# Sex-Specific Medical Research

# Why Women's Health Can't Wait

A Report of the
Mary Horrigan Connors Center
for Women's Health
& Gender Biology
at Brigham and Women's Hospital

BRIGHAM AND WOMEN'S HOSPITAL

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**The Connors Center for Women's Health and Gender Biology and the Division of Women's Health at Brigham and Women's Hospital**, led by Paula A. Johnson, MD, MPH, are committed to improving the health of women and transforming their medical care through the discovery, dissemination and integration of knowledge of women's health and sex- and gender-based differences and the application of this knowledge to the delivery of care. We are committed to building awareness of issues related to women's health and gender biology among clinicians, patients and the general public, advocating for changes in public policy to improve the health of women, and advancing the field of women's health globally by developing leaders with the experience and skills to have a major impact on improving the health of women. For more information, please see www.brighamandwomens.org/connorscenter.

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**AUTHORS**

**Paula A. Johnson, MD, MPH**
Chief, Division of Women's Health and Executive Director, Connors Center for Women's Health and Gender Biology, Brigham and Women's Hospital; Professor of Medicine, Harvard Medical School

**Therese Fitzgerald, PhD, MSW**
Director, Women's Health Policy and Advocacy Program, Connors Center for Women's Health and Gender Biology, Brigham and Women's Hospital

**Alina Salganicoff, PhD**
Vice President and Director, Women's Health Policy, Kaiser Family Foundation

**Susan F. Wood, PhD**
Director, Jacobs Institute of Women's Health, Associate Professor of Health Policy, George Washington University, School of Public Health and Health Services

**Jill M. Goldstein, PhD, MPH**
Director of Research, Connors Center for Women's Health and Gender Biology, Brigham and Women's Hospital; Professor of Psychiatry and Medicine, Harvard Medical School



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## CONTRIBUTING AUTHORS

**Yolonda L. Colson, MD, PhD**
Professor of Surgery, Harvard Medical School;
Director, Women's Lung Cancer Program, Brigham and Women's Hospital

**Laura Cohen, JD**
Senior Health Policy Analyst, Women's Health Policy and Advocacy Program, Connors Center for Women's Health and Gender Biology, Brigham and Women's Hospital

**Usha Ranji, MS**
Associate Director, Women's Health Policy, Kaiser Family Foundation

**Andrea Camp**
Senior Policy Advisor, Communications Consortium Media Center

**Carolyn Luk**
Research Assistant, Women's Health Policy and Advocacy Program, Connors Center for Women's Health and Gender Biology, Brigham and Women's Hospital

**D. Richard Mauery, MS, MPH**
Managing Director, Jacobs Institute of Women's Health, George Washington University

**Janet Rich-Edwards, ScD**
Associate Professor, Harvard Medical School (Department of Medicine) and Harvard School of Public Health (Department of Epidemiology);
Director of Developmental Epidemiology, Connors Center for Women's Health and Gender Biology, Brigham and Women's Hospital



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Finally, we want to express our deep appreciation to the members of Congress, pioneers and advocates whose tireless dedication and force of action made the historic NIH Revitalization Act a reality. They are true champions who ushered in a new era of federal policy focused on gender equity in medical research.

# FOREWORD

Twenty years ago, a bipartisan group of legislators worked with patients, providers, policy makers, and advocates to create and pass the 1993 National Institutes of Health Revitalization Act, a law mandating that women and minorities be included in clinical trials funded by the NIH. In many ways the law has been a success. Women are now routinely included in clinical trials, and we have learned how certain diseases present differently in men and women.

Yet, despite some progress, medical research is too often flawed by its failure to examine sex differences. It is now clear that men and women experience illness differently and this report looks closely at four diseases where this is especially true: cardiovascular disease, lung cancer, depression and Alzheimer's disease. The past two decades have shown not only that sex differences exist, but have produced scientific advancements that enhance our ability to discover why they occur and how we might adapt prevention, detection and treatment strategies for the benefit of women and men alike. Therefore, to ignore these differences challenges the quality and integrity of science and medicine.

While this report focuses on women, understanding health differences is valuable to all who want to understand the impact of different conditions and treatments on men and communities of color as well. Our hope is that this document will fill a void in our collective conscience by highlighting the challenges ahead and inspiring men and women alike to care about the inequities that now exist. Researchers around the world have worked tirelessly on these issues, and many of their studies are cited in these pages. We gratefully acknowledge their important contributions.

In addition to documenting the problem, this report also offers a realistic, concrete action plan for a path forward. We hope this plan will inspire all stakeholders to work together to gain a recommitment to research in which the study of sex differences is the norm, not the exception.

Now is the time for us to act so that we can realize the promise of the NIH Revitalization Act. Embracing the study of sex differences can improve the lives of women and men in the United States and around the globe, for this generation and for generations to come.

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# EXECUTIVE SUMMARY

The historic 1993 NIH Revitalization Act, born from a vision of healthcare based on evidence that incorporates the best knowledge about sex/gender and race/ethnicity differences and similarities, made inclusion of women in health research a national priority. Yet, despite progress during the past 20 years, women still have not achieved equity in biomedical and health outcomes investigations. The science that informs medicine—including the prevention, diagnosis, and treatment of disease—routinely fails to consider the crucial impact of sex and gender. This happens in the earliest stages of research, when females are excluded from animal and human studies or the sex of the animals isn't stated in the published results.[1] Once clinical trials begin, researchers frequently do not enroll adequate numbers of women[2] or, when they do, fail to analyze or report data separately by sex.[3-6] This hampers our ability to identify important differences that could benefit the health of all. Research on these differences must become the norm if we are to achieve equity and, most important, to improve the health and well-being of women and men.

When we fail to routinely consider the impact of sex and gender in research, we are leaving women's health to chance. The evidence on sex differences in major causes of disease and disability in women is mounting, as are the gaps in research.

**Cardiovascular Disease:** We now know that cardiovascular disease, the number one killer of women in the United States, affects women and men differently at every level, including prevalence, underlying physiology, risk factors, presenting symptoms, and outcomes. Racial and ethnic disparities also exist, with black women more likely than their white peers to experience the disease and to die from it.[7] Yet only one-third of cardiovascular clinical trial subjects are female and fewer than one-third (31 percent) of cardiovascular clinical trials that include women report outcomes by sex.[8]

**Lung Cancer:** More women die of lung cancer each year than from breast, ovarian, and uterine cancers combined.[9] It is the leading cause of cancer death in women.[10] While about one in five people who are diagnosed with lung cancer never smoked, nonsmoking women are three times more likely than nonsmoking men to get it.[11-13]

While the number of women participating in lung cancer clinical trials has risen, women—particularly those from racial and ethnic minorities—are still less likely to enroll in these trials than men.[12-14] Even when studies include women, researchers often fail to analyze data by sex or include hormone status or other gender-specific factors, making it difficult to uncover differences in incidence, prevalence, and survivability between men and women and to replicate the studies.[15]

**Depression:** Depression is the leading cause of disease burden worldwide. In the United States, twice as many women than men suffer from depression,[16,17] with direct costs exceeding $20 billion annually.[18] We know that major endocrine changes throughout a woman's life, including puberty, pregnancy, and menopause, have been directly linked to increased risk for this disease. Furthermore, basic research into drug development has shown that women metabolize drugs differently than men. Yet fewer than 45 percent of animal studies on anxiety and depression use female lab animals.

**Alzheimer's Disease:** Two-thirds of the 5.1 million people currently suffering from Alzheimer's disease are women.[19, 20] Women are also the primary caregivers of adult loved ones with Alzheimer's disease, meaning they shoulder both the risks and the burdens of the illness. Even though a woman's overall lifetime risk of developing Alzheimer's disease is almost twice that of a man, the prevailing thinking in the field is that this is simply because women live longer. However, the impact of hormonal changes at menopause and sex differences in gene expression have begun to emerge as potential explanations.

## Equity in Research Is Essential for Quality Outcomes and Value

As the investment in healthcare has skyrocketed, as healthcare reform extends care to more Americans, and as the healthcare system evolves to meet shifting needs, research on sex and gender differences must become the

norm, not the exception. While we celebrate 20 years of the NIH Revitalization Act's important contributions, we must recommit to its intention and authority. The law was enacted to remedy sex/gender and race/ethnicity bias in biomedical research, but we have a long way to go to fulfill its possibilities. Sex and gender equity in research is an essential component of quality research. Without equity in research, we are not getting the full value of our massive public investment.

## A Call to Action

**Don't leave women's health to chance.** Research on sex and gender differences must become the norm, not the exception, for the United States to achieve health equity and, most important, to improve the health and well-being of all. Our leaders, in government and in the field of research, must ensure that all health agencies are actively engaged in women's health research and the evaluation of sex differences across the lifespan. Health agency leaders must prioritize the design, analysis, and reporting of health research by sex. And in this new era of personalized medicine, a multi-stakeholder approach is the best way to ensure quality, safety, value, and efficacy in the methods we use to address disease. All stakeholders must exercise influence in their spheres.



## Act

- **Hold federal agencies accountable.** Government and and other funding agencies, including the National Institutes of Health (NIH), the Agency for Healthcare Research and Quality (AHRQ), the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) should ensure that the design of clinical studies includes a consideration of the sex of the subject, adequate participation of women, and the reporting of sex-stratified findings.
- **Promote transparency and disclosure regarding the absence of sex- and gender-based evidence in research, drugs and devices.** Medical device and pharmaceutical labeling should carry a disclaimer if clinical testing did not include adequate numbers of female subjects. Researchers should be required to disclose in a standardized format (similar to a nutritional label) how their study addresses sex and whether the data are analyzed by sex. An annual review of peer-reviewed journals should be conducted to assess how well and often they present sex- and gender-based research. An online gateway should be developed to provide public access to sex-stratified data from government-sponsored research.
- **Expand sex-based research requirements.** Institutional Review Boards can require that research plans include adequate numbers of female and male human subjects and lab animals. Journals can require authors to report the sex of lab animals and human subjects and encourage the publication of sex-specific results.
- **Adopt clinical care practices and training curricula that incorporate a sex- and gender-based lens in care and research.** Medical education and research on all levels should include differences based on sex and gender.

## Make Your Voice Heard

All women and men can play a role in making sex- and gender-based research the norm. They can demand that their policymakers ensure that women are included in all phases of medical research and that sex differences are studied and evaluated at all levels as is currently required by law. They can demand that the findings be translated from bench to bedside for the benefit of all. And when they seek care, they can ask their doctors if the recommended prevention strategies, diagnostic tests, and medical treatments are based on research that included women.

Two decades after the landmark NIH Revitalization Act was signed into law, we still have much work to do to make certain that its promise is realized. The passage of the law was a critical milestone. Now is the time to recommit to its vision and ensure that research at all levels is performed with a sex- or gender-specific lens. The crucial impact that these factors may have on health outcomes and ultimately on our care still is not routinely or adequately assessed. Without sex- and gender-specific approaches to research and healthcare, our research investments will not provide us with the value so crucial to bettering the health of our nation, improving the quality of care, and controlling the growth in health costs. It is time to act. Future generations are counting on us.

# INTRODUCTION

**"The historical lack of research focus on women's health concerns has compromised the quality of health information available to women as well as the healthcare they receive."**

*Women's Health: Report of the Public Health Service Task Force on Women's Health Issues, 1985*

Just over 20 years have come and gone since the passage in 1993 of the federal NIH Revitalization Act, which had its roots in the report quoted above. Heralded as a landmark in science and public health, this groundbreaking law required for the first time that all "NIH-supported biomedical and behavioral research involving human subjects" include and analyze the impact on women and racial/ethnic minorities.[1, 2] The goal was that, after years of neglect, federal investment would bring equity to health research, thus paving the way for new advances in health. Indeed, today's progress in understanding the role of sex and gender in health, in identifying who is at risk for health conditions, and in recognizing that symptoms and treatment may differ between men and women, is attributable largely to research stemming from that law.

The nation now has offices of women's health in several states and most U.S. Department of Health and Human Services (HHS) agencies, 21 centers of excellence in women's health, and more than $3.8 billion allotted by the National Institutes of Health (NIH) for women's health research. Notable advances have been made in maternal health: the focus on preconception health has increased while infant mortality has decreased. The NIH Women's Health Initiative produced major findings on the connection between hormone replacement therapy and breast cancer. Great strides have been made, according to the Institute of Medicine's (IOM) thorough review, *Women's Health Research: Progress, Pitfalls, and Promise*, in reducing the burdens on women of breast cancer, cervical cancer, and heart disease. Given the combined toll of those diseases on millions of women, these important accomplishments are cause for celebration.

Yet the same IOM report identified other conditions where progress has slowed or, in some cases, stalled. These include epidemics that disproportionately affect women's health and well-being at all stages of their lives, including depression, lung cancer, and Alzheimer's disease. Unintended pregnancy, estimated at half of all pregnancies, is another area where little progress has been made, showing that much remains to be learned in reproductive health as well.

The idea that women's health requires its own focus has not yet been universally embraced by basic science, clinical, and health services researchers. This is unfor-



**1985**
U.S. Public Health Service's Task Force on Women's Health issues report.

**Medical research that is either sex- or gender-neutral or skewed to male physiology puts women at risk for missed opportunities for prevention, incorrect diagnoses, misinformed treatments, sickness, and even death.**

tunate, because sex and gender must be integrated into and embraced in all aspects of research: basic science discovery, clinical research, translation to clinical practice, and measurement and evaluation. Far too often, research fails to illuminate important differences because sex or gender is excluded or inadequately addressed at one of these steps. Too often, important research fails to tease out sex differences at the cellular and animal levels, limiting its value. The lack of sex-based animal studies, typically an early stage in research, perpetuates the gap down the road. Human studies may include women as subjects, but often researchers do not analyze or report results by sex. More often, studies "control" for sex differences instead of investigating them, but this approach is inadequate when the mechanisms underlying health may operate differently in men and women. The U.S. Food and Drug Administration (FDA) does not require sex-specific analysis in the drug-approval process or even when making dosing recommendations, and healthcare delivery systems rarely investigate systems or interventions that may be more or less effective for women.[3]



Many factors lie behind this stalled progress, including a lack of enforcement of the NIH policy, which specifically calls for researchers to describe "plans to conduct analyses to detect significant differences in intervention effect by sex/gender, racial/ethnic groups, and relevant subpopulations, if applicable." Researchers may be inexperienced in conducting sex/gender-based research, and scientific journal editors do not consistently consider sex/gender analysis when reviewing submissions.

In truth, the expectation that one of humanity's most basic distinguishing characteristics be integrated into health research is not new. However, in the two decades since the NIH Revitalization Act, the urgency has heightened. As expense and inequity in services have increased, as healthcare reform extends care to more Americans, and as the healthcare system evolves to meet shifting needs, research on sex and gender differences must become the norm, not the exception. Only then can we continue to make medical breakthroughs worthy of each precious research dollar invested.

While we celebrate 20 years of the Revitalization Act's important contributions, we must recommit to its intention and authority. This recommitment is required from the public and private sectors, scientists and researchers, advocates, policymakers, funders, the pharmaceutical and biotech industries, medical device companies, professional societies, clinicians, journal editors and reviewers, and the public. Several HHS agencies, such as the NIH, FDA, CDC, and the Agency for Healthcare Research and Quality (AHRQ) play a particularly important role as leaders and primary sponsors of biomedical and health services research. Together we must ask how to get back on the road to equity.

## ROUTES AND ROADBLOCKS ON THE WAY TO HEALTH EQUITY: THE FOUR STAGES OF RESEARCH

The entire research process—from discovery at the molecular and cellular levels, to pre-clinical research in animals and humans, to clinical trials, ending in translation into practice and measurement of outcomes—is inequitable because sex and gender differences are so often not embedded within it.

This failure to address sex and gender differences across the full spectrum of research diminishes innovation in medicine and decreases the value of our enormous investment in research and healthcare. Medical research that is either sex- or gender-neutral or skewed to male physiology puts women at risk for missed opportunities for prevention, incorrect diagnoses, misinformed treatments, sickness, and even death.

Women and men have different risks for the onset, expression, course, and treatment response for disease. In this section, we explain why, to improve medical research in women's health and fulfill the promise of the NIH Revitalization Act, the paradigm must shift toward the systematic analysis of sex and gender differences. After describing the stops along the research road, we then present examples of four diseases that have a significant—and different—impact on the health of women and men: cardiovascular disease, lung cancer, depression, and Alzheimer's disease.

## STEP 1: SCIENTIFIC DISCOVERY

### How Can We Ground Women's Health in Basic Science?

Medical research begins with the discovery stage, which includes "bench research" such as work with stem cells and cell lines, and experimental studies with animals and humans. Sex differences must be explored even at the molecular and cellular levels, given that sex differences in disease pathophysiology and prevalence extend beyond the hormonal influences, encompassing each cell and its sex and genotype.[4] To put it simply (and to borrow a phrase from the Institute of Medicine), every cell has a sex.

## THE ROAD TO HEALTH **INEQUITY**

**DISCOVER**

Basic research is usually not designed to study the impact of sex on disease. Animal and human studies typically use males or do not identify sex when females are included.

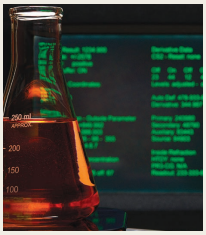
**TEST**

Women are under-represented in clinical trials. Even when they are included, researchers often fail to analyze and report results by sex.

**TRANSLATE**

Sex differences discovered in basic research or clinical trials are often ignored as the findings are translated into clinical practice. Healthcare professionals are often slow to adopt evidence-based guidelines that address sex and gender.

**MEASURE**



Outcome measures are not routinely analyzed or reported by sex.

**1990**

General Accounting Office releases *NIH: Problems in Implementing Policy on Women in Study Populations*. National Institutes of Health (NIH) creates Office of Research on Women's Health.

NIH National Institutes of Health
Office of Research on Women's Health

Animal research, a cornerstone of biomedical investigation, has contributed to almost every medical advance of the last century. Without it, we would not have insulin for diabetes, statins for cardiovascular risk, or chemotherapy for leukemia. To lay a valid foundation for human studies of women's health, animal studies must include female animals and incorporate into the study's design the analysis of differences in outcome by sex.[4,5] Furthermore, an essential component of scientific discovery is the replication of studies, which is virtually impossible without knowing whether the animals involved were male, female, or both.

The discovery phase also includes clinical research in humans with the goal of discovering the pathophysiology of diseases. For instance, researchers may observe how blood vessels react to different stimuli to better understand sex differences in cardiovascular disease, or conduct imaging studies of the brain to identify differences between healthy individuals and those with depression or Alzheimer's disease.

Despite some progress, many basic science researchers do not explore the impact of sex on disease. Their studies, whether of animals or humans, simply do not include females or enough females to analyze nor report on sex differences. There are many examples of discovery research that were not designed to study the impact of sex and thus have blocked progress in women's health.

## STEP 2: CLINICAL TRIALS

### Is Our Discovery Effective and Safe for Women?

Promising new discoveries must be tested to ensure that they are both effective and safe for women. The testing phase includes clinical trials on human subjects. Adequate numbers of women are critical at this phase of research. Designing studies to investigate the impact of sex is critical for understanding the underlying mechanisms of disease, but clinical trials often fail to analyze and report results by sex, significantly hampering their ability to test the safety and efficacy of discoveries.

## STEP 3: TRANSLATING RESEARCH INTO PRACTICE

### How Can We Use Our Research Safely and Effectively?

The third step on the road to health equity for women is the translation of research into clinical practice using a "sex- and gender-specific lens." Translation includes using discoveries to create new prevention, diagnostic, and treatment protocols with the possibility of individualized or personalized treatment. Yet sex and gender differences discovered through biomedical and clinical research are often ignored at this stage and are not integrated into clinical practice. Healthcare professionals have also been slow to adopt evidence-based guidelines that address sex and gender.



WOMEN'S HEALTH INITIATIVE

**1991**

NIH launches Women's Health Initiative, the largest clinical study specifically on women.

# Outcome measures are not routinely analyzed or reported by sex.

## STEP 4: MEASURING EFFECTIVENESS

### What is the Most Effective Way to Prevent, Diagnose, or Treat Disease in Women? What is the Value of this Investment for Women's Health?

The final step on the road to health equity in research is measuring and understanding how sex and gender impact health outcomes, from individual practice to entire healthcare delivery systems. Today, this is especially important as it relates to healthcare reform. Outcome measures, such as quality, are not routinely analyzed or reported by sex, in spite of our understanding that sex differences occur in health and disease and in access to and use of healthcare.[6] For example, HEDIS, the Healthcare Effectiveness Data and Information Set, a tool used by the vast majority of health plans in the United States to measure quality of care and service, does not report results by sex or gender, hindering any evaluation of whether women's outcomes are as good as men's and slowing progress toward improving women's health.

We also cannot measure the value of our investments in biomedical research when we lack sex- and gender-specific research at the discovery, testing, and translation stages. Similarly, we cannot measure the value of the enormous investment in healthcare in the United States without evaluating outcomes in women, who comprise 51 percent of the population. Healthcare reform law requires the collection of certain data—including sex, race and ethnicity—but requires the reporting of health data and outcome data only "to the extent practicable." Yet, without outcomes reported in this way, we risk not achieving the full benefit of healthcare and health system reform.

The IOM notes that there has been little progress in women's health research in the areas of lung cancer and Alzheimer's disease. There has been some progress in depression and major progress for cardiovascular disease (CVD).[4] We need to ensure that the resources allocated to prevent, diagnose, and treat disease are being used effectively and that we are achieving value for our investment. In the following sections, we look at each of these four diseases and discuss both the progress that has been made and the roadblocks that still stand in the way along the road to health equity for women.

#### Sex vs. Gender

This report uses the terms "sex," "gender," and "sex/gender" when discussing the inclusion and implication of biomedical research on women. According to the World Health Organization (WHO), sex "refers to the biological and physiological characteristics that define men and women." Thus, this report uses the term "sex" when discussing the implications of scientific research and clinical trials on women as basic science, discovery and testing most often impact the "biological and physiological characteristics" of women. Gender, according to the WHO, "refers to the socially constructed roles, behaviors, activities and attributes that a given society considers appropriate for men and women." Thus, this report will use the term "gender" when discussing the impact of health systems research (access to care, affordability, utilization, etc.) on women because gender is most often the measure in those types of evaluations. Finally, this report uses the term "sex/gender" when research impacts both the biological characteristics of women's health and the societal roles, behaviors, and activities associated with women.



**1993**

NIH Revitalization Act becomes law, requiring the inclusion of women in clinical research and the analysis of results by sex.

# CARDIOVASCULAR DISEASE

Cardiovascular disease (CVD), which includes coronary artery disease (or ischemic heart disease), stroke, and non-ischemic heart disease, kills more women in the United States than does any other disease. Half of all American women will develop heart disease in their lifetime.[7, 8] The direct costs of cardiovascular disease in this country were estimated at $162 billion per year in 2009.[9] Although progress has been made in identifying sex differences in CVD, much remains unknown.[4]

We know that CVD affects women and men differently at every level, including prevalence, underlying physiology, risk factors, presenting symptoms, and outcomes. Some social and environmental influences on CVD, such as stress and poverty, differ for women and cause differences in the expression, diagnosis, treatment, and outcomes of the disease.[10-12] Certain risk factors, such as diabetes, are more strongly associated with CVD in women than in men.[13] Cardiometabolic disorders of pregnancy (such as preeclampsia, gestational diabetes, and hypertension) and outcomes (such as low birth weight) not only increase women's risk of developing CVD, but also increase the risk for CVD in their children.[14, 15]

Although mortality rates have been decreasing for both women and men, the rate is declining more slowly for women than for men.[16] More women than men die each year of CVD.[7, 8] In addition, CVD death rates for women with diabetes have increased by 23 percent.[17] While women develop ischemic heart disease on average 10 years later than men, younger women who have experienced myocardial infarction have higher in-hospital mortality rates, and women over 40 years of age are more likely than men to die within a year of their heart attack.[18] Racial and ethnic disparities also exist in CVD, with black women experiencing both higher prevalence and higher mortality than white women.[19] The underlying causes for these many sex differences still elude us, and yet only 35 percent of clinical trial subjects in cardiovascular research are women, and just 31 percent of those studies report outcomes by sex.[20]

## Progress

Substantial research on CVD has identified sex differences in the underlying biology. The plaque that causes ischemic heart disease is more diffusely deposited in women's coronary arteries than in men's, and women more often have disease in their smaller blood vessels.[21-23] These differences make the disease harder to diagnosis with the most commonly used diagnostic tests.[22] Sex differences have also been found in acute myocardial infarctions. Autopsies show that younger women who suffer sudden death are more likely to have died as a result of plaque in their coronary arteries eroding; in men, the plaque more often ruptures.[24]

Stroke is the third leading cause of death in women; each year, approximately 55,000 more women than men experience a stroke.[25] Animal studies have shown that the molecular pathways that affect ischemic outcomes in stroke differ in male and female mice, which may have implications for sex-specific treatments.[26]

Premenopausal women are less likely to develop CVD, so researchers have explored the relationship between sex hormones (mainly estrogen) and vascular disease. We know that estrogen receptors exist throughout the vascular system, but still don't understand how this relates to sex differences observed in CVD. There has been little study



**1994**

Centers for Disease Control (CDC) and the Food and Drug Administration (FDA) establish Offices of Women's Health.

## We know that CVD affects women and men differently at every level, including prevalence, underlying physiology, risk factors, presenting symptoms, and outcomes.

of estrogen receptors in the smaller blood vessels, where disease-producing symptoms are more frequently found in women.[27]

Cardiometabolic disorders of pregnancy, such as preeclampsia, put women and their children at a higher risk for CVD.[28] Preeclampsia, characterized by elevated blood pressure and excess protein in urine, complicates approximately 5 percent of pregnancies, and rates are increasing in the United States. Researchers have identified warning signs such as a deficiency of a certain protein (vascular endothelial growth factor) that helps build new blood vessels or the presence of another one (sFlt1) that shuts the vessel-building process down. These early discoveries have also led to hypotheses regarding potential clinical interventions and to practical measures we can take today: doctors are now encouraged to ask about a history of preeclampsia when assessing a woman's risk for CVD.[29] Using the "stress test" that is pregnancy to better understand CVD may lead to new preventive and therapeutic protocols for both women and men.

Large clinical trials including only women, such as the Women's Health Initiative (WHI) and the Women's Health Study (WHS), have focused on the prevention of CVD and greatly influenced medical practice. We now know that hormone therapy in menopausal and post-menopausal women that includes estrogen and progesterone can increase the risk for stroke and pulmonary embolisms,[29, 30] and that aspirin helps prevent strokes in women over the age of 65, which is not the case in men.[31, 32]

Trials that include both women and men have explored the utility and safety of statins for preventing CVD.[33, 34] While we know that statins can prevent recurrent events in those who already have CVD, questions remain regarding the most appropriate use of statins in women to prevent the disease from developing in the first place.[35] A current study of 20,000 women and men is evaluating the use of omega-3 supplements and Vitamin D to prevent CVD and the study is designed to determine the outcomes by sex.[36] The American Heart Association has integrated all of this research on sex differences into three sets of evidence-based guidelines for preventing CVD in women, most recently updated in 2011, with a new guideline focused on prevention of stroke in women published in 2014.[37]

### Roadblocks

Although we know more about CVD than most other diseases, there is much we do not understand about the physiologic mechanisms that underlie its sex differences. While there have been advances in the study of sex differences in vascular function, this has not connected directly to understanding sex differences observed in CVD.[27] Most animals used in research in the areas of physiology, pharmacology, and endocrinology—the basic sciences most closely aligned with CVD research—are male or unspecified.[38] Sex may even influence the behavior of stem cells, yet sex has not been addressed in cardiovascular stem cell research.[39]

Although the number of women in NIH-sponsored clinical trials has increased since passage of the NIH Revitalization Act in 1993, it is still not enough, given the prevalence of CVD in women. In mixed-sex CVD trials, only one-third of the subjects are women, and only one-quarter to one-third of those trials report their outcomes by sex.[20, 40, 41] When researchers conducted an extensive review of



**1999**

FDA approves Plan B, the first emergency contraceptive.

## In mixed-sex CVD trials, only one-third of the subjects are women, and only one-quarter to one-third of those trials report their outcomes by sex.

two decades of medical literature (1991–2011) to assess the comparative effectiveness of major treatment options for coronary artery disease in women, 65 percent of articles that were excluded were omitted because they had failed to report sex-specific data.[42] **Figure 1** provides an overview of the number of articles on coronary artery disease (CAD) reporting data on women per year from that review. "On average, [just] 17 percent of the articles comparing treatment strategies for CAD reported sex-specific outcomes."[42] In the 28 studies that were included in the analysis, only 28 percent of the trial participants were women, in spite of the fact that women represent 46 percent of the population with coronary artery disease. Only a few of the studies conducted subgroup analyses and none reported data by sex and race/ethnicity groups.[42] This lack of parity in enrollment in trials of treatment for cardiovascular disease leaves holes in our knowledge of the risk and benefits of treatment for coronary artery disease in women.[42-44]



An increasing number of trials have evaluated the safety and efficacy of invasive and non-invasive interventions for acute ischemic syndromes and myocardial infarction, which have helped to guide practice.[42] Unfortunately, these studies often lack the statistical power to make definitive conclusions on the efficacy and safety of these interventions in women. They also often do not report data by sex or other subgroups of women, such as age or race/ethnicity, that would assist in understanding risks and benefits of the interventions.

Further, it seems that physicians, even though they are aware of the American Heart Association's guidelines, are not consistently following them.[45] Diagnostic tests for CVD have not kept up with the science. For instance, the blood concentration of biomarkers that indicate acute coronary syndromes differ in women and men, but tests continue to use the cut-off level associated with men.[46] Similarly, we know that women are more likely to experience ischemia with non-obstructive coronary artery disease,[22] but the gold-standard diagnostic test continues to be cardiac catheterization, which may be inadequate for diagnosing the disease in women. Intravascular ultrasound and fractional flow reserve may be better suited, but these are less frequently used and not well studied.[47]

**2000**

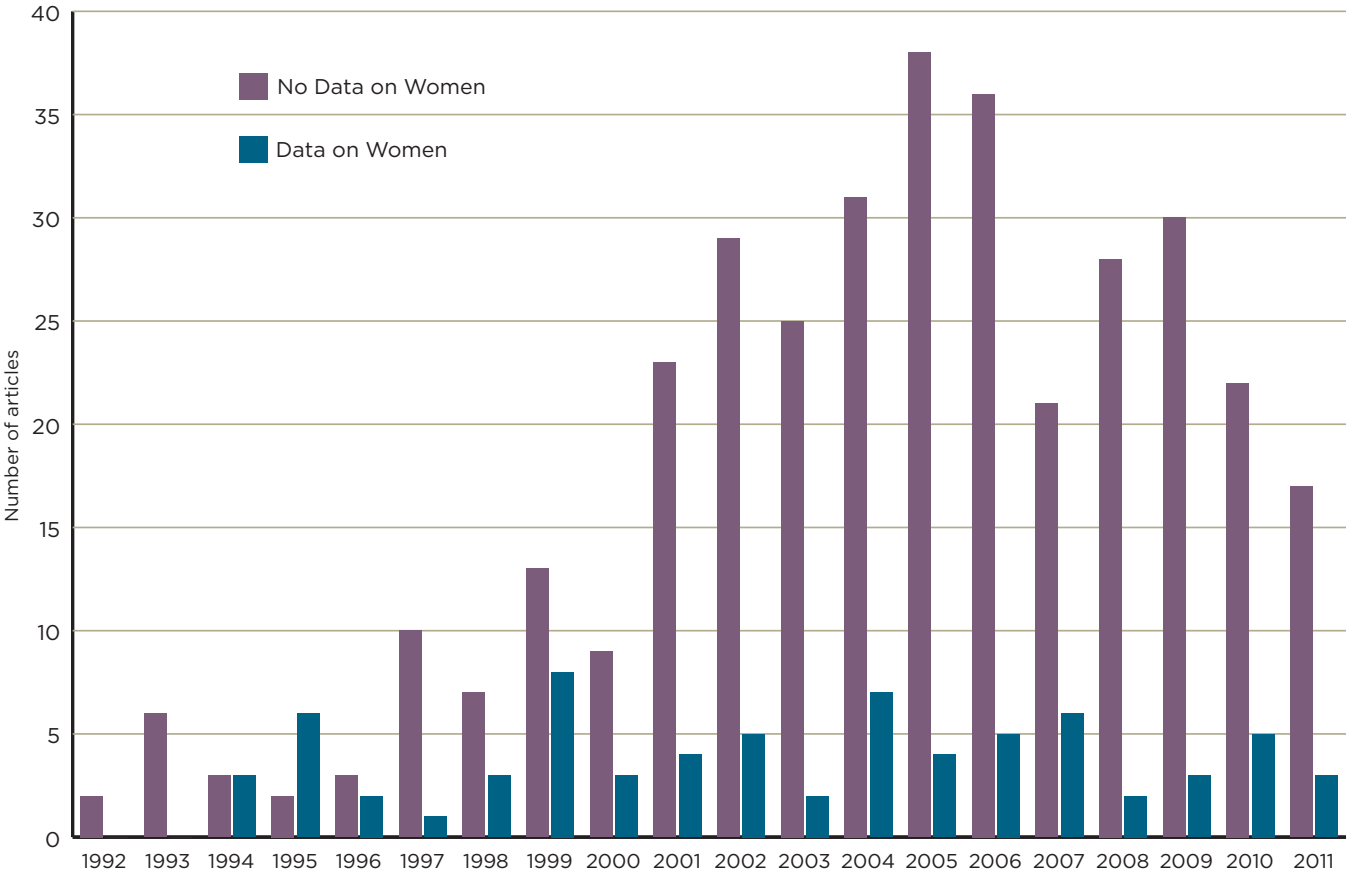
U.S. Surgeon General releases first comprehensive breastfeeding blueprint.

**2000**

NIH creates "Building Interdisciplinary Research Careers in Women's Health" (BIRCWH) mentoring initiative.

FIGURE 1:

## Journal Articles on Treatment of Coronary Artery Disease




Source: Dolor, R. J., Melloni, C., Chatterjee, R., LaPointe, N. M. A., Williams, J. B., Coeytaux, R. R., et al., *Treatment Strategies for Women With Coronary Artery Disease,* Agency for Healthcare Research and Quality, August 2012.



**2001**

**Surgeon General issues report on women and smoking.**

# LUNG CANCER

Lung cancer takes the lives of more U.S. women than breast, ovarian, and uterine cancers combined. Women have a higher incidence than men of adenocarcinoma (i.e., a type of cancer that begins in the glandular cells), the most common type of non-small cell lung cancer and the one that accounts for over 80 percent of lung cancers. Lung cancer incidence and mortality is particularly striking among young, female nonsmokers.[48, 49] While about one in five people who are diagnosed with lung cancer never smoked, nonsmoking women are three times more likely than their male counterparts to get it.[50-52] Racial and ethnic disparities also exist: African-American women are diagnosed with lung cancer at a similar rate to white women despite smoking fewer cigarettes.[53] Many complex factors, from genetics to behavioral and environmental conditions, contribute to these outcomes. Sex and gender differences clearly play an important role in preventing, diagnosing, and treating lung cancer in women.



## Progress

Differences that increase women's susceptibility to lung cancer may start at the molecular level. Genetic mutations associated with certain cancers occur at a higher frequency in women, Asians, and people who never smoked.[51, 54] Researchers have also found that sex hormones, particularly estrogen, influence lung cancer development and mortality. Estrogen triggers estrogen receptors, which are present on 45–70 percent of non-small cell cancers, and may also play a role in activating certain genes within these tumors.[51] A possible link between estrogen and lung cancer growth has raised questions about the impact of combination hormone replacement therapy (HRT) in women with lung cancer, with at least one large clinical trial demonstrating an increased risk of dying when HRT is taken after the lung cancer develops.[55] Estrogens are also thought to make women metabolize nicotine faster than men, a finding that may explain smoking behavior and decreased efficacy of nicotine replacement therapy in women.[51, 56] These findings demonstrate the importance of understanding sex differences in lung cancer at the biological level to prevent cancer, improve treatment, and increase survival rates for the disease.[51]

These basic discoveries regarding estrogens have led researchers to explore anti-estrogen therapy in lung cancer treatment. While this therapy has not resulted in significant differences in the incidence of lung cancer, there are data to suggest that anti-estrogen therapy may decrease mortality rates in women who develop lung cancer.[51, 55, 57, 58]

However, the most significant advancement in lung cancer therapy in the last several decades (for both women and men) is that of personalized medicine, where unique molecular and genetic mutations guide specific drug therapies. Interestingly, sex has been found to play a dominant role in the incidence of specific genetic mutations. For example, an adenocarcinoma of the lung in a woman is far more likely to express specific genetic mutations in proteins found on the surface of cells (i.e., the epidermal growth factor receptors, or EGFR) than a similar tumor present in a man, and these mutations are predictive of a marked therapeutic response to specific targeted therapies (i.e., tyrosine kinase inhibitors (TKI), gefitinib and erlotinib.)[51, 57, 58] The inclusion of more women in clinical trials has resulted in evidence that some lung cancer treatments work better for women. In fact, 82 percent of patients who


**2001**

**Institute of Medicine (IOM) releases *Exploring the Biological Contributions to Human Health: Does Sex Matter?***

**While about one in five people who are diagnosed with lung cancer never smoked, nonsmoking women are three times more likely than their male counterparts to get the disease.**

responded to TKI therapy in the initial clinical trials were women, making sex and smoking history the two most important factors in predicting EGFR status. This targeted therapy has become one of the most effective drugs used in lung cancer treatment, but without assessment of sex differences, this potential benefit would have been missed. This is an important example of why FDA medical product evaluations should present efficacy data separately for men and women.

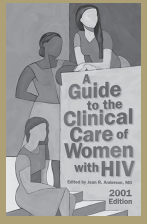
## Roadblocks

While more women are participating in lung cancer clinical trials, they—particularly racial and ethnic minority women—remain less likely to enroll in trials than men.[51, 59] Even when studies include women, they often fail to stratify data by sex or include hormone status, HRT information or other gender-specific factors, making it difficult to uncover differences in lung cancer incidence, prevalence, and survivability between men and women.[51]

We also know of disparities in treatment and survival rates for ethnic minorities, including black women. For example, black patients are 37 percent more likely to develop lung cancer and 25 percent more likely to die from it than white patients, even though they smoke less.[60, 61] Researchers estimate that the survival rates among blacks with early-stage lung cancer would catch up to those of whites if they had equal access to health-care options.[62] Black patients are less likely than whites to be offered and accept surgical treatments, even when controlling for socioeconomic status,[63] and are less likely to receive chemotherapy.[64] Overall, African-Americans are diagnosed at more advanced stages and are more likely to die in the hospital after surgery. Research has shown that social and genetic factors may also increase the likelihood that blacks will die from the disease.[63] Recognizing these racial disparities and the fact that sex differences occur, there has been a paucity of research that has reported on black women more specifically.

Even though we have begun to understand some of the significant biological sex differences related to lung cancer risk and survival—especially at the biomolecular level—we need more research to better understand how to use this information to prevent and treat lung cancer.[51] More research is needed to understand why women who have never smoked are more likely than men to develop adeno-carcinoma, the role of estrogens in lung cancer incidence, metastasis and mortality, and the mechanisms that lead to an increased incidence of certain gene mutations in women and their relationships to the development of lung cancers that occur in more than one location.[51]






**2001**

U.S. Dept. of Health and Human Services releases first comprehensive guide to clinical care for women with HIV.

**2002**

Women's Health Initiative hormone therapy trial is terminated. Higher breast cancer risk and lack of benefit are cited.

# DEPRESSION

Depression is the world's leading cause of disease burden, affecting an estimated 350 million people (16 million in this country alone), with women disproportionately affected.[65] Its social and economic burden is enormous and increasing; every year the direct costs associated with depression in American women exceed $20 billion.[9] Every day in our nation, twice as many women than men are suffering from depression, and women are 70 percent more likely than men to suffer from it over the course of their lives.[65, 66]

The causes of these sex differences remain largely a mystery. Despite similar levels of disability in men and women with depression, women experience a 50 percent higher disease burden than men.[67] The impact extends beyond the individual. Children of women with depression are at risk for poorer developmental and adult outcomes.[65] Employers lose approximately 5.6 hours per week during an employee's major depressive episode.[68] Collectively, these data highlight how significantly major depression impacts everything from individuals and families to societies and economic systems, with the burden shouldered largely by women. This burden will only grow: by 2050 depression is projected to afflict more than 46 million individuals in the United States. Additionally, depression often co-occurs with many other chronic diseases, including CVD and metabolic disturbances such as diabetes, for which women are at higher risk. The co-occurrence of depression with these chronic diseases is associated with higher mortality and morbidity-related consequences, further increasing the burden for women.[69-72]

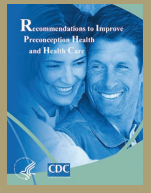


## Progress

Depression is often accompanied by an impairment in biologic pathways that regulate hormone production (i.e. endocrine dysregulation), meaning that the production and levels of sex steroid hormones (produced primarily by the ovaries and testes) and/or stress hormones (such as cortisol) are abnormal. Women are at a higher risk for these conditions. We also know that, when certain adverse prenatal conditions occur, adult female mice express "depressive-like" behaviors more than male mice.[69, 73, 74] Animal studies in genetically engineered mice have further demonstrated that this sex difference may vary depending on the genotype.[69, 74-77] Clinical and basic science research have led to the discovery of genetic abnormalities in regions of the brain associated with the regulation of mood, allowing links to be made between genes, brain, and behavior.[69, 77]

Basic research into drug development has shown that women metabolize drugs differently than men. For example, women have higher concentrations of certain enzymes that metabolize drugs, and these levels can be further raised by smoking or lowered by oral contraceptives.[78] Perimenopausal changes in hormones have affected responses to drug treatments for depression.[79-82] Further, sex-steroid hormones, such as estradiol and progesterone in women, interact with neurotransmitters in the brain, including dopamine, serotonin, glutamate, and GABA, which can either enhance or attenuate drug response.[83] Recently, neurosteroids (sex hormones produced in the brain itself) have been proposed as potential therapeutic targets.[84]

Research now clearly demonstrates that sex hormones play a role in the development of brain regions that regulate mood and the response to stress. Major endocrine




**2006**

CDC publishes *Recommendations to Improve Preconception Health and Health Care.*

**Every day in our nation, twice as many women than men are suffering from depression, and women are 70 percent more likely than men to suffer from it over the course of their lives.**

changes throughout a woman's life, including puberty, pregnancy, and menopause, have been directly linked to increased risk of depression. A recent study found that more than 40 percent of depressive episodes among mothers were experienced postpartum.[85] In adulthood, sex hormones interact with stress hormones to regulate brain activity under stressful conditions.[86, 87] Importantly, women with depression show disruptions in the relationship between the sex hormone estradiol, stress hormones and brain activity.[88, 89] Understanding how sex hormones change the way our brain deals with stress will help elucidate sex-dependent pathways that lead to depression, which will, in turn, help researchers design clinical trials.

Some clinical trials are starting to return useful information. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study, for instance, suggests a slightly higher rate of remission for women than men following antidepressent treatment,[90] although the reasons why remain unknown. This is an example of how crucial it is that the FDA ensure medical product evaluations present efficacy and safety data separately for men and women.

## Roadblocks

Basic neuroscience, pharmacology, and physiology—all related to depression—continue to have strong sex biases. In neuroscience, despite substantial sex differences in risk for most brain disorders, animal studies that rely exclusively on males outnumber studies in females 5.5 to 1. Fewer than 45 percent of animal studies on anxiety and depression use female lab animals, despite the fact that these disorders are twice as common in women.[5]

We know that these sex differences originate during fetal development,[71, 73, 74] but research into why is unfortunately understudied and underfunded. Further, despite ample evidence of sex differences in responses to drug treatments, sex-dependent research in how the body metabolizes drugs (i.e., pharmacokinetics) is rare. Basic science and drug research are often marred by a desire to avoid inconveniences associated with potential variations across the menstrual cycle in female animals. However, designing studies to investigate these sex differences can also uncover valid similarities between the sexes when factoring in sources of variability that are often associated with being male (e.g., aggression to assert and maintain social order, or fighting).[91]

Research that pays attention to a woman's reproductive stage is critical for informing treatment choice and more research is needed into the risks and benefits of antidepressant and anti-anxiety treatments during pregnancy. Drug interactions, too, remain understudied. We know little, for example, about the interaction between antidepressants and oral contraceptives, despite the fact that these are two pharmaceuticals that reproductive-age women commonly use and the potential for the two drugs to influence each other.[4] This is another important example of the type of sex-specific research that the FDA could require drug manufacturers to evaluate.

Women with depression are misdiagnosed from 30 to 50 percent of the time. They are more likely than men to have symptoms of fatigue, sleep disturbance, anxiety, and pain, which are often ascribed to illnesses other than depression. Men, in contrast, may exhibit symptoms of depression that often include anger, aggression, substance abuse and risk-taking behaviors.[92] These differences highlight the importance of sex-specific research for both sexes, not only women.




**2010**

IOM publishes *Women's Health Research: Progress, Pitfalls and Promises.*

# ALZHEIMER'S DISEASE

Women, in general, have better verbal memory than men, a difference that emerges after puberty and continues, in healthy individuals, for life. However, in women at risk for Alzheimer's disease (AD), memory steeply declines just after menopause. A woman's overall lifetime risk of developing Alzheimer's disease is almost twice that of a man, and not only because women live longer. Even when compared to men with similar genetic risk, women have a higher overall risk for the illness. To complicate matters, other chronic diseases with known sex differences, such as depression and cardiovascular disease, are themselves risk factors for Alzheimer's disease. Two-thirds of the 5.1 million people currently suffering from Alzheimer's disease are women.[93, 94] Women are also the primary caregivers of adult loved ones with the disease, meaning they shoulder both the risks and the burdens. Alzheimer's disease costs society (families, businesses, and government) $300 billion per year, a number that may triple in the coming years as baby boomers age.[95]



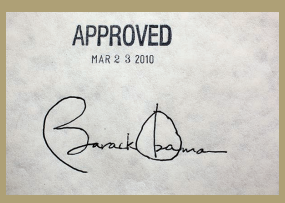
## Progress

The field of sex differences in Alzheimer's disease is in its infancy and still in the discovery phase. Recent animal studies have connected estradiol, the primary form of estrogen that affects the brain, to known risk factors for Alzheimer's disease.[96-99] Current research is focusing on sex differences early in the aging process, as women transition through menopause.[100] Evidence suggests that ovarian decline plays a key role in the changes to the brain as women age. Importantly, different regions of the brain atrophy at different rates depending on sex,[101] a finding that may relate to more severe Alzheimer's pathology found in women than men in postmortem brain studies.

Investigators leading recently funded clinical trials are beginning to be aware of the importance of a sex-dependent lens in Alzheimer's disease research. The hope is that knowledge of sex differences in memory function and brain aging can lead to new sex-specific treatments and prevention strategies for Alzheimer's disease. The Study of Nasal Insulin to Fight Forgetfulness (SNIFF) is a phase II/III study evaluating whether a specific type of insulin, administered as a nasal spray, improves memory in adults with cognitive impairment or early AD. The trial, which includes men and women 55-85, is based on previous findings that insulin resistance and reduced cerebral spinal fluid insulin levels have been observed in AD patients. The Anti-amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) trial is an anti-amyloid study testing the therapeutic effects of the monoclonal antibody drug, solanezumab. The trial will be carried out in adults ages 65-85 who are asymptomatic but at high risk for AD and show early evidence of amyloid beta accumulation. Both trials are enrolling men and women and thus will have the ability to assess sex differences in outcomes.

## Roadblocks

Considering Alzheimer's disease's enormous and unbalanced burden on women as patients and caregivers, too little research on sex differences is taking place and most studies have not been designed to study sex differences. This is in part due to the fact that, until recently, most experts in the field believed that sex differences in the risk for Alzheimer's disease were simply



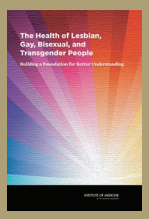

**2010**

Affordable Care Act (ACA) becomes law, requiring the collection and reporting of data on health disparities by race, sex and other factors.

**A woman's overall lifetime risk of developing Alzheimer's disease is almost twice that of a man, and not only because women live longer.**

due to women living longer. Further, once the illness emerges symptomatically and is severe, the differences between the sexes in pathology are smaller than sex differences early in the natural history of the illness just post-menopause when memory first declines. Thus, in order to understand the pathways causing sex differences in Alzheimer's risk, individuals need to be studied early in the course of the illness, prior to the onset of severe symptoms—a difficult task given the necessity to identify those *at risk*. In fact, this early period is a critical time on which the field will be focusing the next generation of treatment trials. Knowledge of sex differences in memory decline can provide a unique window into identifying those at risk for the illness in order to bring them into treatment early, and ultimately, prevent the illness. Thus, it is imperative, given the potential worldwide financial impact of an aging population, that studies of Alzheimer's disease focus on understanding sex differences and then quickly move to translate this knowledge into prevention strategies and treatments.






**2011**

*Health of Lesbian, Gay, Bisexual, and Transgender People* is released by the IOM.

# WOMEN'S HEALTH EQUITY ACTION PLAN

The historic 1993 NIH Revitalization Act, born from a vision of healthcare based on evidence that incorporates the best knowledge about sex/gender and race/ethnicity differences and similarities, made the inclusion of women and minorities in health research a national priority. Despite progress during the past 20 years, women have still not achieved equity in biomedical and health-outcomes research. As long as this continues, we will be hindered in our ability to identify important sex and gender differences that could benefit the health of all.

## Don't Leave Women's Health to Chance

Research on sex and gender differences must become the norm, not the exception, in the United States in order to improve the health and well-being of all. As noted earlier, the science that informs medicine—including the prevention, diagnosis, and treatment of disease—does not routinely or adequately consider the crucial impact sex and gender may have on health and disease. And when we fail to consider sex and gender, we are leaving women's health to chance.

To fulfill the promise of the NIH Revitalization Act in achieving equity in research, a continued commitment and strong oversight by federal policymakers to a sex- and gender-based research agenda is required. Our leaders in government and in health research, must ensure that all health agencies are actively engaged in women's health research and the evaluation of sex differences across the lifespan. Health agency leaders must also push the design, analysis, and reporting of health research by sex. They can fully implement both inclusion and reporting requirements and give funding priority to studies that advance and communicate this research.

We cannot depend only on government action, however, to achieve equity in health research. In a new era of personalized medicine, a multi-stakeholder approach is the best way to ensure quality, safety, value, and efficacy in the methods we use to address disease. All stakeholders must exercise influence in their spheres. These include:

- Government officials
- Policymakers
- Attorneys
- Businesspeople
- Physicians and healthcare professionals
- Pharmaceutical, biotechnology, and medical device companies
- Medical schools and other institutions of science education
- Women's health organizations
- Disease-specific advocacy groups
- Scientific journal editors
- Professional medical organizations

All have a responsibility to ensure that investigators consider sex and gender throughout all stages of research.

## Hold Federal Agencies Accountable

We recommend:

- The government and other funding agencies ensure that the design of clinical studies includes a consideration of the sex of the subject, adequate participation of women, and the reporting of sex-stratified findings. The current policies at NIH, AHRQ, and the CDC must be more actively enforced and strengthened. Proposals



**2011**

IOM panel recommends that insurers provide eight preventive services for women without cost sharing, including contraceptives and well-woman checkups.

that include adequate numbers of women and men and a robust plan for analysis, publication, and distribution of findings should receive higher scores and priority for funding. New mechanisms for research opportunities in women's health should be developed and funded.

- The FDA require all medical product evaluations to include efficacy and safety data separately for men and women. Before approving or labeling all drugs, devices, and biologics regulated by the FDA, reviewers should require data and analyses by subgroups, such as sex, age, and race/ethnicity. These data and analyses should be publicly available.
- The Secretary of Health and Human Services ensure that the oversight and direct evaluation of the implementation of healthcare reform include collection, analysis, and reporting of data stratified by sex, age, and race/ethnicity.

## Promote Transparency and Disclosure Regarding the Absence Of Sex- and Gender-Based Evidence in Research, Drugs and Devices

We recommend:

- Medical device and pharmaceutical labels include a warning or disclaimer, similar to those currently listed for drugs and devices not adequately tested on children, the elderly and pregnant women, when clinical testing has not included adequate numbers of female subjects.
- Researchers publishing in peer-reviewed journals be required to disclose, in a standardized format (similar to a nutritional label), basic information about how the study addresses sex, including the share of subjects that are women (or female animals); the inclusion of racial and ethnic minority women; and whether the research data are analyzed by sex.
- Establishment of an online gateway with a mandatory requirement that investigators provide access to sex-stratified analyses derived from research that is conducted and supported by NIH, CDC, AHRQ, and other government agencies. NIH and other research agencies already require the inclusion of adequate numbers of women and of underrepresented groups in clinical trials, as well as the reporting of such inclusion. These data, however, are not available to other researchers and clinicians. The availability of data for analysis by third parties and for public review could greatly accelerate our understanding of sex differences and similarities, and why they matter.
- An annual review of peer-reviewed scientific journals to be performed by an independent organization. This review would assess how well and how often they present sex- and gender-based research. Journals that consistently publish articles that fail to report on sex differences will receive a rating that cautions readers that the research results are not equitable between the sexes.



## Expand Sex-Based Research Requirements

We recommend:

- Having all biomedical research, where applicable, include adequate numbers of female research animals and report the sex of the animals in the study. Studies of sex differences must start at the cellular and animal-research levels. The NIH and FDA should base funding and regulatory approval on research plans that either include adequate numbers of female subjects or provide a sound rationale for why the research focuses on only one sex.

**2011**

The CDC's health and disparities report highlights differences due to sex, race and ethnicity, income, education, and other characteristics.

- Expanding the mandate of institutional review boards to require that research plans include adequate numbers of female and male human subjects and lab animals. Professional organizations representing scientists should advocate for inclusion of female subjects.
- Making the reporting of the sex of lab animals and human subjects a criteria for publication in medical and scientific journals. Those journals should also encourage presentation of sex-specific results.

## Adopt Clinical Care Practices and Training Curricula That Incorporate a Sex- and Gender-Based Lens in Care and Research

We recommend:

- Educators of health professionals create tools and resources that will improve providers' ability to personalize medicine based on sex and gender.
- Medical education, post-graduate medical education, nursing and allied health education, and graduate-level scientific training programs integrate sex and gender considerations into existing curricula. The next generation of researchers and clinicians should be informed about the essential role of sex differences in research and its translation to healthcare. Medical and health professional schools and PhD programs should educate trainees about sex differences in diseases and, thus, the importance of testing hypotheses in lab animals and human subjects of both sexes.



## Make Your Voice Heard

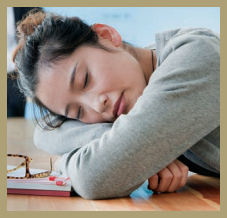
All women and men can play a role in making sex- and gender-based research the norm. They can petition their policymakers to ensure that woman are included in all phases of medical research and that sex differences are studied and evaluated at all levels. They can demand that the findings be translated from bench to bedside for the benefit of both women and men. They can ask their doctors if their prevention strategies, diagnostic tests and medical treatments are based on research that included women. Until scientific and medical research on sex and gender differences becomes the norm, women and the health professionals who care for them should know that these health inequities exist and be warned to use caution when using this research to inform care and treatment.

Policymakers, the research community, industry, advocacy organizations, and health professionals can take specific actions to strengthen and improve the scientific process, from discovery to measurement of health outcomes.

## It's Time to Act

As this report has documented, failing to take sex and gender into account at all stages in the research process has contributed to enormous inequities in women's health. This, in turn, has had a significant impact on the safety and efficacy of preventive measures, treatments, and the use of medical products by women and men alike.

Without sex- and gender-specific approaches to research and healthcare, our investments in both will not provide us with the value so crucial to bettering the overall health of populations, improving the quality of care, and controlling the growth in health-related expenditures. It is time to act. Future generations are counting on us.



**2013**

FDA lowers dosage recommendations for sleep aids containing zolpidem after data show that the drug is metabolized more slowly in females.

# NOTES

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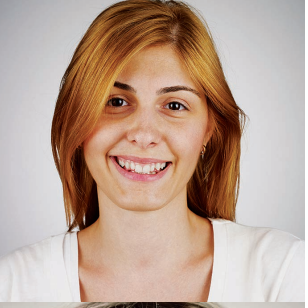

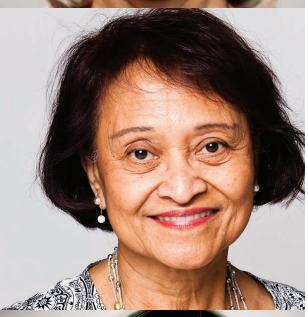
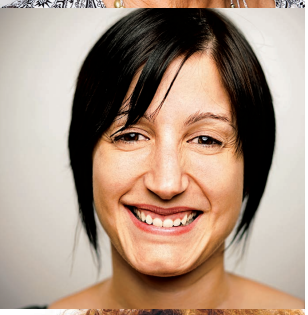

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