Raising the Bar: Putting Science to Work for the Health of Women

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The National Institutes of Health (NIH) Office of Research on Women's Health (ORWH) was founded in 1990 with a mission to expand women's health research, ensure that women are included in NIH research, and promote the advancement of women in biomedicine. In 1993, the NIH Revitalization Act put forward that women and underrepresented racial and ethnic groups must be included in NIH research (NIH Revitalization Act, 1993). Today, women's health research is embedded in NIH research writ large and integral to achieving the mission of turning discovery into health for all. Over the years, NIH policy advances, such as those related to inclusion, enhancing reproducibility through rigor and transparency, and accounting for sex as a biological variable (SABV) have ensured the relevance of biomedical and behavioral research to the health of women. Through the development of the HPV vaccine, medications to prevent maternal to child transmission of HIV, and JAK inhibitors, now used to treat many autoimmune diseases, NIH laid the foundation for women's health research using cutting edge basic science and launched landmark clinical studies leading to novel preventive and therapeutic strategies improving the health of women. Today, women represent over half of the participants in NIH-supported clinical research and years of NIH research investments across the biomedical research continuum, from the lab to the clinic, have generated groundbreaking scientific advances improving women's health.

ORWH History and Programs

What does ORWH do and how did we get to where we are today? ORWH serves as the focal point for NIH women's health research working collaboratively with NIH's 27 institutes and centers (ICs), each of which supports research relevant to the health of women in the context of their mission areas. At ORWH, we imagine a world where all women receive evidence-based diagnostics, treatment, and care, tailored to their own circumstances, goals, and needs. ORWH envisions a world where sex and gender factors are integrated across the biomedical research continuum from the beginning to the end, and a world where all women in science reach their full potential.

To this end, ORWH leads the development of the NIH-wide strategic plan for women's health research providing a roadmap for future directions along with several signature programs to advance women's health research and training across a range of topics (NIH, 2024a). In 2000, Dr. Vivian Pinn, the first full-time director of ORWH, led the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) program—a program developed to expand the cadre of women's health researchers. BIRCWH is a mentored career-development program connecting junior faculty (BIRCWH Scholars) to senior faculty with shared interest in women's health and sex differences research. There are currently 19 active BIRCWH programs and more than 750 scholars have now been trained across the United States; most of whom have remained in research and achieved leadership positions in their field.

The Specialized Centers of Research Excellence on Sex Differences (SCORE) program supports sex differences research in the context of conditions that are relevant to the health of women. The SCORE program began in 2002 as a P50 initiative for Specialized Centers of Research and then expanded in 2018 by adding a career enhancement component. The goal of the career enhancement core is to support pilot research and train the next generation of scientists in the study of sex differences. As NIH's sole center-level disease-agnostic program focused on sex differences, SCORE aims to translate scientific knowledge about how diseases affect women and men differently into new treatments that improve clinical care. These centers include laboratory, translational, clinical research components, pilot funding, and career enhancement. Currently ORWH partners with five ICs to support 12 SCORE programs across the United States that conduct sex differences research on topics including sex differences in cardiovascular disease, the influence of menopause on metabolism, sex differences in impact of substance use, among others. Each SCORE program has three highly integrated, synergistic research projects and an administrative core. As NIH-supported

Centers of Excellence, the SCORE program's centers provide leadership and serve as a national resource in the development and promotion of standards and practices for the consideration of sex differences in biomedical research.

In 2007, then NIH Director Elias Zerhouni, MD, established the NIH Working Group on Women in Biomedical Careers. This group works to address the policies, practices, and programs needed to advance women in STEM. Through programs like continuity supplements supporting grantees who experience qualifying life events and the landmark initiative, Research on Causal Factors and Interventions that Promote and Support Women in Biomedical Careers, evidence-based strategies have expanded opportunities and reduced barriers for women in biomedical research (NIH, 2008; Ten Hagen et al., 2022).

In 2016, the NIH put forward its policy on accounting for SABV (NIH, 2016); development of SABV policy was led by ORWH. The SABV policy outlines expectations that SABV will be factored into research designs, analyses, and reporting for vertebrate animal and human studies and that strong justification must be provided for single-sex studies. This policy is complementary to the NIH inclusion policy for clinical research and supports consideration of sex and gender factors across the research continuum, from the lab to the clinic.

Current and Future Directions in Research

To reap the full potential of health research, it's critical to move "beyond inclusion" of women to the "intentional integration" of considerations of sex and gender factors across the research continuum. That includes how preclinical studies accounting for SABV inform clinical research, as well as how clinical research designed to answer questions relevant to the health of women generates new knowledge and improves health for all people. Adequate consideration of SABV in experiments and disaggregation of data by sex allow for sex-based comparisons and may inform clinical interventions. Appropriate analysis and transparent reporting of data by sex may therefore enhance the rigor and applicability of preclinical biomedical research. These issues can be addressed and the science can be strengthened by considering sex and gender factors, thereby connecting the dots across the research continuum from basic science, through translation of preclinical research to clinical trials, and to interprofessional health education and clinical practice. Doing so advances rigor, relevance, innovation, and equity to generate new knowledge to improve health for all.

For example, sex should be a consideration in preclinical studies, in vitro studies, animal models, and even in silico models as those findings are translated into human studies for phase I, II, and III clinical trials. The definitive results of phase III clinical trials inform regulatory decision making and clinical care. According to Koch and colleagues (2023), 43 percent of NIH Phase 3 clinical trials accounted for sex in the analysis of study results. Journal editors and publishers play a key gatekeeping role in ensuring further progress. Each publication provides new knowledge and insights that are used by others to develop new ideas, new hypotheses, and new studies.

Additionally, it is important to integrate consideration of sex and gender into interprofessional health education to inform and improve the health of women—at the undergraduate and graduate level—for medical students, dental students, pharmacists, and so on. ORWH offers several e-learning courses designed to give users a thorough and up to date understanding of the influences of sex and gender on health and disease along with the NIH requirements to factor SABV into research designs. Continuing education is important for professionals in practice so that they can utilize the latest and most up to date information, practices, and methodologies in their work. It is through an intentional focus on educating current and future generations of professionals that we will be able to deliver sex and gender-informed health care.

Women's health constitutes everything that affects a woman—from head to toe, inside and out, across the life course. It encompasses social determinants of health, environmental, and societal contexts. It is relevant whether these affects are from a toxic relationship or a toxicant exposure. The life course must be considered. For example, research has found that pregnancy-induced hypertension increases the risk for development of cardiovascular disease (Stuart et al., 2022). The National Heart, Lung, and Blood Institute funded studies that found these increases were within three years of the pregnancy-induced hypertension, not 20 years later. In another example, gestational diabetes is associated with an increased future risk of type 2 diabetes (CDC, 2024). Adverse experiences at one point in people's lives can have a lasting effect on health as women's health exists as a continuum rather than as a series of multiple distinct points. There is opportunity to bridge the chasm between the stress test of pregnancy care to postpartum care. Women have more chronic conditions and spend more years of their lives disabled with poor quality of life, even though women live longer than men in general (Crimmins, Zhang, & Saito, 2016). How can research on women's health take advantage of midlife health and menopause transition, a clear inflection point for the increased risk of chronic disease? ORWH is focused on expanding understanding of those chronic diseases—we combined sex and gender,

biology, and social constructs in a research project grant (R01) in 2019, focusing on intersections of sex and gender factors in health and disease. ORWH partners with 11 NIH ICs supporting interdisciplinary research on a range of topics of importance to the health of women.

Women in the United States are sicker than ever. Rates of maternal morbidity and mortality have also increased (MacDorman et al., 2021). These levels are increasing for all women, but are highest for women who are Black or American Indian/Alaska Native, and levels for women who are Hispanic have increased above the levels for women who are White for the first time ever in the United States (Hoyert, 2022). In response to a request from Congress, ORWH has looked at some of the top health issues that women are facing—maternal mortality, stalled cervical cancer survival rates, and chronic debilitating conditions. While women have a longer *lifespan* in general than men, women have a limited *health span*, spending more years with disability or poor quality of life. Women are more likely to have multiple chronic diseases and have poorer outcomes after stroke, for example (ORWH, 2021). Approximately 8 percent of the US population is living with an autoimmune disease, and nearly 80 percent of those with an autoimmune disease are women (Fairweather et al., 2008). In fiscal year 2023, Congress mandated the formation of the Office of Autoimmune Disease Research within ORWH (US Congress, 2023) to identify emerging areas of innovation and research opportunity of autoimmune diseases, coordinate across the ICs, develop a multi-institute and center strategic research plan, regularly evaluate the NIH autoimmune disease research portfolio, provide resources to support planning, collaboration, and innovation, and to create a publicly accessible central repository for autoimmune disease research.

In the *Report of the Advisory Committee on Research on Women's Health: Fiscal Years 2021–2022* (ORWH, 2023), NIH's broad commitment to women's health research is exemplified in reports from each IC highlighting women's health research programs and advances on a biennial basis. Over the years, NIH has a demonstrated track record of launching critical efforts like the groundbreaking Women's Health Initiative, the Nurses' Health Study, and the Study of Women Across the Nation. More recently, examples include technological innovations like development of female reproductive system organoids and paradigm shifting laboratory studies leading to the first-ever treatment for postpartum depression, Brexanolone (NIMH, 2019). Discovery is key to innovation and the improvement of the health of women. Yet more work remains and gaps exist as evidenced by findings that women who experienced a heart attack are less likely to receive guideline-based treatment or diagnostics, have longer hospital wait times for care and are also more likely to receive invasive treatments. The CDC recently reported that 20 percent of women report mistreatment while receiving maternity care (CDC, 2023). Primary prevention of cancer is also more challenging in women.

When contemplating the future of health research, attention to the health of women is critical. There is a need to understand for whom therapeutics work so that health care professionals can provide evidence-based recommendations for everyone. Risk can be mitigated by investigating potential sex-specific effects of interventions on potential therapeutic targets when sex is considered as a biological variable from the beginning. Both beneficial and adverse sex-specific effects have been revealed in pre-clinical animal models, including those for stroke, uncovering critical insights relevant to translation to clinical studies highlighting the importance of accounting for SABV (Ahnstedt et al., 2016).

Routinely examining sex disaggregated data provides us with findings of clinically relevant sex differences. Normal bone density differs by sex and we are learning that the cutoff threshold for elevation of hemoglobin A1c, diagnostic of type 2 diabetes, may also differ by sex (Low et al., 2024). The systolic blood pressure above which the risk of cardiovascular complications rises may be lower in women than in men. There are opportunities to integrate routine consideration of sex influences in biomedicine and care delivery.

ORWH Future Directions

ORWH recognizes the importance of taking a whole-person health approach that integrates internal and external factors to accelerate progress and meet the contemporary health needs of women as outlined in the new 2024–2028 NIH-Wide Strategic Plan for Research on the Health of Women (NIH, 2024a). Interdisciplinary research strategies have the power to bridge scientific disciplines, connect clinical specialties, and combine forces of experts from multiple domains to address important gaps in knowledge and improve women's health outcomes. ORWH has supported the importance of interdisciplinary research from the outset and looks forward to continuing to do so with the White House's Executive Order on Advancing Women's Health Research and Innovation (The White House, 2024). This order will change how women's health research is funded, conducted, and disseminated throughout the United States. It represents a substantial milestone demonstrating that women's health is being prioritized at the presidential, and

therefore national, level. The executive order will focus on investments in women's health research, integrate women's health across the federal research portfolio, galvanize new research on women's midlife health, and assess unmet needs to support women's health research (The White House, 2024). As a first step, NIH published an enterprise-wide notice of special interest on women's health (NIH, 2024b) that links women's health research to standing funding opportunities across a wide range of health conditions and funding options including research program grants, SBIR/STTR grants, career development awards, and other mechanisms that could be used for a variety of types of programs.

The mission of ORWH remains steadfastly focused on improving the health of women through rigorous research—from lab bench to patient bedside, and beyond. ORWH developed several initiatives aimed at ensuring that women are appropriately included in clinical trials, increasing application of SABV, developing interprofessional training programs for clinicians and researchers at all levels and creating funding opportunities for research and training specifically focused on the health of women across the lifespan. ORWH coordinates with NIH ICs to meet the challenges faced by women today, fostering innovation, expanding our knowledge base, and ensuring that discoveries reach and improve the health of all women across the life course.

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