

Barriers and solutions in women's health research and clinical care: a call to action



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Summary

It is now recognized that there are significant differences between the sexes affecting prevalence, incidence, and severity over a broad range of diseases, although the extent of the differences is not fully elucidated. Until the early 1990s, women were excluded from most clinical trials and the limited research including women focused primarily on diseases affecting fertility and reproduction. For these reasons, the prevention, diagnosis, and treatment of chronic diseases in women continue to be based primarily on historical findings in men, and sex-specific clinical guidelines are often lacking. Many illnesses, ranging from cardiovascular disease to cancer to mental health issues, for example, differ by sex in terms of prevalence and adverse effects. Research is needed to understand how medically relevant biological sex differences optimally inform sex-specific prevention, diagnosis, and treatment strategies for women and men. In this way, sex-specific clinical guidelines can be developed where warranted, using evidence-based data.

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Introduction

The health of women remains significantly understudied in spite of longstanding recognition that there are clear differences between the sexes affecting the prevalence, incidence, and severity of a broad range of diseases.¹ Thus, women often receive care which is not grounded in sex-specific scientific evidence. Although not all diseases may differ between the sexes, we do not

currently know enough about the differences to determine appropriate diagnoses and treatments with certainty for women. In many cases, women continue to receive care based on evidence, observations, and outcomes that were accrued in men. Please note that in this discussion, we will use the term women to refer to individuals who are biologically female, recognizing that not everyone who identifies as a woman is biologically female. In addition, while gender is grounded in social, psychological, cultural and sociodemographic factors that are integral contributors to health, this paper focuses on the biological sex differences of biomedical relevance to women's health research, education, and clinical care, in order to improve the health of women. While we acknowledge that research on diseases of

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women's reproductive health, e.g., fibroids, endometriosis and menopause, remains understudied and underfunded, the aim of this discussion is to highlight the gaps in understanding sex-based differences in diseases common to men and women, since even less is known about the impact of these on the health of women.

This paper is a Call to Action from the steering committee of the Leaders Empowering the Advancement of Diversity in Education, Research and Science (LEADERS) in the Health of Women group. The LEADERS group is a national network specific to Internal Medicine and related disciplines, established in 2013 at Harvard University to increase clinical, education and research focus on the health of women, as well as to focus attention on the importance of women's health by increasing the number of endowed chairs in women's health. This national consortium includes academic physicians and research scientists in fields related to Internal Medicine, who bring critical expertise in the health of women, in research, education, and clinical care as well as in sex differences and in the investigation of Sex as a Biological Variable (SABV). Many members of the LEADERS group have endowed Chairs in women's health and/or are directors of Centers focused on women's health research and/or clinical care. The overarching aim of LEADERS is to elevate the importance of good healthcare for women and to advance the understanding of the health of women, including all biomedical conditions that are unique to women, more prevalent in women, or more consequential in women, and which focus on sex as a biological variable in health and disease. The goal of this Call to Action is to accelerate the pace of research and

education into women's health and factors related to sex, referring to biological attributes, e.g., chromosomes, gonadal organs and genetics. Equally important are initiatives to ensure that this knowledge is translated into clinical practice. Women will ultimately benefit enormously because of the gain in terms of sex-specific evidence guiding care.

This piece was developed from a US perspective and although US experiences and initiatives are the central examples, the call for action is not intended as a local movement but rather aims for change in how we approach sex differences and their impact on women's health research and clinical practice at a global level.

Prior to the NIH Revitalization Act of 1993 (Fig. 1), the limited research conducted on women's health focused primarily on diseases affecting reproductive system conditions such as breast cancer. In fact, women were excluded from most biomedical clinical trials at that time.¹ Hence, highly prevalent chronic diseases and related risk factors were not a subject of research or clinical focus in women for the most part until recently. For these reasons, the understanding of prevention, diagnosis and treatment of chronic diseases in women, including cardiovascular diseases, diabetes, non-reproductive cancers, neurologic, autoimmune and endocrine disorders, has been slow to evolve. Equally problematic has been the resistance of providers to rethink how they provide sex-specific care to women, since it is now well established that many sex differences underlie chronic and acute disease states in terms of risk factors and pathophysiology.²⁻⁴

Much more needs to be understood about sex differences in the pathophysiology of organ systems as well as in therapeutic approaches. Type 2 diabetes, for

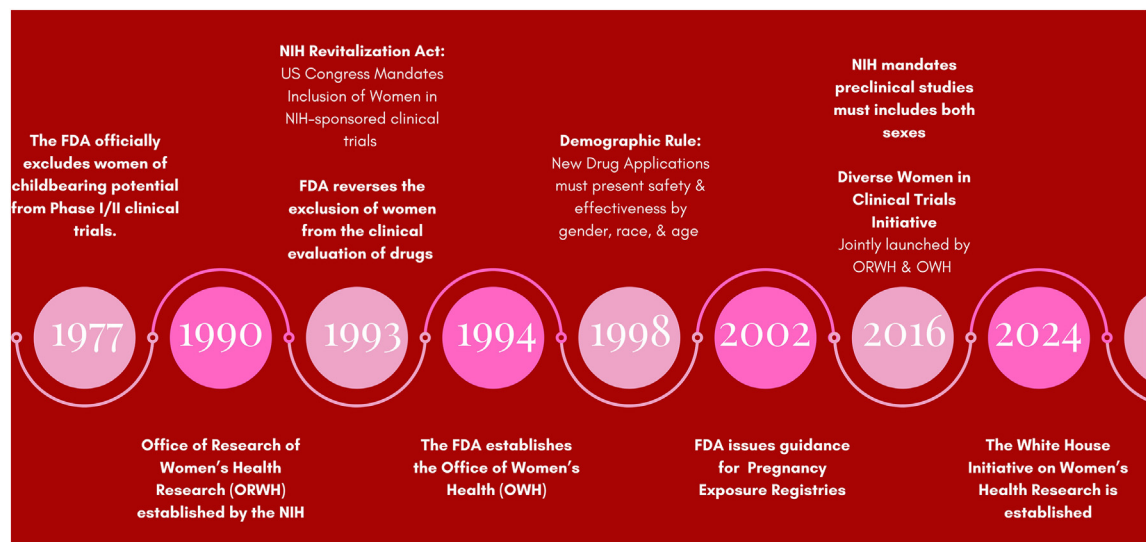


Fig. 1: Timeline for Women's Health Research. This timeline reveals the time course of women's health research at the federal level in the USA.

example, is associated with sex differences, but translation to sex specific care remains inconsistent.⁵⁻⁷ Even when diseases are not different in men and women in other ways, risks often are. For example, women have higher bleeding rates than men, intrinsically and with use of anticoagulation.⁸ Women also have higher procedural complication rates for cardiovascular procedures.⁹ In addition, while women generally have more side effects from medications than men,¹⁰⁻¹² sex differences in pharmacokinetics and in pharmacodynamics have been inadequately explored and continue to definitively impact diagnoses, treatments and outcomes.^{13,14} Accelerating the pace of quality research on sex-based health differences is essential to make up for lost time.

As noted, research in sex differences was not addressed at the national level in the USA until 1993, when, under the leadership of Dr Bernadine Healy, the NIH established the policy requiring that any trial seeking NIH funding needed to include women in numbers reflecting the prevalence of the disease. However, much work remains to be done to advance crucial research, education and clinical initiatives in the health of women. The Institute of Medicine (now the National Academies of Medicine) addressed this in 2001 and again in 2010,^{1,14} and although there have been significant gains in the inclusion of women, significant gaps remain, not just in the understanding of sex-based differences in disease, but also in the best strategies to implement a change in clinical care when new information becomes available.

In light of the relative dearth of research, the potential to improve the health of women remains under-realized with more questions than answers about diagnosis, prevention and treatment of diseases that primarily or solely affect women, and the influences of sex in disease pathophysiology are not well understood. Leadership of the Office of Research in Women's Health (ORWH) has greatly helped to bring this issue to the fore. In 2014, Drs. Janine Clayton and Francis Collins instituted an NIH policy requiring scientists to consider SABV in all research as a part of NIH's initiative to enhance reproducibility, rigor, and transparency.¹⁵ This has resulted in fundamental changes in thinking about the importance of considering sex differences in scientific domains.^{16,17}

In 2021, to further address NIH efforts to prioritize and coordinate women's health research, the ORWH, on behalf of the Advisory Committee on Research on Women's Health (ACRWH), convened a program, "Advancing the Health of Women," in which chronic diseases were characterized as those that are (1) female-specific, such as ovarian cancer and endometriosis, (2) more common in women and/or with higher morbidity in women, such as rheumatoid arthritis, Alzheimer's disease and migraine headaches, (3) found in both sexes but potentially understudied in women, such as

osteoarthritis, and (4) associated with high morbidity in women, such as heart disease, diabetes and immune-related diseases.¹⁸⁻²⁰ The compelling conclusion reached at this conference was that, "Improving the health of women benefits all members of our society," and that "fundamental basic and translational knowledge gaps in many female-specific conditions and diseases with sex-specific presentations, symptoms, or responses to treatments have hampered the generation of robust scientific data needed to provide high-quality, evidence-based care to women". Importantly, the research that informed the conference, as measured by the Manual Categorization System-Women's Health reporting module (MCS-WH), showed that research focused specifically on the health of women accounted for merely 10.8% of the NIH budget in fiscal year 2020 (\$4466 million).^{21,22} This analysis was done by Mirin, who examined sex disparity with regard to the allocation of research funding among diseases. He concluded, based on sophisticated modelling, that in nearly three-quarters of the cases where a disease affects primarily one sex, the funding pattern favours males, in that either the disease affects more women (with respect to burden) and is underfunded, or the disease affects more men and is "overfunded". Notably, due to the lack of research, there are few clinical care pathways that take sex differences into account and provide evidence-based optimal care for both women and men.^{23,24} Changing the paradigm of one size fits all, e.g., that of men, both in research efforts and in clinical practice, will require significant and sustained attention.

In this Call to Action, we delineate three key barriers and steps that may be taken to address them. The goal is that women's health and sex differences are approached with high quality research in studies designed to yield understandable and durable evidence, and that strategies are developed to facilitate the incorporation of new understanding of sex-based differences in women's health.

Critical barriers to progress in women's health and sex differences research

Barrier 1: Inclusion and other study design issues

Lack of inclusion of women in clinical trials and female animals in basic science studies has resulted in extensive gaps in the data with which to make evidence-based clinical recommendations. Despite improvements, women are still inconsistently included in trials and when they are included, the data are often not disaggregated by sex. Other study design issues also prevent progress.

Women remain underrepresented in clinical trials, and female animals and cell lines are even more underrepresented.²⁵ Women are therefore receiving treatments that were identified through studies conducted entirely or mostly in men, lacking data to differentiate whether they work the same in women as in men.

Including women in clinical studies, as well as female animals and cells, is critical in order to develop treatments that will benefit women as well as men.^{26,27} While women are currently included more often in clinical research studies than was formerly the case, in most fields of medicine this is still a work in progress and enrollment does not consistently reflect the burden of disease in affected populations.^{10,28–31} One significant example to consider is that research in heart failure still does not always include sufficient numbers of women for conclusive results to be established for both sexes.³⁰ As well, although there is recognition today that women must be included in drug development trials, many drugs were approved in the past without adequate differentiating data. Women experience adverse drug reactions nearly twice as often as men, for reasons still poorly elucidated.¹⁰ In one well-publicized case of the sedative zolpidem, it was found that not having sex-specific dosing actually led to harm because women were found to metabolize zolpidem more slowly than men, resulting in much higher serum levels and neurocognitive adverse consequences.³²

Because women were not included, studies of many commonly used medications for cholesterol and blood pressure were almost exclusively developed in men.^{33,34} Sex differences have often not been considered adequately in studies which purport to seek an understanding of key cardiovascular risk factors, where women are less likely than men to be treated to goal.^{4,35} In some cases, large studies have failed to recruit enough female participants to draw conclusions about women as well as men.³⁶ These large prospective studies are highly unlikely to be repeated due to cost and logistical considerations, which is problematic given the therapeutic implications. Studies have suggested, for instance, that some statins may be associated with development of diabetes in women,³⁷ but since these treatments are FDA approved and widely used, these nuances are difficult to determine. Clearly, the FDA should not accept new drug or device applications unless they have sufficient women enrolled to inform the results.

Notably, the lack of inclusion of women in biomedical research is even more acute in Black, Asian, and Latina women, as well as those in other race and ethnic subgroups, as is also true for many other aspects of women's health. Additional challenges in serving these women include barriers such as bias and lack of recognition of the needs of diverse women, all contributing to suboptimal care. While pervasive, this is exemplified by the well-recognized racial and ethnic disparities in severe maternal morbidity and mortality.³⁸

Compounding the failure to include women or recruit women in studies appropriately, there is not always consensus or clear guidelines about how to include women appropriately in terms of study design, study conduct and analysis of data. There have been

successful initiatives to drive this agenda in the past and the NIH has put weight behind requiring scientists designing studies to include both sexes, both for clinical and preclinical studies, in the rigour and reproducibility section of NIH in 2016.¹⁶ These efforts have had impact, but much more work and more stringent requirements are needed.

Potential solutions

There is an obvious need to recruit women in appropriate numbers for all trials. New methods for recruitment and for codifying requirements for the numbers of women in trials are essential to achieve this goal. Not closing trials where sex differences should be assessed until there is an adequate sample size of women is also essential. In terms of other study design issues, the role of the scientist is to consider women's health as well as the sex differences underpinning the field when they design a study, analyze data, mentor a trainee and write grants and papers. These concepts play a critical role, not only for each researcher's own scientific endeavours, but also for the people whom they mentor. Funders, regulatory bodies, and journals also play a critical role in requiring that investigators both include women in appropriate numbers and have designed trials according to best practices. Instructions for investigators and journals regarding the inclusion and reporting of sex-specific data are found in guidelines such as those by the Sex and Gender Equity in Research (SAGER) group. These guidelines are endorsed and enforced by many journals, including the Lancet journals, Journal of the American Medical Association journals and the New England Journal. However, they are not enforced universally.^{39,40} Recently, Li et al. have highlighted the importance of sex differences in cancer research⁴¹ and Usselman et al. have developed Guidelines on the use of Sex and Gender in Cardiovascular Research.⁴² This latter document provides clear guidance on how to consider the important concepts of sex, but much more work is required in this area; these guidelines could potentially be extrapolated and used more extensively.

Solutions for past trials are also being sought in novel data science techniques which can be harnessed to study sex differences.^{43,44} Recent advances in computation and machine learning approaches hold great promise for improving our understanding of sex differences and leveraging that knowledge for improved health for all. Relevant approaches include: predictive analytics, including machine learning and time series analysis to forecast health outcomes, risk assessment to predict female-specific conditions like uterine cancer, or traits more common among women such as autoimmune conditions, machine learning techniques such as neural networks, to identify patterns in large datasets (including clinical trials), natural language processing for analyzing textual data from patient records, and network analysis to visualize relationships between

health factors. Data science techniques are now being explored in a number of disease states and may offer a partial solution to the issue of the inadequate historical data in women in some cases as well as an approach to future research.

Research initiatives must be driven with funding priorities. Importantly, focused contract funding was the first major deliverable of the 2024 White House Initiative on Women's Health Research.⁴⁵ The Advanced Research Projects Agency for Health (ARPA-H) aimed to galvanize the innovator, investor, researcher, and patient advocate communities to understand women's health challenges better, take action, and spur innovation. ARPA-H committed \$100 million towards transformative research and development in women's health as part of a new request for solutions funding opportunity. In March of 2024, NIH constituent agencies were directed by executive order to develop and strengthen research and data standards on women's health across all relevant research and funding opportunities, placing a spotlight on interdisciplinary women's health research. In order to advance and promote improvements in health and healthcare for women, the science community needs to maintain the momentum so that progress continues to build.

Barrier 2: Inadequate teaching and training tools for researchers and clinicians on content and methods relevant to sex differences

Research curricula

There is not a fully realized curriculum for research in the health of women that adequately addresses the fundamental principles of women's health research as well as the critical concepts of sex differences that inform it. Lacking for researchers are standardized curricula that integrate sex differences throughout the full continuum of preclinical and clinical research training.

Research curricula must be developed with the essential content which will help solidify, build and coalesce the field of women's health research so that it is a well-defined field that people will want to join. "Incorporating sex as a biological variable into basic and biomedical research requires a deliberate plan that weaves concepts of basic genetics, cellular and molecular physiology, and pharmacology into translational medicine".⁴⁶ Such a curriculum could guide understanding of and provide tools for incorporating sex differences into medical research design, analysis, and publication. Free online training modules for medical and other science researchers currently include the excellent resources created by the ORWH and those created by the Canadian Institutes of Health Research, among others, but there is not currently a comprehensive university-based curriculum that considers women's health and sex differences in research.⁴⁷ This lack of broadly disseminated

information has had a detrimental impact on women's health since it has impeded development in the field of women's health/sex differences research.

Clinical curricula

Currently, foundational training for medical and health science students does not require an understanding of how sex may influence disease. With regard to the lack of clinically-focused curricula, there have been prodigious and excellent efforts to address this, including the ORWH ELearning Curricula,⁴⁸ Sex and Gender Specific Health Curriculum at Texas Tech University Health Sciences Center,⁴⁹ the Society of General Internal Medicine's, *Sex and Gender-Based Women's Health*,⁵⁰ and *How Sex and Gender Impact Clinical Practice: An Evidence-Based Guide to Patient Care*,⁵¹ and the AMWA Sex and Gender Collaborative,⁵² but none that have been embedded in medical and scientific training in a cohesive, systematic way. Prior studies have noted that medical students have not received information regarding sex and gender aspects of medicine consistently during their training.^{51–53} In fact, medical schools around the US and in Canada reported inconsistent results as to whether medical students learn about women's health outside of the reproductive system and breast cancer.^{54,55} This lack of broadly disseminated, standardized information can lead to discrepant clinical care.

Potential solutions

Incorporation of more comprehensive educational tools and curricula focused on women's health research as well as the sex-based concepts that underpin this area are critical. The ideal research curriculum will include information on sex for preclinical and clinical research. A non-exhaustive list of 7 key components suggested for such curricula is compiled in Box 1.

Box 1.

Components of a women's health research curriculum focused on sex will include but are not limited to the following, adapted in part from Kantarci and colleagues (reference⁴⁶).

- Understanding the definitions of sex; history of and need for sex differences research;
- Review of sex chromosomes: genes, X inactivation, X dose effect, sex chromosome effects (4 core genotype model).
- Integrating sex as a biological variable in translational research.
- Defining the role of the sex hormones in sex differences research: strengths and limitations
- Reviewing epigenetics and sex differences
- Describing research considerations for basic science and clinical science sex differences research: strategies and methods.
- Incorporating sex differences in drug and device development and prescription.

To summarize, scientists at all levels of training must work to incorporate scientific thinking that considers concepts about biological sex and sex differences. As with study design and conduct, mentors should work to embed this approach into their mentoring practice. Early career faculty interested in women's health and sex differences research must try to find mentors who share their interest. If mentors are not willing to fully consider these concepts, it will be difficult and frustrating for young scientists to proceed and alternate mentors should be sought, which is challenging. Increasingly, scientists at all levels of training are interested in looking at sex differences, since noteworthy findings are discovered when sex differences are considered.²⁴ However, there is a long way to go.

In parallel, medical and health science students must receive standardized curriculum-based training which focuses on all aspects of women's health.

Barrier 3: Inconsistent implementation of new research-based evidence and guidelines into clinical practice

Implementation strategies to address clinician behavior and facilitate incorporation of new information about women's health and sex differences into clinical practice have been inadequate

Women's healthcare remains highly understudied and there has been a failure to incorporate what we do know into training programs and curricula, or into practice guidelines in a comprehensive and systematic fashion. In part as a result, clinicians have been slow to incorporate new knowledge into practice. Understanding of the roles of sex and instituting sex-specific guidelines in clinical medicine is overdue. Clinical guidelines based on sex may not need to exist for every type of disease but we do not currently know which diseases differ in their diagnosis and treatment needs based on sex. Therefore, before recommending that men and women receive identical treatments, it is important to ensure that recommendations are data driven.

Additionally, the adoption of sex-specific information into clinical care has been suboptimal. Changing clinician behaviour in the face of new information is difficult, and sex-based biases about the care of patients remain. Examples of the failure to incorporate new information include the lack of attention to adverse pregnancy outcomes in the estimation of an individual's subsequent risk of cardiac events; the new PREVENT cardiovascular risk calculator does not include these factors despite evidence that they are equally or more important than some of the traditional risk factors.⁵⁶ It is also important to recognize inherent bias in the clinical care of patients. Examples of sex and gender bias in clinical care include the failure to initiate statins in women and the fact that clinicians are less likely to refer

women with known cardiovascular diseases for revascularization or for cardiac rehabilitation after myocardial infarction.^{57,58} As well, Kautzky-Willer and colleagues observed that standard insulin regimens led to significant differences in glycemic control, with fewer women achieving target HbA1c of <7% and with women more likely to experience severe hypoglycaemia.⁵⁹ Yet, insulin treatment protocols continue to ignore sex-differences in the response. Hofer-Zani et al. looked at sex differences in the diagnostic algorithm of screening for heart failure by symptoms and NT-proBNP in patients with type 2 diabetes and found that the current classification may not be the most suitable.⁶⁰

Potential solutions

New approaches to holding clinicians accountable for understanding and incorporating sex differences into practice must be established.

As noted previously, prioritizing the acquisition of data on women's health through research, disaggregated from data on men is critical. Holding medical schools accountable by Liaison Committees for Medical Education review for robust sex-based curricula is also critical. Current regulations are generally met by obstetric and gynecologic training objectives with no focus on the teaching of sex-based information in health and disease.

Clinical proficiency should include testing about sex-based differences on certification exams such as the National Board of Medical Examiners testing and specialty certification exams such as the American Board of Internal Medicine and Subspecialty Examinations. It is long overdue that quality measures for practicing providers are stratified by patient sex. For example, most health care systems now report diabetes metrics and CV risk factor metrics by a gender-neutral mechanism; differentiating by sex could be a motivator to address implicit bias and more accurately collect data.

Conclusions

Women face consequential challenges in healthcare related to lack of sex-specific care that contributes to suboptimal health outcomes. Addressing these disparities is crucial for promoting health equality between the sexes and creating optimal health outcomes for all. To effect positive change in the health of women across the nation, the Leaders Empowering the Advancement of Diversity in Education, Research and Science (LEADERS) in the Health of Women group has issued this Call to Action. We must prioritize and elevate the understanding and investigation of women's health and sex differences, and develop effective implementation strategies to both change the educational content we provide our trainees and to ensure that new advances are incorporated into clinical practice. When we study sex differences, we are studying both sexes. Accelerating women's health research, providing excellent research

curricula on women's health, developing sex-specific guidelines, holding all medical trainees accountable for new and more complete knowledge of women's health on certifying exams, and providing sex-specific quality metrics will both advance the health of women and will benefit the health of the nation. We are a long way from that point, but our path forward is clear.

Contributors

All authors contributed ideas for writing the manuscript and provided feedback for the revision. All authors participated in the writing of the manuscript and provided feedback for the revision. Drs. Klein and McNeil participated in the writing of the manuscript and the revision. Dr. Regensteiner, as first author, participated in the writing of the manuscript and the revision.

Declaration of interests

CNBM is in the Board of Directors and discloses stock options from iRhythm. SF reports royalties to Mayo Clinic, consulting fees from Era Women's Health Platform and The Menopause Society, and honoraria from PriMed and Medscape. MG reports consulting fees from Novartis and Medtronic, honoraria from Zoll and Medscape. HJ reports consulting fees from Merck.

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