

# NOT JUST FOR MEN

Researchers and doctors must dig deeper into gender differences before they can provide women with better treatments

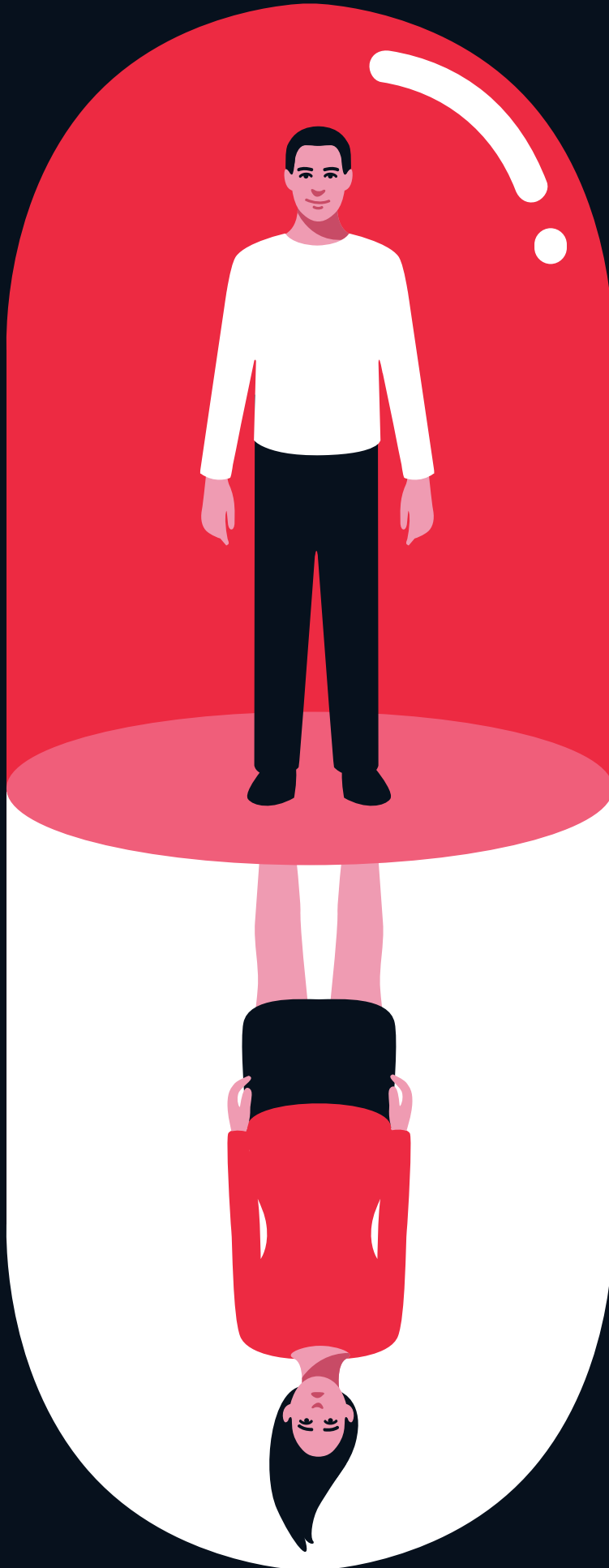
BY MARCIA L. STEFANICK

IN JANUARY 2013 THE U.S. FOOD AND DRUG ADMINISTRATION CUT THE recommended dose of the nation's most popular sleep drug, Ambien, in half for women but not for men. The FDA had determined that 15 percent of the 5.7 million American women using zolpidem products (the active ingredient in Ambien) were experiencing driving impairment eight hours after taking the drug, compared with 3 percent of the 3.5 million male zolpidem users.

Researchers had known for a long time that women, on average, clear zolpidem from their body much more slowly than men do. Indeed, drug metabolism, tolerance, side effects and benefits differ significantly between the average man and woman for many widely prescribed medications, with women having a 50 to 70 percent higher chance of an adverse reaction. Body size, proportion of fat to muscle and a host of other factors, including hormonal influences, account for these differences. But physicians rarely consider these dynamics when writing prescriptions. Ambien, which now comes in bottles with pink (low dose) and blue (original dose) labels, is a rare example of a "sex-specific" medical recommendation.

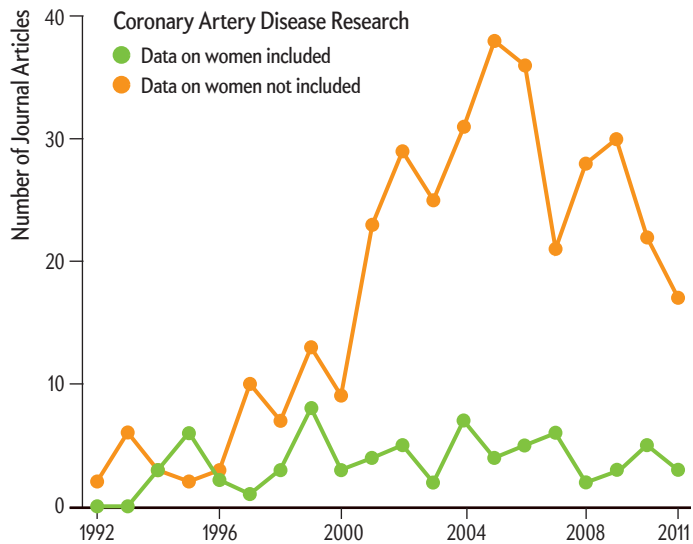
Drug-dosing problems are just one example of how the health care system is blind to biological sex differences. As a result, women are too often treated like men. Moreover, the system can be blind to gender bias; some disorders are considered "a man's" or "a woman's," even when both sexes suffer from them. Doctors often fail to diagnose stereotypical "male" conditions in women, and vice versa, until the condition has become dangerous.

These problems arise from a serious gap in our understanding of sex differences. The vast majority of animal research has been conducted only on males, mostly on rodents. And women have been grossly underrepresented in human clinical trials. Even when both sexes are included, sex-specific analyses are generally not reported—and because most subjects are men, the findings may not pertain to women. A 2003 review of 258



## Research Bias

Medical studies often involve only male subjects or do not break out statistics for women if they are included. For example, a 2012 analysis of coronary artery disease therapies found that 355 of 427 journal articles (83 percent) either included no data for women or did not analyze data for women versus men. The paucity of research makes it difficult for doctors to assess treatments that could help women.



cardiovascular treatment trials, for example, revealed that only 27 percent of the participants were women and that only a third of the trials with men and women reported data by sex.

Not surprisingly, no one understood why a young woman hospitalized with a heart attack was twice as likely to die as a young man. Failure to include women in biomedical research was exacerbated by 1977 Food and Drug Administration guidelines that barred women of childbearing potential from participating in phase I (safety) and phase II (efficacy) trials, whether they were planning a pregnancy or not. Although the FDA now allows for inclusion of pregnant women in research that does not threaten pregnancy, few drugs are approved for pregnant women because safety and effectiveness data are not available.

### FIXING THE PROBLEM

CHANGES IN PRACTICES have been long in coming. In 1990 scientists, advocates and members of Congress pushed the National Institutes of Health to establish the Office of Research on Women's Health. In 1991 the late cardiologist Bernadine Healy, the first and only woman director of the NIH, launched the Women's Health Initiative, which enrolled nearly 162,000 women across the U.S. The study led to important changes in clinical care; without it, for example, physicians might still be-

### IN BRIEF

**Doctors often assess** women patients as if they were men because most medical research is based on male animals and men. This can lead to poor or dangerous therapies.

**Physicians miss,** or improperly diagnose, heart disease in women because their symptoms differ from those men typically experience. Bias is widespread in screening for mental illnesses, too.

**Progress is under way,** but mandates may be needed to ensure that female biology is properly, and widely, included in testing protocols, medical diagnoses and treatments.

lieve they should put most older women on hormone therapy, leading to many more heart attacks and strokes and cases of breast cancer. The 1993 NIH Revitalization Act required enrollment of female (and minority) participants in federally supported phase III trials—those designed to determine how a new treatment works in a large group. The act did not, however, require enrollment of enough women to determine how a given treatment affected women specifically.

More change came in 2001, when a landmark Institute of Medicine (IOM) report emphasized the important role that “sex” played in the basic biology that underpins health care. It concluded that “every cell has a sex.” Yet almost no cell biologists consider, or even know, the sex of the cells or tissues they study. Nor do they address how sex chromosomes affect the systems they are investigating. The IOM report defined sex as a biological quality or classification of sexually reproducing organisms, generally male or female, derived from chromosomes and sex hormones. Gender was defined, in human studies, as sociocultural—a person’s “self-representation as male or female.”

This concept can be expanded to include gender norms (social expectations of “masculine” and “feminine” behaviors) and gender relations (how people react to one another because of gender), all of which can exert powerful influences on biology. For example, men are generally stronger than women not only because of biological factors such as larger muscles but also because of gender roles: in many societies, men lift and carry most of the heavy objects. Another example might be the twofold greater incidence of (unipolar) depression in women, which may result from an interaction of biological and social factors, such as women being more likely to be sexually assaulted.

Since the IOM report, scientists, academicians and health policy advocates have been urging their institutions, journals and government agencies to confront the need to include women and female animals in research and to study sex differences. In 2009 the Gendered Innovations project at Stanford University engaged collaborators across the U.S., Canada and the European Union to develop practical methods for sex and gender analysis and to track progress on including sex and gender in research. In 2010 the Office of Research on Women's Health issued a strategic plan that identified the need to integrate sex and gender perspectives in basic science and medical research.

That same year the Canadian Institutes of Health Research went further and began asking grant applicants to indicate whether sex or gender was accounted for in their study proposals. Four years later a May 2014 notice in the journal *Nature*, written by NIH director Francis Collins and Janine Clayton, director of the Office of Research on Women's Health, unveiled policies designed to ensure that NIH-funded preclinical research consider both females and males, as well as the sex of cells. And in January 2016 the NIH began to require that sex as a biological variable be factored into

research designs, analyses and reporting. If grant applicants propose to study only one sex, they must present persuasive justification for doing so. In contrast to the Canadian Institutes, however, the NIH did not address the influence of gender on biology.

## A MAN'S DISEASE

GENDER BIASES profoundly influence diagnoses and treatments and therefore health outcomes. Despite years of “Red Dress” campaigns, most people and many physicians still think of heart disease as a man's disease. They are surprised to learn that heart disease is the number-one killer of U.S. women, far exceeding deaths from breast cancer. Younger women, in particular, often go undiagnosed because physicians do not consider the possibility. Furthermore, women commonly report a range of symptoms beyond chest pain, which is the key complaint of men, including back pain, nausea, headache and dizziness. Physicians often refer to these as atypical symptoms because men do not report them.

In addition, although men and older women are likely to have a blockage in one or more of the coronary arteries from localized plaque—a buildup of cholesterol, fat and other substances—younger women are more likely to have diffuse plaque that lines and narrows the entire artery. Even though this leaves the heart muscle with an inadequate blood supply, no specific blockage is detected. A woman may be diagnosed as “free of heart disease” even though she is at high risk of a fatal heart attack. Fortunately, newer diagnostic tests can detect this nonobstructive disease, along with other issues more common for women. But for those tests to work, a physician has to consider the possibility that a young woman might have heart disease and order them. Research continues to reveal sex differences in risks and beneficial treatments, but prevention and treatment guidelines for women are still based predominantly on male data.

Pregnancy, now recognized as a major cardiovascular stress test, also contributes to sex disparities, yet researchers have only recently begun to realize the serious long-term consequences. Pregnancy-related hypertension and preeclampsia, as well as gestational diabetes (high blood glucose developed during pregnancy), increase a woman's chance of developing subsequent cardiovascular disease nearly twofold, as well as her risk of developing type II diabetes.

## HARD TO DECIPHER

SEX DIFFERENCES and gender biases influence medical diagnoses and treatments for *everyone*. Osteoporosis, characterized by reduced bone strength, is considered a woman's disease because white women have twice the lifetime risk of fracturing a bone than white men do. Fracture prevention trials have included few men. Yet men account for nearly one in three hip fractures, and their medical outcomes are worse.

Men are more susceptible to viral, bacterial, para-

sitic and fungal infections than women are, although women have greater rates of sexually transmitted infections such as HIV and herpes simplex virus 2. On the other hand, the more robust immune system of women may explain why they constitute 70 percent of the 20 million Americans with autoimmune diseases, in which the immune system attacks one's own body tissues. Pregnancy may play a role here as well. Some fetal cells cross into the mother's blood and are found in her circulation decades later, and they have been implicated in some autoimmune diseases.

Sex and gender also shape neurological and mental diseases. Accumulating evidence suggests that the placenta of the male fetus responds to environmental stressors by promoting fetal growth, whereas the female placenta promotes gene and protein expressions that increase chances of survival. This difference may contribute to developmental disorders that are diagnosed more often in boys, such as autism and dyslexia—although diagnostic methods may overlook girls.

Gender bias surrounding mental illnesses seems to be widespread. The suggestion that boys and men manifest depression with anger, rather than withdrawal, may arise from a biased expectation that males externalize behaviors and females internalize them. Some mental health professionals around the world still assign certain symptoms almost exclusively to women, such as being “hysterical,” whereas men are likely to be diagnosed as “antisocial.” These biases affect treatments and health outcomes.

Bias is rampant when it comes to the brain. Pop psychology loves the idea that men and women have different brains. Reports show that males have more cortical connections within each of the brain's two hemispheres, whereas women have more connections between the hemispheres. But the reports fail to mention that 86 to 88 percent of all these combined connections are similar—suggesting that male and female brains are more alike than different. Research also increasingly shows that any individual's brain development over a person's lifetime is greatly influenced by neuroplasticity—the ability of brain cells to rewire over time. If the daily experiences of boys and men differ markedly from those of girls and women, differences in brain structure and function should be expected [see “Is There a ‘Female’ Brain?” on page 38].

This complicated picture makes it difficult to pin down causes and treatments for brain illnesses. Two thirds of the more than five million Americans who have Alzheimer's disease are women, not only because many more women than men survive to age 65 but also because more women acquire the disease across all age groups. In aging female cells, abnormal pairing of maternal and paternal X chromosomes during cell division may play a role. In men, only the X (maternal) chromosome may survive cell division, and the Y chromosome may no longer be present. Sex certainly influences the disease's progression, and it should be investigated.

## LOPSIDED SCIENCE

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The ratio of neuroscience studies that incorporate only male animals compared with ones that use just females. Animal research provides the underpinning for many psychoactive drugs.



**Marcia L. Stefanick** is a professor of medicine at the Stanford Prevention Research Center and a professor of obstetrics and gynecology at the Stanford University School of Medicine. She is also director of the Stanford Women and Sex Differences in Medicine Center and is conducting a large trial of older women related to heart disease prevention and healthy aging.

# Note to Doctor: Women Are Not Men

Medical studies relied heavily on men or male animals in the past, which slowed progress in women's health care, according to the Institute of Medicine. Although researchers are finally improving the mix, women and female animals are still in the minority. Parity is needed because many illnesses affect women differently than men. Women often respond differently to treatments as well. Here is just a sample.

## CANCER

Overall, cancer kills more men than women, but averages mask important sex differences in specific types of cancer. Recognizing disparities could prevent doctors from overlooking or misdiagnosing symptoms.

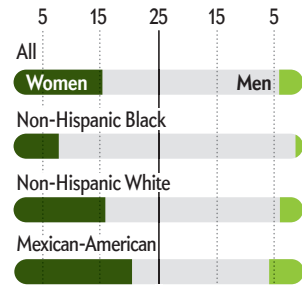
Women have a higher risk than men of developing right-sided colon cancer, a more aggressive killer than left-sided colon cancer. Diagnosis in women also tends to be more delayed.

More men than women die from lung, colon, kidney and liver cancer. But overall cancer risk is higher for women under age 50.

Being taller is a risk factor for many cancers in both men and women and may account for one third of the greater total cancer risk in men.

Side effects from fluorouracil, a common chemotherapy drug, are significantly worse in women; so are effects from many other cancer drugs.

**Prevalence of Osteoporosis** (percent of U.S. residents aged 50 and up, 2010)



## BONES AND JOINTS

Sex and gender differences work both ways. White women are twice as likely as white men to have osteoporosis—fragile bones—but the risk of death from fragile-bone fractures is 50 percent greater for men.

Women undergo about two thirds of all knee replacements, but there is no evidence that “gender-specific” knees, marketed by manufacturers, improve outcomes. Overemphasizing sex differences can be a problem.

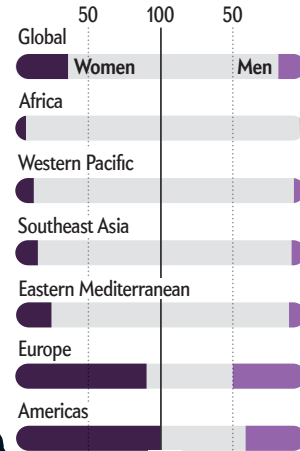
## DISEASE

Certain thyroid autoimmune illnesses such as Hashimoto's disease and Graves' disease are 7 to 10 times higher in women; so is lupus.

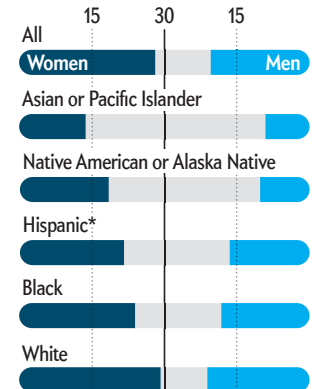
Rheumatoid arthritis, multiple sclerosis and scleroderma are at least 2 to 3 times higher in women.

More women than men are infected by herpes simplex virus 2.

**Prevalence of Multiple Sclerosis** (cases per 100,000 people, 2015)



**Deaths from Alzheimer's Disease** (age-adjusted deaths in U.S. per 100,000 people, 2014)



\*Includes Hispanic black and Hispanic white

## MENTAL ILLNESS

Twice as many women as men are diagnosed with anxiety or depression.

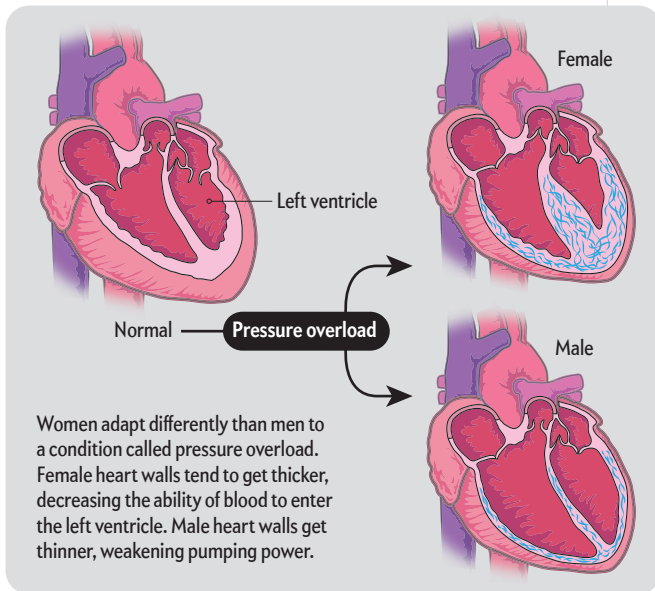
Almost two thirds of Americans with Alzheimer's disease are women. The *APOE4* gene is more strongly linked to the disease in women. X and Y chromosomes may also play a role.

The number of older U.S. women dying of Alzheimer's is now greater than all U.S. women who die of breast cancer.



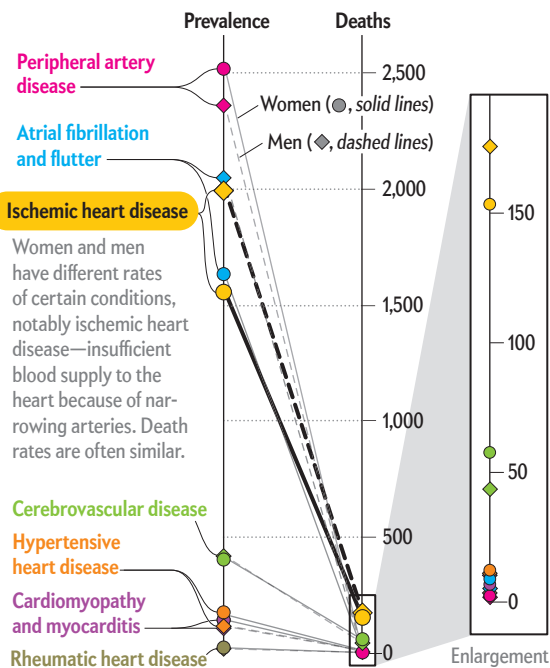
## HEART PROBLEMS

Heart complications often take different forms in women and men. Heart failure in women is more likely to result from left ventricle walls that stiffen and thicken (*illustration*). Among electrical problems, an irregular heartbeat is more common in men, while rapid heartbeat is more common in women—and certain drugs can make the condition life-threatening. Heart valve diseases vary, too. Blood clotting is greater in women, which can affect treatments; that trait may have evolved to prevent excess blood loss during childbirth.



SOURCES: "THE RECENT PREVALENCE OF OSTEOPOROSIS AND LOW BONE MASS IN THE UNITED STATES BASED ON BONE MINERAL DENSITY AT THE FEMORAL NECK OR LUMBAR SPINE," BY NICOLE C. WRIGHT ET AL., IN *JOURNAL OF BONE AND MINERAL RESEARCH*, VOL. 29, NO. 11, NOVEMBER 2014 (osteoporosis); "GBD COMPARE" INSTITUTE FOR HEALTH METRICS AND EVALUATION, SEATTLE, WA, ACCESSED JULY 2017 <http://vizhub.healthdata.org/gbd-compare> (multiple sclerosis and heart disease); "DEATHS: FINAL DATA FOR 2014," BY KENNETH D. KOCHANEK ET AL., IN *NATIONAL VITAL STATISTICS REPORTS*, VOL. 65, NO. 4, JUNE 30, 2016 (Alzheimer's disease); "MECHANISTIC PATHWAYS OF SEX DIFFERENCES IN CARDIOVASCULAR DISEASE," BY VERA REGITZ-ZAGROSEK AND GEORGIOS KARARIGAS, IN *PHYSIOLOGICAL REVIEWS*, VOL. 97, NO. 1, JANUARY 2017 (heart illustrations)

### Cardiovascular and Circulatory Disease (cases per 100,000 people in U.S., 2015)



Terminology for charts was taken from studies cited.

## TIME TO GET PERSONAL

CLEARLY, MEDICAL RESEARCHERS and physicians have a lot of untangling to do before they can offer better health care to women. A deeper understanding of sex differences will improve health directives for men, too. In 2015 the NIH launched a Precision Medicine Initiative to address the problem that most treatments have been designed for the “average patient” instead of each individual. “Precision” or “personalized” medicine is expected to take into account variability in genes, environment and lifestyle for each person. Yet genome-wide studies that try to pinpoint genetic variants that may be linked to specific diseases have generally excluded X and Y chromosomes, suggesting that sex is not an important focus of precision medicine.

The 2015 NIH mandate that researchers consider sex as a biological variable in animal and human studies provides promise. That same year the Canadian Institutes of Health Research rolled out an online training course on sex and gender in health research. And the League of European Research Universities released a report on how to integrate sex and gender into research processes. In October 2015 the Mayo Clinic hosted the Sex and Gender Medical Education Summit to tackle the serious problem that medical schools do not teach students about sex differences. The summit called for participants to create a road map for integrating sex- and gender-based evidence into medical education and to improve curricula within the next five years. In 2016 a panel of 13 experts representing nine countries developed the Sex and Gender Equity in Research guidelines, a comprehensive procedure for reporting sex and gender information in study design, data analyses, results and interpretation of findings.

These developments are encouraging. More is needed. We might need further mandates, through policy and funding restrictions, to ensure that female biology makes it into textbooks and testing protocols. We might also need to require best practices—standards of care that must be adhered to as part of the ethical code of “do no harm”—to ensure that clinicians and health care providers consider both sex and gender in medical diagnoses, screening and treatments. Both women and men would benefit enormously. Without sex and gender as a focus, physicians cannot achieve the precision medicine, specific to each one of us, that we all hope to receive. **SA**

### MORE TO EXPLORE

- Exploring the Biological Contributions to Human Health: Does Sex Matter? Institute of Medicine. National Academies Press, 2001.
- Gendered Research and Innovation: Integrating Sex and Gender Analysis into the Research Process. League of European Research Universities, September 2015.
- Gendered Innovations project, Stanford University: <http://genderedinnovations.stanford.edu>

### FROM OUR ARCHIVES

- Hormone Hysteria? Dennis Watkins; October 2003.

[scientificamerican.com/magazine/sa](http://scientificamerican.com/magazine/sa)