic approach. Although there are many medications for treating patients with ADs, I don't believe there is a magic pill for each condition. Patients with AD—or any disease—need a holistic treatment, including guidance on diet and exercise, psychological support, and other forms of care. ADs often have heterogeneous presentations and tend to affect multiple pathways, organs, systems, and tissue types. Given the nature of these diseases, research would benefit from multi- and inter-disciplinary collaboration between clinicians and researchers, including a direct connection between clinicians and basic science researchers. OADR-ORWH could act as a hub to foster collaboration and move toward a better understanding of AD, better diagnostic tools, and better treatments to help patients currently struggling with these diseases.

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NIH Establishes the Office of Autoimmune Disease Research Within ORWH

In 2022, in response to the National Academies of Sciences, Engineering, and Medicine report Enhancing NIH Research on Autoimmune Disease, the U.S. Congress enacted Public Law 117-328 directing NIH to establish an Office of Autoimmune Disease Research within the Office of Research on Women's Health (OADR-ORWH).

The Consolidated Appropriations Act, 2023 directs OADR-ORWH to:

- Coordinate the development of a multi-institute and center (IC) strategic research plan;
- Identify emerging areas of innovation and research opportunity;
- Coordinate and foster collaborative research across the ICs;
- Annually evaluate the NIH AD research portfolio;
- Provide resources to support planning, collaboration, and innovation; and
- Develop a publicly accessible central repository for AD research.

Victoria Shanmugam, MBBS, MRCP, FACR, CCD
Director, Office of Autoimmune Disease Research, ORWH

ORWH initially leveraged its existing expertise and infrastructure to establish the new office's FY 2023 activities. The OADR-ORWH core federal staff who laid the strategic and programmatic groundwork for OADR-ORWH's future activities include:

- Janine Austin Clayton, M.D., FARVO, Director of ORWH
- Rajeev Agarwal, Ph.D., Senior Research Program Officer
- Lisa Begg, Dr.P.H., RN, Senior Research Program Officer
- Kelly Chandler, Ph.D., Health Science Policy Analyst
- Benjamin Johns, Ph.D., M.P.A., M.A., Social and Behavioral Scientist Administrator
- Balkissa Ouattara, M.D., Ph.D., M.P.H., Physician
- Sarah Temkin, M.D., Associate Director for Clinical Research
- Dave Thomas, Ph.D., Special Advisor to the Director
- Xenia Tigno, Ph.D., Associate Director for Careers
- Miya Whitaker, Psy.D., M.A., Health Scientist Administrator/ Program Officer
- Karen Wylie, Ph.D., Health Science Policy Analyst

A Coordinating Committee for Autoimmune Disease Research (CCADR) with representation from all NIH institutes and centers was created to provide a structured forum to leverage NIH's autoimmune disease research expertise. In November 2023, OADR-ORWH welcomed its inaugural Director, Dr. Victoria Shanmugam, who will the lead the way forward for this office.

As 1 of the 14 cross-cutting offices within the NIH Office of the Director, ORWH regularly works with NIH ICOs to create pathways for collaboration, foster innovation, and mobilize multidisciplinary efforts to advance the health of women. Leveraging ORWH's existing expertise, infrastructure, and stature will support and amplify the efforts of OADR as it works to catalyze AD research across NIH.

ORWH has established OADR-ORWH and has laid the strategic and programmatic groundwork needed for future activities. The

CCADR includes representation from all the ICs and will provide a structured forum to leverage NIH's AD research expertise.

In FY 2023 OADR-ORWH supported a total of 41 awards across 12 separate ICs. This included 15 extramural co-funding awards, 3 R56 bridge funding awards, 2 Accelerating Medicines Partnership® Autoimmune and Immune-Mediated Diseases (AMP® AIM) awards, 10 intramural co-funding awards, 5 intramural scientific fellowships, and 6 EXACT-PLAN (EXposome in Autoimmune Disease Collaborating Teams PLANning) awards. The EXACT-PLAN Awards (NOT-OD-23-112) were developed by OADR-ORWH with NIAMS, the National Institute of Environmental Health Sciences, and ICO partners to support the design, development, and implementation of a future, national, interdisciplinary, collaborative, team science research network that will advance the study of the exposome in autoimmune disease. These awards spanned basic to translational, clinical, and public health research focused on ADs.

OADR-ORWH also looks forward to supporting innovative and groundbreaking science via two Requests for Applications related to chronic conditions in women (RFA-OD-23-013 and RFA-OD-23-014), as well as through the Notice of Special Interest focused on research on the health of women of understudied, underrepresented, and underreported (U3) populations (NOT-OD-24-032).

Early in 2024, OADR-ORWH will release a Request for Information inviting input on the NIH-wide strategic plan for AD research focused on identifying emerging areas of innovation and research opportunity and fostering collaborative research across ICs. We welcome input from the community as we develop this strategic plan.

Please also join us in May 2024, at the 8th Annual Vivian W. Pinn Symposium, which will focus on Sex Differences in Autoimmune Disease. For more information, please visit the OADR-ORWH webpage.

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IN THE JOURNALS

Researchers Describe Link Between Periodontal Disease and Rheumatoid Arthritis

(Original article by Brewer et al. 2023. Sci. Transl. Med. PMID: 36812347.)

A recent article published by R. Camille Brewer, William H. Robinson, M.D., Ph.D., Dana E. Orange, M.D. M.Sc., and colleagues suggests a causal connection between periodontal disease (PD) and rheumatoid arthritis (RA). PD is more common in individuals with RA, and previous research has established that the gingival bleeding associated with PD can result in oral bacteria entering the blood stream. The researchers report that patients with RA and PD frequently experience episodes of increased oral bacteria in circulating blood and that the immune response to these bacteria likely contributes to the onset and persistence of RA in susceptible individuals.

The researchers conducted a complex series of analyses and observations, including RNA sequencing analysis of blood samples from patients with RA with and without PD, analysis of bacteria in oral mucosal sites and other body sites, gene expression analysis, screening for monoclonal antibodies, analysis of a mass spectroscopy dataset of human saliva samples, and clinical observations. The investigators found that citrullinated oral bacteria can enter circulating blood in patients with PD and can result in detectable levels of anticitrullinated protein antibodies (ACPAs) in the blood and synovia (i.e., the naturally secreted fluid that lubricates joints and tendon sheaths). ACPAs, in turn, can trigger inflammatory monocytes resulting in the inflamed joints associated with RA. Although the immune response to citrullinated oral bacteria seems to be associated with RA pathogenesis and persistence, the researchers emphasize that not all oral bacteria trigger RA-associated inflammatory pathways. The investigators suggest that future studies may determine whether improved oral care may help to manage RA symptoms and flares.

New Protocol Suggests Systematic Meta-Analysis Methodology for Assessing Sex-Dependent Differences in Sepsis and Other Diseases

(Original article by Zhang et al. 2023. Syst. Rev. PMID: 36945012.)

MengQi Zhang, Dean A. Fergusson, Ph.D., M.H.A., Manoj M. Lalu, M.D., Ph.D., and colleagues recently proposed a systematic process for reviewing and assessing the scientific literature on the effect of biological sex on the induction

and treatment response to sepsis, a host response to infection that currently contributes to one in five deaths worldwide. Although the influence of sex on sepsis outcomes remains unclear, some preclinical research suggests that female animals may be less susceptible to sepsis than males. However, the researchers emphasize that sex bias and equivocal clinical evidence on sex-dependent differences in sepsis may have limited research findings to date. Although the investigators proposed this systematic process for their review of the literature on sex differences in sepsis, a similar methodology could strengthen other types of sex-based reviews as well.

The protocol involves careful clarification of terms often used synonymously. "Sex" indicates biological attributes determined largely by genetics, physiology, gene expression, and hormones. "Gender" refers to sociocultural constructed roles, behaviors, and identities. "Sex- and gender-based analysis" refers to research approaches that examine sex-based and gender-based differences among women, girls, men, boys, and gender-diverse individuals.

The protocol specifies eligibility criteria for the types of studies that will be considered. Criteria include articles on studies that involve interventional mammalian models of infectious sepsis; stratify data by sex; examine interventions hypothesized to improve sepsis outcomes; and report on outcomes including death, organ dysfunction, injury, bacterial load, and/or inflammation. The eligibility criteria exclude articles on studies that use in vitro, ex vivo, and nonmammalian models; do not stratify data by sex; involve interventions hypothesized to contribute to sepsis pathogenesis or worsen outcomes; and were published as review articles, letters, editorials, or "gray" literature.

The protocol also includes well-defined search parameters as well as guidelines for risk-of-bias assessment, data analysis, sex-based analysis, subgroup analyses, and meta-biases assessment. The proposed protocol will inform a forthcoming review that will describe the current understanding of sex differences in sepsis, identify knowledge gaps, and make some initial progress toward better sepsis treatment.

Study Identifies Racial, Ethnic, and Gender Inequities in Opioid Access for Older Patients Dying of Cancer

(Original article by Enzinger et al. 2023. J. Clin. Oncol. PMID: 36626695.)

Opioids remain an essential part of pain management and end-of-life palliative care for patients with cancer. Over recent decades, regulations aimed at curbing opioid misuse have also functioned to restrict clinically appropriate access to opioids for patients with cancer, and previous studies have shown that patients of color are more likely than White patients to have undertreated pain.

A recent study supported by the U.S. Department of Health and Human Services by Andrea C. Enzinger, M.D., and colleagues found racial, ethnic, and inequities in opioid access for older patients with terminal cancer. The investigators analyzed Centers for Medicare & Medicaid Services data from 2007 to 2019 from more than 300,000 patients with cancer older than age 65 and near the end of life (i.e., within 30 days of death or hospice).

The researchers found that race, ethnicity, and gender influenced opioid access for older patients with cancer at end of life. Compared with White patients, Black and Hispanic patients were less likely to receive any opioid or long-acting opioids. Black and Hispanic patients also received lower daily doses and lower total doses of opioid than White patients. The investigators translate these findings into a concrete comparison: in the last month of life, the average Black or Hispanic patient with terminal cancer receives approximately 28 or 24 fewer 5-mg doses of oxycodone, respectively, than the average White patient. Patients of color were also more likely to be subjected to urine drug testing than White patients, despite the lack of clear clinical guidelines for such testing in terminally ill patients. Overall, women were less likely to receive end-of-life opioid pain medications, with the exception that Black women were more likely to receive opioids than Black men. White women were less likely to fill an opioid prescription than White men, and White and Hispanic women were prescribed lower doses than their male counterparts. Black patients received fewer opioid prescriptions than White patients, and Black men experienced disproportionately lower access to opioids and higher rates of urine testing. These disparities persisted even when the researchers adjusted for socioeconomic factors.

FEATURED RESEARCH AND PERSPECTIVES

Neuroscientists Recognize Women Engaged in Groundbreaking Research on Multiple Sclerosis

(Review article by Barateiro et al. 2023. Front. Mol. Neurosci. PMID: 36818652.)

A recent *Frontiers of Molecular Neuroscience* article by Andreia Barateiro, Ph.D., Adelaide Fernandes, Ph.D., and colleagues highlights the often underrecognized contributions of women researchers to the study of multiple sclerosis (MS). Many women have made major breakthroughs in the study of the disease, and the authors note "that improving recognition of female researchers will contribute to changing traditional mindsets and encourage more girls and women to pursue solid science careers," a sentiment consistent with ORWH's mission areas.

Historically, studies of MS concentrated on the physical symptoms of the disease. However, research led by several innovative women has elucidated the cognitive effects of the disease and contributed to the contemporary understanding that cognitive dysfunction is also a primary symptom of MS. In 1989, Elizabeth K. Warrington, Ph.D., Emeritus Professor of Clinical Neuropsychology at University College London, identified cognitive deficits in patients with CIS (clinically isolated syndrome), part of the MS disease course. At the same time, Patricia A. Beatty, Ph.D., of the Neuropsychiatric Research Institute (now part of Sanford Health), demonstrated that patients with the relapsing–remitting form of MS (RRMS), the most prevalent form of the disease, have deficits in verbal fluency, problem solving, and information processing. The article also details the work on cognitive dysfunction in MS of Maria Pia Amato, M.D., Maria A. Rocca, M.D., and others.

In the past, scientists classified MS as a disease of the brain's white matter, but several studies by women researchers showed that the disease also affects gray matter, which contributes to overall brain atrophy and disability in MS. In 1999, Isabelle Catalaa, M.D., identified cortical and deep gray matter lesions in patients with RRMS. More recently, multiple studies by Olga Ciccarelli, Ph.D., have characterized how damage to specific areas of gray and white matter contribute to MS pathology. Matilde Inglese, M.D., Ph.D., and colleagues have identified sodium concentrations in gray and white matter in patients with MS that differ from those of healthy controls.

As an autoimmune disease, MS pathology results when the immune system damages the nervous system. Several noteworthy women researchers have characterized the types of immune cells that cause this damage, their mechanisms, and their pathological effects, including Estelle Bettelli, Ph.D., Nathalie Arbour, Ph.D., Anne H. Cross, M.D., Nancy L. Monson, Ph.D., Francesca Aloisi, Ph.D., and Athena Soulika, Ph.D. Over recent decades, researchers have also elucidated the involvement of the gut–brain axis—the two-way communication between the intestine and the central nervous system—in MS. Many investigators have led pioneering work in this area, including Joan Goverman, Ph.D., Mitzi Nagarkatti, Ph.D., Jennifer L. Gommerman, Ph.D., Carmen Espejo, Ph.D., Sachiko Miyake, M.D., Ph.D., and Laura Cox, Ph.D. Finally, many women have made advances in describing how microRNAs mediate translational repression in patients with MS, including Raija L. P. Lindberg, Ph.D., Amy E. Lovett-Racke, Ph.D., and Rosanna Asselta, Ph.D.

ORWH thanks Dr. Fernandes, Dr. Barateiro, their coauthors, and the editors of *Frontiers of Molecular Neuroscience* for highlighting the contributions of these brilliant scientists who have advanced our understanding of a debilitating disease that affects 2.8 million people worldwide, the majority of whom are women.

SCIENTIST SPOTLIGHT

After earning a bachelor's degree in neuroscience and dance from Pomona College, Elizabeth Volkmann, M.D., M.S., completed her medical degree, internship and residency in internal medicine, and fellowship in rheumatology at the University of California, Los Angeles (UCLA). During her fellowship, she participated in the Specialty Training and Advanced Research (STAR) Program and earned a master of science degree in clinical research and biostatistics. She is now an Associate Clinical Professor in the Division of Rheumatology at UCLA, where she also serves as the Director of the UCLA Scleroderma Program and the founder and Co-Director of the UCLA Connective Tissue Disease-Related Interstitial Lung Disease (CTD-ILD) Program. Her research focuses on developing personalized treatment algorithms for patients with systemic sclerosis and CTD-ILD through the discovery of novel biomarkers. She endeavors to understand the role of molecular imaging in defining ILD phenotypes and predicting response to ILD-targeted therapies. She also

Elizabeth Volkmann, M.D., M.S.

has an enduring interest in exploring how the gut microbiome contributes to the pathogenesis of ILD and leads an international consortium of microbiome investigators in systemic sclerosis.

Please describe your research on sex and gender differences in autoimmune disease.

Clinical observations on sex and gender differences in the course of autoimmune ILDs inspired me to pursue research in this exciting area. Using data from randomized controlled trials in systemic sclerosis-related ILD, we discovered that, compared with women, men have accelerated ILD progression both with and without ILD treatment. Although the reasons for these sex differences are largely unknown, our proteomic analysis of bronchoalveolar lavage fluid from patients with systemic sclerosis-related ILD revealed that men have a more profibrotic immune signature, whereas women have a more proinflammatory immune signature. I now seek to understand whether these distinct immune profiles translate into unique molecular imaging patterns in men and women with autoimmune ILD.

How could this research help patients with autoimmune ILD?

Unraveling the complex biological and social underpinnings of sex and gender differences in autoimmune lung diseases will improve our understanding of the pathogenesis of these diseases and reveal new therapeutic targets. In addition, deepening our insight into why women and men respond differently to treatments will help clinicians personalize care plans for their patients. Finally, research in this area could inform the development of interventions that prevent not only disease progression but also disease onset. Ultimately, patients of all sexes and genders will benefit from this research.

What advice would you give to young women scientists?

Surround yourself with likeminded individuals who lift you higher. Early in my rheumatology training, I worked [for] a man who treated me poorly and tried to destroy my career researching scleroderma. However, I followed my intuition and began working with individuals who were supportive and collegial. I now strive to support other women in science, and some of my closest women collaborators are among my dearest friends. Being a woman in science has unique challenges, but finding your tribe makes it an incredibly gratifying calling.

INSTITUTIONAL SPOTLIGHT

Worcester Polytechnic Institute, Promoting Women of Diverse Creative Expertise

In 2021, NIH recognized Worcester Polytechnic Institute (WPI) with an NIH Prize for Enhancing Faculty Gender Diversity in Biomedical and Behavioral Science for its initiatives aimed at improving equity in its faculty promotion processes. Prior to developing the equity-based initiatives grouped under the title *Promoting Women of Diverse Creative Expertise*, WPI had made substantive improvements in recruiting and retaining early-career women faculty in STEMM fields, including biomedical and behavioral sciences. However, data analysts found that WPI's promotion system systematically disadvantaged women because of ambiguities inherent in the promotion process, the value placed on different types of academic work, implicit biases, and other gender-associated factors.

WPI addressed these problems through a collection of approaches: (1) changing WPI's promotion policies for tenure-track faculty to recognize multiple forms of scholarship and clarifying promotion criteria to reduce ambiguity; (2) establishing a mentoring system for mid-career associate professors; (3) providing small grants to support individual associate women faculty members toward promotion to full professor; and (4) institutionalizing a new "annual review conversation" between associate professors and department heads to promote understanding, recognition, and reward for the diverse academic activities valued by individual faculty.

After implementing these new practices, WPI saw increases in the number of women promoted from associate to full professor. In the 4 years prior to implementation (2014–2017), 13 men and 5 women were promoted to full professor (28% women); in the 4 years after (2018–2021), 19 men and 19 women were promoted to full professor (50% women). Further, from 2017 to 2021, the percentage of women faculty rose from 18% to 24% at the full professor rank, 28% to 31% at the tenured rank, and 35% to 45% at the assistant rank.

ORWH thanks WPI for its innovative equity initiatives. To read more about 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.

IN CASE YOU MISSED IT

Data Show Record-High Involvement of Women in Workforce but Some Persistent Pandemic-Era Setbacks

Recent statistics compiled by the U.S. Bureau of Labor Statistics show that companies have more women on their payrolls than ever before in U.S. history. In April of this year, 77.5% of women ages 25–54 were employed or looking for work, the highest-ever rate of workforce participation for this group.[1] These record-high rates follow the "she-cession" of the COVID-19 pandemic years in which many U.S. women—as many as 2 million according to some estimates—lost their jobs or left the workforce.[2] These pandemic-era losses were particularly telling in the majority-women health care field (i.e., as of early 2021, 30% of the health care workforce quit or lost their jobs since the onset of the pandemic in March 2020[3]). Economists cite many contributing factors underlying this increase in women's employment, including continuing trends of remote work, more women earning college degrees, and economic necessity spurred by high inflation and the end of pandemic-era government aid.[1,2]

Although this recent milestone represents a significant step toward reversing some of the pandemic's effects on women's participation in the workforce, experts caution that some of the pandemic's economic setbacks persist for women workers. Workforce participation among women ages 55 and older remains at pandemic-era lows.[2] Many current vacancies are for lower-paying positions, such as those in the hospitality and home health services industries.[2] Former U.S. Labor Secretary Marty Walsh repeatedly expressed concerns about both the economic and the public health importance of the struggling caregiving industry, which is staffed largely by women of color.[2] Further, pandemic-related employment gaps may hinder many job-seeking women or require recertification or additional training for some positions.

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NOTEWORTHY

ORWH's 7th Annual Vivian W. Pinn Symposium Explores Menopause and Women's Midlife Health

Former ORWH Director Vivian W. Pinn, M.D.

On May 16, ORWH hosted the virtual 7th Annual Vivian W. Pinn Symposium both as an acknowledgement of the contributions of the first full-time Director of ORWH and as part of the office's observation of National Women's Health Week. This year's symposium, "Menopause and Optimizing Midlife Health of Women," aimed to (1) familiarize attendees with the state of the science related to the risk factors and mechanisms that lead to reproductive aging; (2) understand women's unique morbidity and multimorbidity burden to identify points of intervention; (3) identify the needs of populations at risk for iatrogenic menopause and early or complex menopausal symptoms; (4) identify priorities to address the influence of environmental, social, and other exposures as they relate to the menopausal transition and symptoms in diverse populations of women; and (5) understand current recommendations on menopausal hormone therapy (MHT) prescribing, including doses, formulations, and durations of use. For more, please visit ORWH's Research on Menopause and Midlife Health webpage.

VPS Keynote Speaker JoAnn Manson, M.D., M.P.H., Dr.P.H., MACP

After opening remarks by ORWH Associate Director for Clinical Research Sarah Temkin, M.D., and ORWH Director Janine A. Clayton, M.D., FARVO, JoAnn Manson, M.D., M.P.H., Dr.P.H., MACP, Professor of Medicine and the Michael and Lee Bell Professor of Women's Health, Harvard Medical School, Chief of Preventive Medicine, Brigham and Women's Hospital, provided the keynote address, "Menopausal Hormone Therapy: 30 Years of Lessons from the Women's Health Initiative." Dr. Manson discussed the 30th anniversary of the Women's Health Initiative (WHI), the tendency to oversimplify the results of MHT studies, the

clinical priority of assessing the risks and benefits of MHT for chronic disease prevention among postmenopausal women, her articles in the *New England Journal of Medicine* on MHT for effective treatment of vasomotor symptoms and in the *Journal of the American Medical Association* on the comprehensive results of two WHI MHT trials and postintervention follow-ups, and related topics.

The symposium continued with panel discussions on (1) the menopausal transition and associated definitions, basic biological considerations, health implications, and future avenues for research; (2) premature and early menopause and its acceleration of multimorbidity; (3) the metabolic actions of estrogens; (4) menopause in high-risk patients, including women with HIV; (5) social determinants of health related to menopause, women in midlife, and Latinas during their menopausal transition; (6) menopause and patient advocacy; (7) personalized hormone treatments for menopause; (8) balancing evidence and clinical judgment for using MHT for menopausal symptom management; and (9) strategies and research priorities for healthy menopause and aging.

Dr. Pinn provided concluding remarks to end the symposium. She reminded participants of the important lessons of the WHI and advised judicious prescription of MHT, which may not be appropriate for all women reaching menopause. Dr. Pinn called for greater support of research into the sex and gender factors that affect the midlife health of women and noted that women's health concerns extend well beyond the reproductive years.

A video recording of the VPS is available here.

In-Hospital Maternal Death Rates Decline by 57%, HHS Study Shows

An observational study of more than 11 million hospital discharges in the United States conducted by the Office on Women's Health (OWH) of the U.S. Department of Health and Human Services (HHS) showed that in-hospital delivery-related maternal mortality declined by 57% between 2008 and 2021. Historically, U.S. women from minoritized populations have experienced higher rates of maternal deaths than White women; however, the HHS study showed some decreases in these disparities—with greater reductions in maternal mortality among American Indian women (92%), Asian women (73%), Black women (76%), Hispanic women (60%), and Pacific Islander women (79%) than among White women (40%). These findings, published in *JAMA Network Open*, suggest the efficacy of national and local initiatives to improve delivery-related hospital care in response to the United States having one of the highest rates of maternal death among high-income nations.

In spite of the recent declines in maternal death, the HHS study found that severe maternal morbidity (SMM) increased over the same study period. SMM complications—such as disseminated intravascular coagulation, acute respiratory distress syndrome, acute kidney failure, sepsis, and eclampsia—increased across all U.S. racial and ethnic populations, with particularly high rates among Asian, American Indian, and Pacific Islander women. The researchers attribute these increases, in part, to (1) risk factors such as obesity, gestational diabetes, tobacco use, gestational hypertension, and asthma; (2) an increase in health conditions arising prior to and during pregnancy; and (3) national trends toward higher maternal age.

You can read more about the HHS study and about maternal health and NIH's efforts to improve pregnancy outcomes and obstetric safety on ORWH's Maternal Morbidity & Mortality Web Portal.

Nature Article Describes Disproportionately Low Funding for Women's Health Research

A recent article in *Nature* examines a 2021 study by independent researcher Arthur A. Mirin, Ph.D., whose analysis revealed disparities in funding for research on diseases and health conditions that primarily affect one gender, such as migraines, mental illness, and chronic fatigue syndrome. Through a series of interactive infographics, the *Nature* article presents Dr. Mirin's findings that, in almost three-quarters of cases, NIH funding patterns favor those diseases primarily affecting men over those primarily affecting women. Factoring disease burden into his statistical analysis, Dr. Mirin found that these funding disparities nearly double in favor of diseases more prevalent in men.

The Nature article also identifies similar health disparities in funding practices from other global biomedical research organizations. The article cites efforts to address these disparities, such as the NIH Sex as a Biological Variable Policy and recent reports from the Women's Health Access Matters advocacy group and the RAND Corporation. These reports describe statistical models in which funding increases for women's health research result in increased life expectancy, productivity, and quality of life; remarkable societal cost savings because of decreased disease burden; and "staggering" returns on investment.

The *Nature* article quotes ORWH Associate Director for Clinical Research Sarah Temkin, M.D., who said that Dr. Mirin's analysis "demonstrates that the funding of research for women is not aligned with burdens of disease." Dr. Temkin also indicated that it would take "a long time to recover from the gaps in the evidence base that resulted from exclusion" of women, girls, female animals, and female cells from historical biomedical research.

Commenting on the *Nature* article, ORWH Director Janine A. Clayton, M.D., FARVO, stated, "These unique graphics convey a

comprehensive reflection of the funding landscape vis à vis disease burden in a particularly compelling way. There is much more work to be done to advance science for the health of women."

You can read the *Nature* article and see the interactive infographics.

HHS-OWH and NIA Host Q&A on Women's Health and Aging

On May 15, 2023, to kick off National Women's Health Week, the Office on Women's Health (OWH) of the U.S. Department of Health and Human Services and the National Institute of Aging (NIA) hosted an informational, virtual Q&A titled "Women's Health and Aging." The live YouTube session featured experts Dorothy Fink, M.D., the Director of OWH and Deputy Assistant Secretary for Women's Health, and Arun Karlamangla, M.D., Ph.D., Professor of Medicine/Geriatrics at the University of California Los Angeles and an NIA-funded researcher. Dr. Fink and Dr. Karlamangla discussed menopause, cognitive health, sarcopenia, bone health, and how women can better maintain health and independence as they age. You can watch a recording of the Q&A online.

ORWH Grants OSSD Travel Awards to Two Junior Investigators

Earlier this year, ORWH awarded grants to Alice Abernathy, M.D., and Tanya Saraiya, Ph.D., to attend the annual meeting of the Organization for the Study of Sex Differences (OSSD), held in Calgary, Canada, on May 7–11. ORWH created the Science Policy Scholar Travel Award program in 2019 so that junior investigators interested in sex and gender differences, women's health, and research policy could present their work at the annual meeting. A panel of scientists from across NIH reviewed all of this year's applications and selected Dr. Abernathy and Dr. Saraiya for the merit, uniqueness, and thoroughness of their research.

Alice Abernathy, M.D.

Dr. Abernathy is a National Clinician Scholar in the Obstetrics and Gynecology Department of the University of Pennsylvania. Dr. Abernathy's research interests include exploring the links between legislation surrounding family planning services and the racial, socioeconomic, and geographic disparities in maternal morbidity and mortality. She also studies how expansion of Medicaid postpartum affects maternal morbidity and mortality and how improved care coordination for cardiovascular disease, diabetes, and other chronic medical conditions improves maternal morbidity in the postpartum period. Dr. Abernathy is also involved in legislative advocacy locally and nationally. During the OSSD meeting, Dr. Abernathy gave a presentation titled "Changes in Contraception and Sterilization Use Patterns Among Reproductive Age Males and Females in Pennsylvania Following Constrained Abortion Access."

Tanya Saraiya, Ph.D.

Dr. Saraiya is a licensed Clinical Psychologist and an Assistant Professor at Rutgers University. Earlier in her career, she completed a clinical psychology internship and a T32 postdoctoral fellowship funded by the National Institute on Drug Abuse (NIDA), and was a Research Assistant Professor at the Medical University of South Carolina, where she remains an adjunct Assistant Professor. Dr. Saraiya's research seeks to enhance treatments for substance use disorders and co-occurring psychiatric diagnoses, such as post-traumatic stress disorder (PTSD). She explores modifications of treatments for marginalized groups, including women and minoritized populations, and the relationship between psychological trauma and substance use. Her current work is funded by a NIDA K23 award to examine how to modify and test an integrated psychosocial treatment for individuals with opioid use disorder (OUD) and co-occurring PTSD. At this year's OSSD meeting, Dr. Saraiya presented "The Lived Experience and Treatment Needs of Women with OUD and PTSD Symptoms."

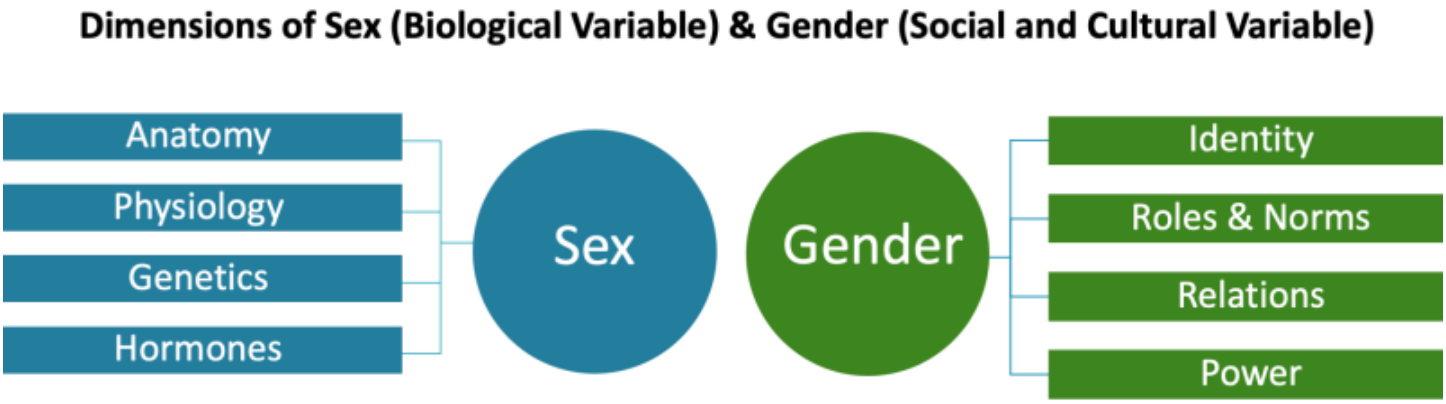
OSSD facilitates interdisciplinary research on sex and gender differences at all levels of biological organization; advances the understanding of sex and gender differences by bringing together scientists and clinicians of diverse backgrounds; encourages the application of new knowledge of sex and gender differences to improve health and health care; and promotes the field of sex and gender differences research through education, mentoring, and outreach. The Society for Women's Health Research founded OSSD in 2006, and OSSD became an independent nonprofit educational organization in 2012.

Sallie Rosen Kaplan Fellowships Support Women Scientists in Cancer Research

The Sallie Rosen Kaplan (SRK) Postdoctoral Fellowship, sponsored by the Foundation for the National Institutes of Health (FNIH) and the family of Sallie Rosen Kaplan, supports women pursuing careers in cancer research. Initially conceived as a one-time stipend to supplement the typically low compensation for postdoctoral trainees and to recruit female researchers to the National Cancer Institute (NCI), the SRK Fellowship evolved in response to studies showing that women are significantly more likely than men to leave the science field. Now in its 10th year, the revised SRK Fellowship is a highly

competitive, unpaid, 1-year program that provides life coaching, career mentoring, networking, seminars, and workshops to 10–12 women postdoctoral fellows at NCI each year.

FNIH and the Kaplan family established the SRK Fellowship in memory of a woman who was deeply committed to the education of others, especially women. Born in the early 1900s, Sallie Rosen Kaplan graduated from high school and was accepted to attend the University of Michigan. As the youngest of three children and the only daughter, however, she paused her education to care for her parents while her older brothers pursued law school and careers as attorneys. She never returned to higher education but remained strongly supportive of the education and careers of family members, including her nephew Jeffrey M. Rosen, Ph.D., the CC Bell Distinguished Professor and Co-Leader of the Breast Cancer Program at Baylor College of Medicine. You can read more about the SRK Fellowships online.



ORWH Introduces New Sex and Gender Webpage

Earlier this year, ORWH updated and expanded the Sex & Gender section of its website with the Sex and Gender in Health and Disease webpage and an accompanying downloadable Fact Sheet. These new resources highlight sex and gender differences across 10 different health areas and illustrate the importance of understanding sex and gender in health, disease, diagnosis, and treatment. The webpage provides pragmatic definitions of terminology (e.g., "'Male' and 'female' refer to sex assigned at birth. In addition, while we use the terms 'male' and 'female' for the purposes of this discussion, we recognize that sex is not a binary variable and variations do occur. These variations are called differences in sex development or intersex conditions."). In addition, infographics and interactive features enable users to explore sex and gender in relation to cancer, mental health, substance use disorder, cardiovascular health, autoimmune disease, chronic pain, and other areas of health and disease.

Senate Confirms Monica Bertagnolli as NIH Director

NIH Director Monica Bertagnolli, M.D.

On November 7, 2023, the Senate voted to confirm NCI Director Monica Bertagnolli, M.D., as the 17th Director of NIH. She assumed her duties on November 9, 2023. Dr. Bertagnolli is the first surgeon and second woman ever to lead NIH. A world-renowned surgical oncologist, cancer researcher, educator, and physician-leader, Dr. Bertagnolli previously served as the 16th Director of the National Cancer Institute (NCI), and was the first woman to serve in this position.

"Dr. Bertagnolli has spent her career pioneering scientific discovery and pushing the boundaries of what is possible to improve cancer prevention and treatment for patients and ensuring that patients in every community have access to quality care," President Joe Biden said in a statement announcing her nomination for Director of NIH.

Before joining NCI, Dr. Bertagnolli served as the Richard E. Wilson Professor of Surgery in the field of surgical oncology at Harvard Medical School, a surgeon at Brigham and Women's Hospital, and a member of the Gastrointestinal Cancer Treatment and Sarcoma Centers at the Dana–Farber Cancer Institute. She is a member of the National Academy of Medicine, a past president and chair of the board of directors of the American Society of Clinical Oncology, and a past member of the board of directors of the American Cancer Society and the Prevent Cancer Foundation.

Jane Simoni Joins NIH as New Director of OBSSR

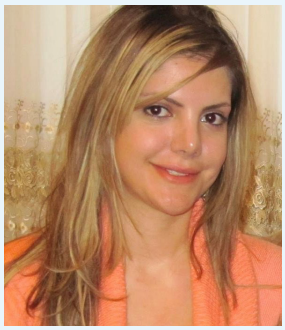
In July 2023, Jane M. Simoni, Ph.D., joined NIH as the Associate Director for Behavioral and Social Sciences Research and Director of the Office of Behavioral and Social Sciences Research (OBSSR). She leads OBSSR's efforts to advance and coordinate behavioral and social sciences research at NIH. Dr. Simoni is a clinical psychologist with more than 25 years of experience in research focused on health disparities and resilience among populations that have been socially marginalized. Her intervention research has examined behavioral aspects of chronic illness and uses mixed methods and clinical trials to evaluate strategies such as peer support, medical record alerts, and provider training to promote treatment engagement and improve health outcomes. She joins NIH from the University of Washington in Seattle where she was a professor and the Director of Clinical Training in the Department of Psychology. ORWH welcomes Dr. Simoni and congratulates her on her new position.

OBSSR Director Jane M. Simoni, Ph.D.

STAFF UPDATES

Vivian Ota Wang, M.Phil., Ph.D., M.S., joined ORWH as Deputy Director in October 2023. As a genetic counselor, genomicist, and psychologist, Dr. Ota Wang brings a wealth of experience in research, education, science policy, and ethics that spans psychological, genomic, nanoscale, and data sciences. Prior to joining ORWH, she served as the Policy and COVID Lead at the Office of Data Sharing Strategy in the Division of Program Coordination, Planning, and Strategic Initiatives, Office of the Director at NIH, where she was responsible for ethics, equity, and issues related to data access, sharing policy development and implementation, and COVID-related activities. Dr. Ota Wang received a master's degree in genetic counseling from the University of Colorado, and a master of philosophy degree and a doctorate in counseling psychology from Columbia University. She is a Fellow of the American Medical Association and American Psychological Association, Diplomate of the American Board of Medical Genetics and American Board of Genetic Counseling, a Clinical Laboratory Specialist in Cytogenetics, and a licensed psychologist.

STAFF UPDATES



Reihaneh Bahramali, M.S., joined ORWH as an Executive Assistant in April 2023. She holds a master's degree in health informatics administration and a bachelor's degree in computer software technology engineering. She has more than 3 years of experience working at NIH, the Volunteers of America Chesapeake and Carolinas, and AstraZeneca.

Annina Burns, Ph.D., RD, joined ORWH as a Health Science Policy Analyst in the Clinical Research Section in April 2023. She received her Ph.D. from the University of Oxford as a Marshall Scholar where she studied public health and nutrition. Dr. Burns wrote her thesis on the founding years of nutrition science and the implications of early methodology on the measurement of nutritional status today. Her clinical expertise involves nutrition for fertility and maternal health. She worked in the White House as the Associate Director for Policy for the "Let's Move!" childhood obesity prevention initiative. She also served as a Senior Advisor in the Office of the Director at the Centers for Disease Control and Prevention; a Study Director for the Food and Nutrition Board at the National Academies of Sciences, Engineering, and Medicine; and a Project Officer at the World Health Organization.

UPCOMING EVENTS

Diverse Voices: Graphic Medicine
January 25, 2024
3:00 p.m.–4:00 p.m. EST

HIV & Women Scientific Workshop Keynote Address
March 21–22, 2024
10:00 a.m.–5:00 p.m. EST

Diverse Voices: Endometriosis
March 28, 2024
3:00 - 4:00 p.m. EST

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

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