

Research on Women's Health

Progress and Opportunities

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THE CONCEPT OF RESEARCH ON WOMEN'S HEALTH HAS evolved and expanded during recent years in ways that have paralleled, and perhaps even anticipated, some of the current challenges of biomedical and behavioral research. Fifteen years ago, women's health research primarily focused on reproductive health. Although women were not always excluded from clinical studies of conditions outside the reproductive system, clinical research involving conditions that affect both women and men did not routinely seek to identify differences between women and men. In attempts to broaden the concept of women's health and to recognize the increasing numbers of women of postmenopausal age, advocates for research emphasized the need to address the health of women across the entire life span, including the effects of normal aging. Research priorities were addressed in terms of life stages; however, as the influence of early life factors on the health of postmenopausal and elderly women became better appreciated, women's health has come to be addressed as a continuum throughout life. This broad concept of what constitutes women's health has led to the recognition that research priorities in women's health must be comprehensive and interdisciplinary and should include not only clinical studies but also the full spectrum of research, from molecular and genetic studies to those of prevention, behavior, outcomes of interventions, and clinical translation of newly proven hypotheses.

Multiple Research Approaches

Simply put, multiple approaches to research on women's health are needed. Today's approach to research on women's health is to investigate sex/gender differences or similarities between women and men, the lifespan of women including reproductive-related health and menopause, and biological, behavioral, or other factors that result in health disparities among women. Not all clinical studies must of necessity compare women with men; in fact, the National Institutes of Health (NIH) policy for inclusion of women and minorities in clinical research (which conforms with the NIH Revitalization Act of 1993¹) allows for single-sex composition of studies when that is justifiable.² The most obvious instances for sex/gender-specific clinical research would be studies of the reproductive systems and of menopause. In addition, results from studies that have previously

been conducted only in men—such as a number of studies related to diagnosis and treatment of cardiovascular disease (CVD)—now should be validated with women.³ Furthermore, women and men vary greatly among themselves, and it is important to address the causes, treatments, and prevention of disparities among those subpopulations. Such studies or study analyses might require single-sex composition and be especially directed to address the complex interaction between women's genetic and biological dispositions, their environment, personal health behaviors, racial/ethnic/cultural attributes, access to health care, and many other aspects that may contribute to differences in health status or outcomes between different populations of women.⁴

However, the major focus, as required by current NIH inclusion policies, is to design and implement clinical studies of conditions that affect both women and men in such a way that analyses by sex/gender can be conducted to determine if differences do exist for women, thereby providing information that can be used in sex/gender-specific health care.⁵ This policy continues to provide an impetus for NIH-funded researchers to pursue studies of sex/gender factors in health and disease and encourages the reporting of analyses of such differences in manuscripts submitted for publication.

The Nature of Sex/Gender Research

The Institute of Medicine report *Exploring the Biological Contributions to Human Health: Does Sex Matter?*⁶ recognizes the need to establish a clear definition of the terms “sex” and “gender” and a consistent use of these terms in the medical literature. The report recommended that the term “sex” be used when differences are primarily biological in origin and may be genetic or phenotypic (ie, genetic or physiological characteristics of being male or female) and that “gender” be used when referring to responses to social and cultural influences based on sex.^{6(p17)} This report also supports the concept that women's health research is more than just clinical trials or that sex differences are limited to reproductive tissues. It argues that “there are multiple, ubiquitous differences in the basic cellular biochemistries of males and

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females that can affect an individual's health . . . [that] are a direct result of genetic differences between the two sexes"^{6(p4)} and provides an in-depth discussion on the need for basic biological studies concerning molecular and cellular differences between the sexes in nonreproductive areas, with valuable consequences for health care.

During the women's health movement of the latter decade of the 20th century, a repeated theme from advocates was to decrease the fragmentation of health care for women. In the research arena, this perception has led to a new focus on interdisciplinary research for women's health and sex/gender studies. For example, the NIH Office of Research on Women's Health, in collaboration with many of the NIH institutes and centers and the Agency for Healthcare Research and Quality, developed an institutional career development award—Building Interdisciplinary Research Careers in Women's Health. This award grants support to mentored career-development research teams of women and men with multiple areas of scientific expertise to facilitate the integration of basic science, clinical and translational research, population studies, behavioral and social research, and outcomes research. This program thus simultaneously promotes interdisciplinary research and the ability of investigators at awardee institutions to become independent career scientists in women's health.⁷

The concept of interdisciplinary research has been reinforced and enhanced through NIH Roadmap initiatives for novel interdisciplinary training and clinical approaches.⁸ With avenues of interdisciplinary communication and collaboration established through research efforts, interdisciplinary clinical collaboration may be another benefit.

NIH Research Priorities for Women's Health

The NIH identifies priorities for women's health research, based on the *Agenda for Research on Women's Health for the 21st Century: A Report of the Task Force on the NIH Women's Health Research Agenda for the 21st Century*,⁹ through yearly cycles of reviews of advances and continuing or emerging scientific gaps in knowledge. Priorities for women's health research have begun to emphasize chronic and preventable illnesses in addition to focusing on specific diseases or conditions. Opportunities for advancing knowledge about etiologic mechanisms to elucidate sex differences in cellular, tissue/organ, physiological, and immune responses to environmental and infectious agents are many and diverse, and are important for clinical care of women and men in the future.

Two current areas of special emphasis demonstrate the range of opportunities for new studies: prevention research and research on the effects of sex as a modifier of gene function and response. As science increasingly shows that many diseases—such as cancer, CVD, Alzheimer disease, and osteoporosis—develop subtly over decades, prevention studies and interventions become a reasonable and urgent approach. Prevention research spans the con-

tinuum from the most basic biological studies to understanding the basis and effects of risk behaviors across the lifespan and the interventions to change them. For example, the NIH's attention to obesity through the Strategic Plan for NIH Obesity Research¹⁰ will be important for women's health, especially among minority women, because of the impact of diet, nutrition, and weight patterns on many conditions that are more prevalent in women or that affect their longevity, including CVD, the leading cause of death for women in the United States.

Development, testing, and validation of sex/gender differences in preventive and curative strategies for conditions and diseases that affect women, including obesity and other conditions such as sexually transmitted diseases, musculoskeletal disorders, cancer, addictions, and a variety of chronic multisystem diseases, can have significant clinical implications.¹¹ Defining the effects of sex on gene expression and genetic polymorphisms in disease penetrance, incidence, course, and response to treatment is another important priority for women's health research. With more discovery about the genetic, molecular, and cellular influences on the differential effects of action of pharmacological agents in women and men, more opportunities arise for the study of the impact of sex on genetic differences underlying pharmacokinetics, pharmacodynamics, drug efficacy, and adverse effects.¹²⁻¹⁵ Many questions about genetic polymorphisms that modify the actions of diet, drugs, or toxins on mother and fetus during pregnancy remain and provide rich opportunities for study.

Research on reproduction—from menarche, including infertility and pregnancy, to the natural history of the menopausal transition—and studies to define the susceptibility to, and protection from, diseases and conditions of postmenopausal women, have greatly increased clinical information but have also raised many new questions for scrutiny.¹⁶ The results of the randomized clinical trials on menopausal hormone therapy of the Women's Health Initiative (WHI) have been among the most important and most discussed recent findings on women's health.^{17,18} The WHI studied, among numerous other outcomes, the widespread assumption that menopausal hormone therapy prevents CVD. The WHI found that, to the contrary, the combination estrogen and progestin hormone therapy studied did not reduce the risk of myocardial infarction and increased the risk of stroke, and thus the study was stopped.¹⁷ Consequently, the US Preventive Services Task Force has issued a grade D recommendation against the routine use of combined estrogen and progestin for the prevention of chronic conditions in postmenopausal women.¹⁹ Spontaneous premature ovarian failure associated with sex steroid deficiency and intermittent symptoms of menopause in women younger than 40 years presents another aspect of needed information about the risks and benefits of replacement of ovarian hormones for informed management of this disorder and how it differs from normal (permanent) menopause.²⁰

Further research is needed to better understand the menopausal transition and postmenopausal health, including clarification of age-associated aging that may be independent of menopause. Continued examination of prevention strategies for overall enhancement of health in postmenopausal women may answer questions about the efficacy, and the risks and benefits, of different hormone formulations (for short- or long-term use), modes of administration, dosages, and when to start or stop therapy. Studies can provide more clinical and pharmacological information on complementary and alternative therapies, such as herbal products, to determine efficacy, mechanisms of action, and risks and benefits.²¹

While further results are expected from the WHI on the role of nutrition in maintaining postmenopausal health, additional research should help to provide definitive behavioral interventions and expectations of their benefit. Molecular, genetic, biological, and physiologic properties of hormones and hormone receptors are required to reconcile the results of animal and observational studies with clinical findings, including their neuroregulatory potential and role in sex differences in cognition and dementias, and to identify estrogen-sensitive genetic phenotypes and markers for adverse effects.

The NIH's strong emphasis on discovering and evaluating effective treatments for CVD in women has led to multiple studies that contribute to a better understanding of the role of heart disease in women's health and the differences and similarities between women and men with CVD. Several studies that did not include men were directed to learning more about how to provide the best prevention and care for women. For example, the Women's Ischemia Syndrome Evaluation^{22,23} explored the distinctive ways in which women present with myocardial infarction or chest pain and developed diagnostic algorithms specifically for use in women. The Women's Health Study²⁴ evaluated use of low-dose aspirin for primary prevention of CVD in women and reported different outcomes for women than those that had been shown in earlier studies in men. In this large, primary prevention trial among women, aspirin lowered the risk of stroke without affecting the risk of myocardial infarction for women younger than 65 years, whereas there was a significant reduction of major cardiovascular events, including myocardial infarction, among women 65 years or older. Similar findings were reported from a randomized clinical trial of the Women's Health Study on the use of vitamin E. Benefit for the prevention of cardiovascular events was demonstrated only for older women.^{25,26} A continuing focus on sex/gender contributors to cardiovascular health and disease will have significant clinical implications and public health benefits for the prevention, detection, and treatment of CVD in women as well as men.²⁷

Numerous other gaps in scientific knowledge about women's health help determine priorities for women's health research and studies of sex/gender factors. Studies of the pathogenesis of diseases that differentially affect women, such as

autoimmune diseases, are ripe for advancing the understanding of the role of sex in the interaction of genetic, regulatory, and environmental factors, as well as for promoting understanding of why certain populations of women may be more affected by some forms of autoimmune disease.²⁸ Related studies to explain the premature occurrence of atherosclerosis in patients with systemic lupus erythematosus may also provide information for further understanding the pathogenesis of atherogenesis in women as well as to improve clinical ability to more effectively manage those who are affected by lupus and are at increased risk for CVD.^{29,30}

Emerging microbial threats are bringing attention to biological and behavioral factors that may cause women globally to have increased risk for some infections or to experience more severe complications.^{31,32} Identification and determination of sex/gender-appropriate interventions for preventing or treating infectious diseases, such as malaria, tuberculosis, and schistosomiasis, that may affect outcomes of pregnancy or that may affect women in other distinct ways are important for public health initiatives. Examples of the latter include the global disparity of the burden of human immunodeficiency virus among women (especially young heterosexual women, who have the fastest-rising rates of new infection); infections of group B streptococcus; human papillomavirus and the increased risk for subsequent development of cervical cancer; and hepatitis B and C.

Exciting breakthroughs have occurred in the understanding of prevention, detection, and treatment of breast cancer, the most common nonskin malignancy that affects women. The discovery of the *BRCA1* and *BRCA2* mutations is one of the most striking breakthroughs in the current understanding of genetic risks for cancer and has resulted in many new clinical preventive approaches for women who are found through genetic testing to be predisposed to breast cancer.³³ Yet, only a small proportion of breast cancers are associated with these mutations, and, although decreasing, death rates from breast cancer remain high. Thus, continued exploration of the entire spectrum of detection, pathogenesis, prevention, and treatment of breast cancer must remain among the priorities for women's health research.

As research clarifies more about the interaction of environment and hormones on genetic susceptibility to a number of cancers that affect women, death rates and the impact of associated morbidity on women and their families can be reduced.³⁴ Other priorities for research on malignancies in women are to address sex differences in lung cancer—the leading cause of cancer deaths in women in the United States³⁵—as well as sex/gender differences in techniques for smoking prevention and cessation. Successful development of biomarkers for ovarian cancer and efficacious vaccines to prevent the transmission of the human papillomavirus will result in a decrease in the incidence and mortality of cervical cancer and deaths from ovarian cancer. Many studies have been reported on cancer disparities among women of racial and ethnic minorities, but more work is needed to address the biological characteristics

and the medical, behavioral, and societal interventions that can reduce these disparities.³⁶

Many other important scientific opportunities exist among priorities for defining, preventing, and treating diseases and conditions that are more common in women than in men, including mental health conditions, especially the disproportionate effects of depression and postpartum depression; the effects of stress and caregiving on women's health; uterine leiomyomas and improved nonsurgical approaches to their management; chronic fatigue syndrome; and irritable bowel syndrome.³⁷

Conclusion

The NIH inclusion policies have enhanced the attention given to women's health research and to determining sex/gender factors in health and disease. One important result has been an increase in biomedical and behavioral studies that are helping to answer questions that women, and their physicians, have about their health but for which science has not yet provided answers. As biomedicine and biotechnology expand current abilities to pursue new avenues of investigation, both basic research and clinical trial methods are essential to further knowledge about the health of women and men, but with sex/gender perspectives. Evaluation of innovative clinical trial methods and study designs with novel recruitment strategies are imperative for future studies.

Dissemination of evaluations published in peer-reviewed journals and the reporting of sex-differentiated statistics for these studies are critical to the rapid advancement of the state of the science of research on women's health and on sex/gender factors in health and disease. Continued emphasis on increasing and enhancing women's careers in research, including studies of the behavioral correlates that affect their selection of and advancement in biomedical sciences, must be integral to initiatives that will stimulate both women and men to pursue the many avenues of exciting endeavors that contribute to women's health research.

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