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Research on Women's Health: Ready for the Future

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Abstract

The National Institutes of Health (NIH) Office of Research on Women's Health (ORWH) was established in 1990. With the completion of the office's 30th anniversary year, we look back and recount some of the key events and overall zeitgeist that led to ORWH's formation, and how it became the focal point at the nation's primary biomedical research agency for coordinating research on science to improve the health of women. We discuss ORWH's mission and signature programs and the bold vision that drives the NIH-wide strategic, interdisciplinary, and collaborative approach to research on women's health and efforts to promote women in biomedical careers. Also discussed are several of the many scientific advances in research on the health of women, policy innovations and their effects, and career advancements made by women in medicine and related scientific fields. We also highlight key challenges for the health of women, the need to continue pushing for equity in biomedical research careers, and NIH's approach to addressing these problems to ensure progress for the next 30 years and beyond.

Keywords: women's health, National Institutes of Health, policy, research advances, sex as a biological variable, personalized medicine

Introduction

In the 1970s and 1980s, many became aware that women were not benefiting equally from the major advances in biomedical research and health care. One of the driving factors for this inequity was an astonishing lack of knowledge on conditions that are unique to or more prevalent among them. Society was changing rapidly, with the public demanding solutions to multiple inequities, chronic diseases, and emerging health problems. The National Institutes of Health (NIH) responded accordingly and grew in size, scope, and ambition.[1] Knowledge was also expanding, and as we learned more about human biology, fundamental sex differences in physiology not related to reproductive systems emerged. For example, research revealed that myocardial and vascular structure and function—and some important clinical outcomes (*e.g.,* the mortality rate after myocardial infarction)—differed between women and men.[2] In addition, studies documented more adverse drug reactions among women.[3,4]

Despite the fact that women and men shared the top three causes of death (heart disease, cancer, and stroke), most knowledge on their etiology, progression, and treatment had been derived from all-male studies.[2] A vanguard of leaders at the U.S. Public Health Service established the Task Force on Women's Health Issues, and this group's report and recommendations charted a course for future research to remedy the inequity and improve the health of women.[5]

Principal recommendations were the expansion of biomedical and biobehavioral research on conditions particularly affecting women of all ages and the development of guidelines to ensure adequate numbers of women in clinical trials of medications.[5] The Congressional Caucus for Women's Issues campaigned for implementing these recommendations, and one result of these efforts was the establishment of the

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Table 1. National Institutes of Health Office of Research on Women's Health Mission and Signature Programs

ORWH's mission is to
(1) serve as a focal point for coordinating women's health research at NIH;
(2) enhance research related to diseases and conditions that affect women and ensure that research conducted and supported by NIH addresses women's health issues;
(3) ensure that women are appropriately represented in NIH-supported biomedical and biobehavioral research; and
(4) develop opportunities and support for recruitment, retention, re-entry, and advancement of women in biomedical careers.

Program name	*Grant mechanism/funding opportunity announcement number*	*Description*
Building interdisciplinary research careers in women's health (BIRCWH)	K12 Physician Scientist Award Program/RFA-OD-15-001	The program offers mentored career-development institutional grants to connect junior faculty (*i.e.,* BIRCWH Scholars) to senior investigators with a shared interest in women's health and sex differences research. Throughout its 20-year history, the BIRCWH program has awarded 88 grants to 44 institutions (with 22 active programs in 2020). The program has nurtured >700 BIRCWH Scholars, most of whom have gone on to earn R-level NIH funding (70%) or receive one or more foundation, institutional, or other type of grant (77%).
Specialized centers of research excellence (SCORE) on sex differences program	U54 Clinical Trial Optional, Specialized Center-Cooperative Agreements/RFA-OD-19-013	The program supports disease-agnostic, multilevel translational research to identify the role of biological sex differences in the health of women. As NIH-supported Centers of Excellence, the SCORE sites serve as vital hubs for training and education—and their investigators lead the field by developing and promoting standards and policies for the consideration of sex as a biological variable (SABV) and sex differences in biomedical research.
Administrative supplements for research on sex/gender differences	Grant Supplement/PA-13-018	With these supplements, ORWH aims to expand foundational research in women's health differences by providing additional support to ongoing NIH-funded projects to investigate sex and gender differences within their stated scopes. The funded research has resulted in greater awareness of the need to study both sexes, demonstrated how research can incorporate sex and gender, and reinforced the value of taking these crucial factors into account as investigators build the knowledge base in their fields. The funded projects span a wide array of science from bench to bedside—including basic immunology, cardiovascular physiology, neural circuitry, and behavioral health.
U3 administrative supplement program	Administrative Supplement Program/ PA-18-676	This program supports interdisciplinary studies that address health disparities among populations of women that are understudied, underrepresented, and underreported (U3) in biomedical research. Supporting preclinical, clinical, behavioral, and translational studies, the U3 program focuses on the intersection of sex with social determinants of health.

(*continued*)

Table 1. (Continued)

Program name	*Grant mechanism/funding opportunity announcement number*	*Description*
The intersection of sex and gender influences on health and disease	R01 Grant/RFA-OD-19-029	This 2019 funding opportunity announcement invites investigator-initiated applications on the influence and intersection of sex and gender in health and disease. It represents an important milestone as NIH's first investigator-initiated disease-agnostic R01 on sex and gender. The aim is to advance rigorous research on the health of women, foster innovation, expand emerging areas of science, and address issues of public health importance.

ORWH, Office of Research on Women's Health; NIH, National Institutes of Health.

NIH Office of Research on Women's Health (ORWH) in 1990. For more information on the history of the office's formation, see https://orwh.od.nih.gov/about/mission-history.

The landmark *Report of the National Institutes of Health: Opportunities for Research on Women's Health* (commonly referred to as the Hunt Valley report) in 1991 set out an agenda to address gaps in scientific knowledge about the health of women of all ages and to increase the use of research designs that would potentially identify sex and gender differences in outcomes.[2] Standing on the foundation that report helped build, we are now able to envision a world in which the biomedical research enterprise thoroughly integrates sex and gender influences across the life course, every woman receives evidence-based disease prevention and treatment tailored to her own needs and circumstances, and women in scientific careers reach their full potential.

That vision—set out in *Advancing Science for the Health of Women: The Trans-NIH Strategic Plan for Women's Health Research*[6]—is possible because there has been a congressionally mandated focal point for coordinating research on the health of women at NIH since ORWH was enshrined by statute in this role in the NIH Revitalization Act of 1993 (Public Law 103–43, section 486).[7]

ORWH's core areas of focus dovetail with NIH's mission to seek fundamental knowledge about the nature and behavior of living systems and apply that knowledge to enhance health, lengthen life, and reduce illness and disability. The 27 constituent NIH Institutes and Centers (ICs) address women's health in their respective scientific areas. Part of the NIH Office of the Director, ORWH plays a vital coordinating role, collaborating with ICs to ensure that interdisciplinary research on women's health is part of the scientific framework at NIH and throughout the biomedical community—as reflected in the *Trans-NIH Strategic Plan for Women's Health Research*. Throughout its three decades, ORWH has acted on its mission and worked with its IC partners to build signature programs that advance research on sex and gender, and support women as biomedical scientists (Table 1).

ORWH's milestone 30th anniversary year caused us to reflect and focus on the future. This article will briefly review (1) a few of the many scientific advances in research on the health of women—some of which were highlighted at the ORWH 30th Anniversary Scientific Symposium (videocast available at https://videocast.nih.gov/watch=40060), (2) policy innovations and their effects, (3) the research career advancements made by women in science, technology, engineering, mathematics, and medicine (STEMM), and (4) prominent key challenges for the health of women and NIH's approaches to addressing them.

Thirty Years of Scientific Advances Result in Better Health for Women

Perhaps the most important advancement has been the paradigm shift in the way biomedical researchers conceptualize women's health, from a narrow focus on the reproductive system and maternity (women were viewed to be the same as men except for these functions) to a perspective that encompasses the health of the whole woman over the life course. ORWH has emphasized the life course perspective since its inception[2] and continues on this path in the *Trans-NIH Strategic Plan for Women's Health Research*.

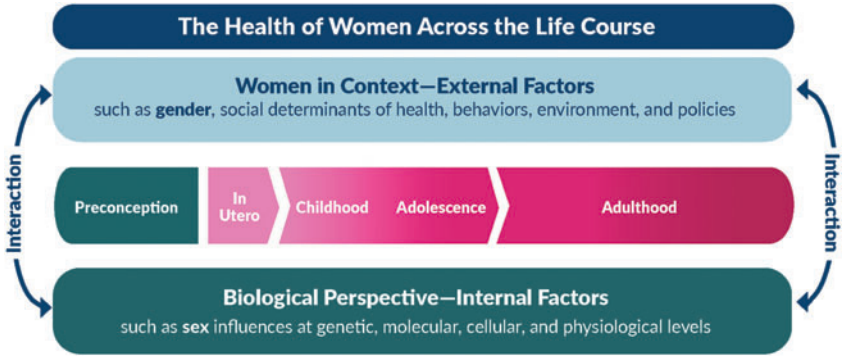

FIG. 1. The multidimensional framework represents the intersection of multiple internal factors (*e.g.,* sex influences at genetic, molecular, cellular, and physiological levels) and external factors (*e.g.,* social determinants of health [including gender], behavior, and policies) that affect the health of women across the life course.

ORWH champions the intentional integration of the multidimensional framework (Fig. 1) in interdisciplinary multifactorial studies across the continuum of biomedical research to build a knowledge base for personalized medicine.[8–11] Achieving personalized medicine will be bolstered by the inclusion of sex and gender awareness in clinical care and the provision of evidence-based care tailored to every woman's needs, which requires embedding the concepts of sex and gender health into the educational curricula of all health professionals.[12]

It is perhaps not surprising that major scientific advances stem from interdisciplinary research that applies the multidimensional framework. Such is the case with the second scientific accomplishment highlighted in this study: knowledge about the impact of environmental exposures on women of all ages. Exposures are conceptualized broadly and can include lifestyle factors (such as stress, local access to healthful food, substance use, and physical activity), as well as chemicals, radiation, infectious agents, and climate change.[13] Researchers now understand that across the life course, environmental exposures during windows of susceptibility contribute to the developmental origins of disease.[14,15]

As early as the 1980s, scientists reported changes in human reproduction—such as declining sperm counts in males[16] and earlier puberty in females[17]—as well as deleterious genital and physical alterations among wildlife.[18–20] Since then, research has linked these changes to endocrine-disrupting chemicals (EDCs)—compounds that interfere with sex hormones' production and mechanisms of action.[21–24] EDCs warrant close attention because exposures to them are universal (*e.g.,* they are present in pesticides, plastics, and fuels).[21] In addition, scientists have established that environmental exposures can have transgenerational effects.[25]

EDCs act at receptors, alter hormone synthesis, induce epigenetic changes, and disrupt hormone breakdown or clearance to have detrimental effects on health. Crucially, their effects depend on whether the exposure was before or after puberty.[26] It is important for researchers to pay special attention to the impacts of exposures to personal care, consumer, and occupation-related products—such as cosmetics, scented shampoos, hair sprays, lotions, and household deodorizers—which are affected by gender. For example, as alluded to earlier, the EDC compounds (*e.g.,* phthalates, parabens, and phenols) contained in these items have been linked with earlier pubertal timing—to a greater extent in girls than in boys, perhaps because of girls' greater use of these items.[27]

Our colleagues at the National Institute of Environmental Health Sciences (NIEHS) lead efforts to understand the complex effects of potential exposures, the influence of timing and sensitive periods across the life course, and a multitude of individual and contextual factors. NIEHS supports an approach that incorporates the exposome—the totality of environmental exposures experienced over the life course, the individual biological responses to them, and how those exposures affect health.[14] For more information on NIEHS's efforts to ensure that researchers explicitly incorporate sex and social determinants of health into investigations of individual susceptibility and to advance our understanding of exposure burdens and health disparities, see www.niehs.nih.gov/research/supported/exposure/hhear/index.cfm[28] Importantly, NIEHS and colleagues have outlined the intersectionality of climate change, gender, geography, and socioeconomic status and proposed policy directions to address their negative effects on women's health.[29]

Great progress in our understanding, detection, and treatment of postpartum depression (PPD) is the third scientific advancement in research on the health of women featured in this study. When ORWH was founded in 1990, PPD was not yet officially recognized by the Diagnostic and Statistical Manual of Mental Disorders. (That would occur in 1994, with the publication of DSM-4.)[30] Many researchers, clinicians, and members of the public now understand that many women do experience the ''baby blues,'' a temporary bout of worry, sadness, and fatigue after delivery that resolves without intervention.[31]

In contrast, PPD—experienced by about 13% of women with a recent live birth in the United States in 2018[32]—is an intense persistent sadness that can interfere with a woman's ability to care for herself and the baby,[33] last for up to 3 years in some women,[34] and elevate depressive symptoms up to 11 years after childbirth.[35] Worryingly, the rate of women with a depression diagnosis at delivery increased sevenfold between 2000 and 2015.[36] Moreover, PPD is most likely underdiagnosed (because women may be reluctant to report symptoms), which highlights the need to integrate mood disorder screening and treatment services into standard prenatal and postnatal care.[37] The National Child and Maternal Health Education Program, sponsored by our colleagues at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, aims to increase awareness of mental health around the time of pregnancy through science-based information and resources.

Brexanolone, the first medication specifically for persistent postpartum mood disruption, was approved by the Food and Drug Administration (FDA) in 2019.[38] Incorporating the multidimensional framework into research on women's mental health across the life course illuminated the risk factors for PPD—most notably, stress and adverse life events and subsequent neuroendocrine alterations and hormonal fluctuations—and then generated valuable knowledge about their underlying mechanisms.[39] Researchers identified sensitivity to the reproductive hormones estrogen and progesterone (rather than absolute levels), which modulate the neurotransmitter γ-aminobutyric acid (GABA), and dysfunction of $GABA_A$ receptors as contributing factors to PPD.[40,41]

As a synthetic analog of allopregnanolone, brexanolone is thought to boost the ability of $GABA_A$ receptors to adapt, thereby improving symptoms.[41,42] Brexanolone is currently available as an injection for intravenous use in medical settings, offering effective and immediate relief from what can be a debilitating and potentially life-threatening mood disorder.[42,43] An oral version of brexanolone, zuranolone (SAGE-217), is in Phase III trials.[44] If shown to be safe and effective, this more accessible formulation might help many more women who experience PPD.

The fourth scientific advancement reflects a central tenet of NIH Innovative policies that change the way scientists conduct their investigations are crucial and potentially even more transformative than specific experimental findings. In 1986, NIH responded to the recommendation of the Public Health Service Task Force on Women's Health Issues to

ensure adequate numbers of women in clinical trials by establishing a policy encouraging researchers to include women in studies. Subsequently, Congress passed the NIH Revitalization Act of 1993 (Public Law 103–43), which requires NIH to ensure that women and minorities are included in all clinical research (unless there is a compelling scientific reason for exclusion) and that trials are designed and conducted in a way that permits an analysis of outcomes by sex/gender, race, and ethnicity.[7]

The full history of NIH's efforts to ensure that women and underrepresented minorities are included in the clinical research it supports are detailed on the ORWH website. (https://orwh.od.nih.gov/toolkit/recruitment/history and https://orwh.od.nih.gov/womens-health-research/clinical-research-trials/nih-inclusion-policies/including-women-and) Although movement in this area has not always been straightforward, the following examples show that progress has been made and that NIH's policy on inclusion continues to adapt to public health needs.

In 2018, more than half (52.4%) of participants in NIH-supported clinical research were women.[45] However, we recognize that the need to expand inclusion in NIH-sponsored clinical trials continues. For example, women's inclusion in clinical trials lags behind that of men in some important areas,[46] such as clinical trials on cardiovascular conditions.[47] In alignment with the 21st Century Cures Act (Public Law 114–255), the inclusion of pregnant women and lactating women in clinical trials is currently a focus at NIH, led by our colleagues at NICHD and the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC). (See www.nichd.nih.gov/about/advisory/PRGLAC) NIH's view is that our clinical enterprise should change to protect pregnant people and lactating people *through* research, not *from* research.[48]

By the 2000s, NIH had seen steady progress in implementation of its inclusion policy, but the consideration of both female and male animals and cells in preclinical research had generally not advanced at the same pace.[49] As part of broader efforts to improve scientific rigor, transparency, and reproducibility,[50,51] NIH set out to address the lack of attention to sex as a biological variable (SABV) 7 years ago by announcing its intention to require applicants to report plans for including male and female cells and animals in preclinical investigations.[52]

ORWH then led an extensive process of internal and external consultation[53] and an in-depth exploration of methods, experimental designs, and approaches for statistical analysis that consider the incorporation of male and female animals, cells, and tissues in preclinical research.[54] The SABV policy (NOT-OD-15-102) went into effect January 25, 2016, and since then, NIH has expected that ''sex as a biological variable will be factored into research designs, analyses, and reporting in vertebrate animal and human studies.''[55] NIH subsequently provided additional guidance for researchers and grant reviewers to facilitate implementation of the SABV policy.[56,57]

There has been progress in SABV implementation, as the omission of sex has decreased and investigators are increasingly using both females and males in preclinical research.[58,59] More NIH grant applicants are appropriately addressing sex in their proposals, and grant reviewers report increased acceptance of the SABV policy.[60] However, basic research and preclinical research continue to over-rely on male cells and animals,[58,61] and there has been minimal progress in the disaggregation, analysis, and reporting of data by sex.[62] A detailed summary of NIH's multipronged efforts to increase SABV implementation was published last year.[63] Among the most important efforts to advance SABV implementation is the development of online educational modules (discussed in ''The Next 30 Years: Facing Challenges to Improve Health for Everyone'' hereunder).

The fifth advancement during the past three decades is the increase in the proportion of women working in laboratories, medical schools, and academic research centers across the nation. Building the participation of women in medical and biomedical research careers has been a core mission area for ORWH since its inception and is part of larger efforts by the NIH Scientific Workforce Diversity Office. NIH is committed to diversity because we need the brightest minds to contribute to the biomedical research enterprise, regardless of

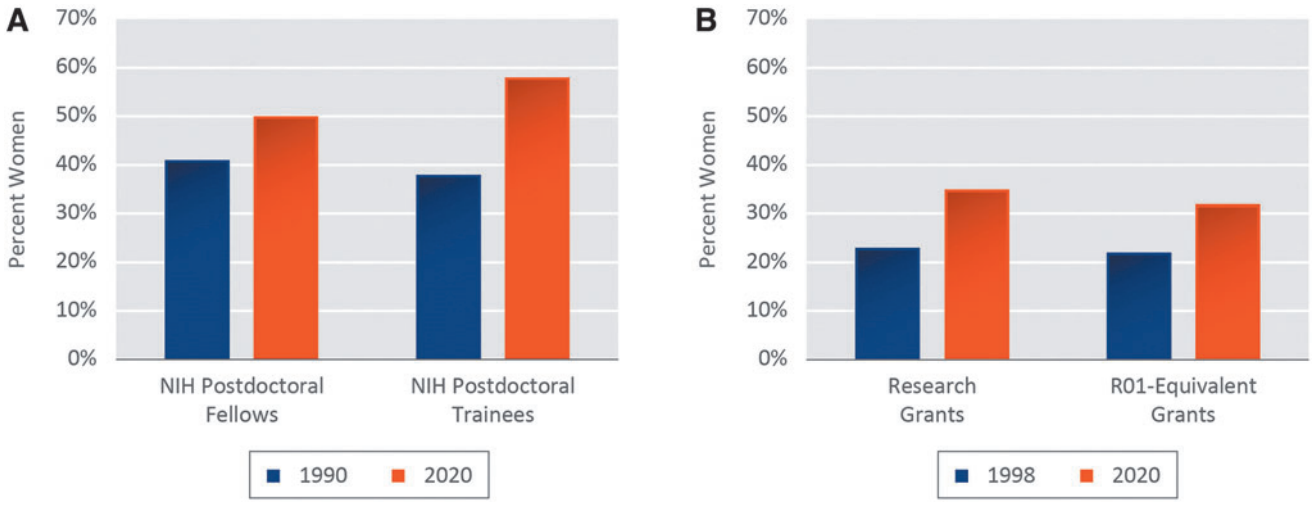

FIG. 2. **(A)** The representation of women in positions as NIH postdoctoral fellows and postdoctoral trainees increased between 1990 and 2020. **(B)** The percentage of women earning NIH research grants and R01-equivalent grants increased between 1998 and 2020. Data sources: National Institutes of Health.[68–70] NIH, National Institutes of Health.

background. Workforce diversity is also a best practice backed by research—as heterogenous interdisciplinary teams make better decisions and outperform homogenous ones, particularly when addressing complex problems.[64,65]

When ORWH was established in 1990, about one-third of medical school graduates and faculty members were women.[66] Now about half (48%) of medical school graduates and about three-fifths (58%) of graduate students enrolled in biomedical doctoral programs are women. The overall proportion of full-time medical school faculty members who are women is now at 41%.[67] Data from NIH also show some progress for women at various stages of their careers (Fig. 2).[68–70] This progress reflects concerted efforts by NIH to improve biomedical workforce diversity,[71] including those focused on promoting the careers of women.[72]

The most seminal moment in all of ORWH'S decades-long work in this crucial area was the 2008 release of the request for applications (RFA) titled ''Research on Causal Factors and Interventions that Promote and Support the Careers of Women in Biomedical and Behavioral Science and Engineering'' (RFA-GM-09-012).[73] NIH's unprecedented investment of $16 million resulted in an explosion of evidence contributing to our understanding of how individuals make career choices, how workplaces may inadvertently impede advancement, the existing barriers, and effective interventions. The research resulted in >100 publications, but the most profound contribution was the identification of best practices in the recruitment, retention, and advancement of women in academic medicine—with the ultimate effect of accelerating change and progress.[74] NIH is taking an innovative approach to improving women's representation in leadership, described in the next section.

The Next 30 Years: Facing Challenges to Improve Health for Everyone

The coronavirus disease 2019 (COVID-19) pandemic continues to cause widespread illness and deaths (254,215,816 cases and 5,112,710 deaths worldwide and 47,272,975 cases and 765,127 deaths in the United States as of November 16, 2021, according to the Johns Hopkins COVID-19 Dashboard). The FDA approval of one vaccine and authorization of two other vaccines for emergency use have brought some hope, and 58.9% of the U.S. population was fully vaccinated as of November 16, according to the Centers for Disease Control and Prevention.[75] Although COVID-19-related mortality seems to be lower for women, they have greater risk of exposure because of their overrepresentation among the frontline health care workforce and essential workers.[76,77]

Much more research is needed to understand the effects of COVID-19 on all women. Specifically, rigorous research (*i.e.,* studies that are fully aligned with the NIH inclusion and SABV policies) is needed for all COVID-19-related areas (*e.g.,* immune responses, sex differences in risk profiles, mental health effects, vaccine efficacy, and novel therapeutics). Released in July 2020, the *NIH-Wide Strategic Plan for COVID-19 Research* outlines five strategic priorities for COVID-19 research and NIH's commitment to addressing the needs of health disparity populations and other vulnerable people—including research on COVID-19-related maternal health and pregnancy outcomes.[78]

To complement the NIH-wide strategic plan and guide its COVID-19 response, ORWH developed *Guiding Principles: Sex and gender influences in COVID-19 and the health of women*. The principles promote rigorous research, advance health equity, and enhance the nation's response to the pandemic by laying out a systematic approach to incorporating sex and gender into research to inform and improve the health of women.[79] The document also addresses the disproportionate negative effects of the pandemic on the careers of women scientists, a topic that is discussed as follows. As in all research that includes both sexes, it is crucial to disaggregate data from COVID-19 studies by sex so they can be analyzed for potential differences.[80] A recent study found that although men have a higher COVID-19 mortality rate overall, black women had died at a higher rate than white men

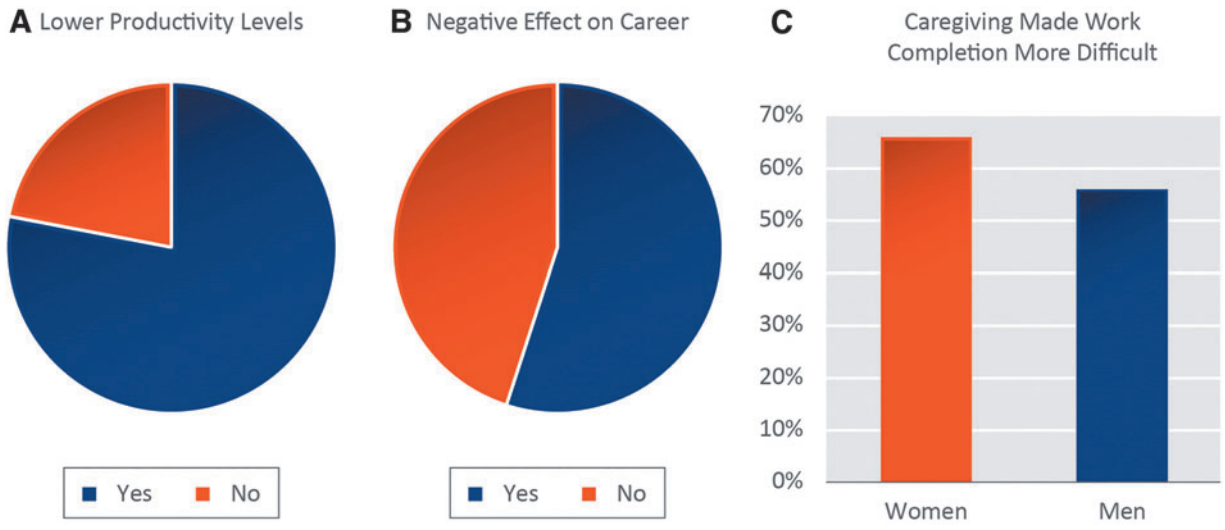

FIG. 3. Reported effects of the COVID-19 pandemic among the NIH extramural scientific workforce: **(A)** lower productivity, **(B)** negative effect on career trajectory, and **(C)** more women than men with children under age 5 years saying caregiving made work completion more difficult. Data source: Bernard and Lauer.[85]

in Michigan and Georgia—illustrating the importance of disaggregating and analyzing data for sex, gender, and race interactions in COVID-19 outcomes.[81]

Since the beginning of the pandemic, NIH has realized that reassignment to fight COVID-19 and restrictions on physical workspaces would have significant negative effects on the biomedical workforce. Sensitive to the notion that this situation would most likely have a greater effect on early-stage investigators (ESIs) and on scientists who are in populations that are underrepresented in medicine (URiM)[82,83]—including women scientists, who are disproportionately affected by additional caregiving and family responsibilities[84]—NIH objectively documented COVID-19's impact on the workforce through an online survey of extramural researchers in October 2020.[85] Some of those findings are shown in Figure 3. NIH provides numerous flexibility options, offers an opportunity for scientists to apply for an extension of their ESI status because of COVID-19-related delays, and supports efforts to retain early-career biomedical investigators during critical life events (NOT-OD-20-054 and NOT-OD-20-055).

The second major challenge to the health of women is the abysmal rates of maternal morbidity and mortality in the United States—the highest among wealthy nations[86]—and the marked racial disparities in these outcomes. In 2019, deaths from complications while pregnant or within 42 days of termination of pregnancy numbered 754.[87] About 60% of maternal deaths are considered to be preventable.[88] Black women and American Indian and Alaska Native (AI/AN) women have rates of maternal mortality that are about two to three times higher than those of white and Hispanic women.[89]

Table 2. Selected National Institutes of Health Initiatives to Address High Rates of Maternal Morbidity and Mortality in the United States

Initiative name	*Supporting IC(s)*	*Mechanism*	*Aims*
Administrative supplements for research on Women's Health in the IDeA States	ORWH, the National Institute of General Medical Sciences, and 12 other ICs	Notice of Special Interest (NOT-GM-21-018)	Expand research on women's health across the lifespan in states that historically have had low levels of NIH funding and are among those with the highest maternal and infant mortality rates.
Supporting Women's Health Research in the IDeA States through the Centers of Biomedical Research Excellence (COBRE) Phase I Program	ORWH, the National Institute of General Medical Sciences	NOT-GM-21-056	Expand women's health research in states that historically have had low levels of NIH funding and are among those with the highest maternal and infant mortality rates.
Addressing racial disparities in maternal mortality and morbidity	National Institute on Minority Health and Health Disparities	R01 Clinical Trial Optional (RFA-MD-20-008)	Support multidisciplinary research of racial and ethnic disparities in maternal morbidity and mortality, including projects to test prevention and treatment interventions to reduce these disparities.
U3 administrative supplement program	ORWH	Administrative Supplement Program (PA-18-676)	Supports research on the biological and social determinants of maternal morbidity among populations of women that are understudied, underrepresented, and underreported (U3) in biomedical research.
Implementing a Maternal health and PRegnancy Outcomes Vision for Everyone (IMPROVE)	NIH-wide—co-led by NICHD, OD, and ORWH		(1) Reduce preventable causes of maternal deaths and improve health for women before, during, and after delivery by supporting comprehensive interdisciplinary research that engages communities with high rates of maternal deaths and complications—with a focus on their leading causes and contributing factors. (2) Develop and disseminate a variety of maternal health resources to pregnant women and postpartum women.

IC, Institutes and Centers.

Importantly, higher levels of education and income do not mitigate the risk for maternal deaths among black women.[89,90] A recent scoping review found that black mothers were particularly vulnerable to environmental exposures (*e.g.,* air pollution, ozone, and heat) that are exacerbated by climate change and their negative effects on pregnancy outcomes.[91]

In addition, too many U.S. women—>50,000 annually and disproportionately black women—experience severe maternal morbidity (*e.g.,* requiring a transfusion, infection, or high blood pressure).[92,93] NIH has mounted a robust response to address the crisis—increasing research funding in this area from $334 million in fiscal year (FY) 2019 to $345 million in FY 2020—and makes information on these projects available to the public through the NIH Research Portfolio Online Reporting Tools (RePORT) website.[94] See Table 2 for selected NIH initiatives to address the maternal morbidity and mortality crisis in the United States.

The third challenge covered in this study is the furtherance of some aspects of NIH's SABV policy—particularly the analysis and reporting of sex-specific results in scientific articles, which has lagged despite guidance in the literature.[54,80,95–98] A study that examined SABV implementation across nine biomedical disciplines found that in eight of the disciplines, there was no change in the proportion of studies that included data analyzed by sex.[59] Analysis and reporting by sex—whether significant differences are found or not—is crucial for seeing patterns of results, accurately interpreting data, and guiding the next steps in the research.[95]

A lack of analysis and reporting by sex is a lack of transparency that perpetuates an incomplete and possibly inaccurate knowledge base, as aggregated data may mask important sex differences—such as variance in treatment response, toxicity, symptoms, and adverse effects. In addition, analysis and reporting of results by sex facilitates meta-analysis, helps avoid duplication, guides sample size calculations for future studies,[95] improves the design of clinical trials, informs sex- and gender-aware diagnosis and treatment, facilitates personalized medicine, and advances a system-based understanding of sex and gender influences on health and disease.[80,96]

ORWH and its partners have developed several educational modules on the influences of sex and gender on health—with SABV as a linchpin concept—for researchers and practitioners. Through its e-learning program (found at bit.ly/ORWHeLearning), ORWH offers free online tools to help researchers apply a sex-and-gender lens (including analyzing and reporting data by sex) to their work (Table 3). These courses would greatly benefit researchers who serve on NIH study sections, scientific peer reviewers, and journal editors.[60,98] Because of the myriad influences of sex on health and the impact of gender on how individuals are treated in the health care system, we believe that SABV and information on sex and gender should be included as part of the standard training of physicians, nurses, and other practitioners to advance precision medicine.[99,100]

The final challenge highlighted in this study is the need to increase the number of women in leadership roles in STEMM fields in academia, particularly women who are in URiM racial and ethnic groups. Inclusive and diverse leadership in academic medicine—the central driver of medical education, biomedical research, scientific training, and clinical care—is a crucial component of spurring innovation, attracting top scientists, and maximizing return on taxpayer investment.[101] Data indicate that the academic medicine workforce pipeline is not the problem.[67] However, women still only represent 18% of department chairs and 18% of deans.[67] A 17-year longitudinal cohort study indicates that women are half as likely to hold senior leadership positions at medical schools, even after controlling for publication productivity.[102]

Table 3. Recently Expanded Free Online Learning Modules That Cover Sex as a Biological Variable

ORWH has collaborated to expand learning modules that cover the requirements of NIH's SABV and inclusion policies, how sex and gender affect health and disease, and ways to improve the rigor and reproducibility of research.

Module name	*Developed by*	*Intended audience*	*Description*
Sex as a biological variable: a primer	ORWH with support from the National Institute of General Medical Sciences and the NIH Office of the Director	Biomedical researchers	Helps learners understand and apply the SABV policy in research design, analyses, and reporting.
Bench to bedside: integrating sex and gender to improve human health	ORWH and the Food and Drug Administration Office of Women's Health	Biomedical researchers, clinicians, and students in the health professions	Provides knowledge learners with skills that they can apply in designing and conducting research and/or interpreting evidence for clinical practice in key disease areas.
Introduction: sex- and gender-related differences in health	ORWH	Researchers, clinicians, and policymakers	A self-paced course (with a Facilitator's Guide) that offers resources intended to initiate a dialogue about how and why it is important to incorporate a sex-and-gender lens into research and clinical care.

Moreover, URiM women were only 13% of faculty in 2018, and it seems that progress has stalled, as the figure was 12% in 2009. In addition, the majority of URiM women work at the rank of assistant professor. Among the already small proportion of women chairs in basic science and clinical science departments, only 15% were from URiM groups in the 2018–2019 academic year.[67] ORWH continues to support innovative collaborative programs to advance women's participation in biomedical careers and foster their leadership opportunities (Table 4)—particularly addressing the barriers identified by research.[74]

Reasons for Optimism: Responsiveness, Collaborations, and Strategic Thinking

Although these challenges are significant, NIH can leverage collective ability, experience, and infrastructure to solve these problems. We have a clear way forward, as *Advancing Science for the Health of Women: The Trans-NIH Strategic Plan for Women's Health Research* provides a solid framework for advancing strategic goals and improving the health of women. And we understand that the value of NIH investments in women's health research goes beyond the individual to have a significant impact on society, as demonstrated in recent microsimulation analyses that found large returns from very small health improvements among women.[103]

ORWH knows that it cannot do it alone. At the 5th Annual Vivian W. Pinn Symposium, ORWH explicitly focused on building a broad-based network of government, nonprofit, academic, and business organizations to integrate sex and gender into biomedical research. ORWH's strong collaborative partnerships—so crucial to the progress achieved in its first three decades—ensure that the office will meet pressing needs, rise to future challenges, and catalyze the scientific breakthroughs, resulting in optimal health for all women during the next 30 years and beyond.[6,104]

Table 4. Examples of National Institutes of Health's Efforts and Leadership to Advance the Careers of Women in Biomedicine

Launching continuity awards to support the transition and retention of investigators to minimize departures from the biomedical research workforce at (1) the transition from a mentored career development award to an independent research project award (NOT-OD-20-054) and (2) the move from a first independent research project award to sustained funding (NOT-OD-20-055).
Transforming the scientific workplace more broadly by establishing the NIH Prize for Enhancing Faculty Gender Diversity in Biomedical and Behavioral Science to reward academic institutions for identifying and implementing best practices that support gender diversity among their faculty members. (See www.challenge.gov/challenge/nih-prize-for-enhancing-faculty-gender-diversity)
Advancing women in NIH leadership positions.
Currently, 11 of NIH's 27 ICs are led by women.
Women are central to building a modernized and integrated biomedical data science ecosystem at NIH—serving as role models and changing attitudes about who can excel in a crucial field that currently lacks diversity.
Sustaining efforts through leadership. NIH Director Francis S. Collins, MD, PhD, serves as a co-chair of the NIH Working Group on Women in Biomedical Careers (along with ORWH Director Janine Austin Clayton, MD, FARVO). This group:
Launched an initiative to assess institutional barriers to women's full participation in academic STEMM fields, culminating in the 2008 release of the RFA titled *Research on Causal Factors and Interventions that Promote and Support the Careers of Women in Biomedical and Behavioral Science and Engineering*.
Develops innovative programs and advocates for NIH workplace policies to reduce barriers to women's advancement.
Setting a positive climate for women at NIH.
NIH was cited as a ''high scorer on gender equality'' in the latest report from Global Health 50/50, which conducted an in-depth assessment of the advancement of gender equality within international health organizations and programs.

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Authors' Contribution

R.D. and J.A.C. conceived the structure of the information presented and provided references. L.A.W. searched for supporting references and wrote the article with support from R.D. and J.A.C.

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