

INSTITUTE OF MEDICINE

Shaping the Future for Health

EXPLORING THE BIOLOGICAL CONTRIBUTIONS TO HUMAN HEALTH: DOES SEX MATTER?

Over the past decade new discoveries in basic human biology have made it increasingly apparent that many normal physiological functions—and, in many cases, pathological functions—are influenced either directly or indirectly by sex-based differences in biology.

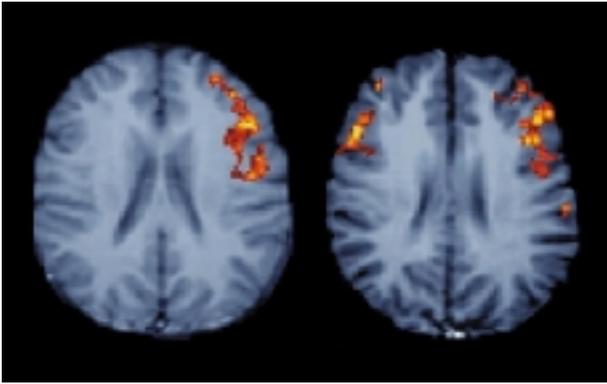
This realization, however, has been slow in coming. Considerable attention has focused on differences and similarities between females and males at the *societal* level by researchers evaluating how individual behaviors, lifestyles, and surroundings affect one's biological development and health. Similarly, at the level of the *whole organism* clinicians and applied researchers have investigated the component organs and systems of humans. However, scientists have paid much less attention to the direct study of these differences at the basic *cellular* and *molecular* levels. Where data are available, they have often been a by-product of other areas of research. Historically, the research community assumed that beyond the reproductive system, such differences do not exist or are not relevant. Still, scientific evidence of the importance of sex differences throughout the life span abounds.

Although an individual can be characterized initially by the presence of particular reproductive organs, sex differences encompass much more than that. Evidence suggests that the distinct anatomy and physiology that develop as a result of having been dealt two X chromosomes (XX) or an X chromosome and a Y chromosome (XY) at fertilization can have a much broader influence on an individual's health than was previously thought. While it is anatomically obvious why only males develop prostate cancer and only females get ovarian cancer, it is not at all obvious why, for example, females are more likely than males to recover language ability after suffering a left-hemisphere stroke or why females have a far greater risk than males of developing life-threatening ventricular arrhythmias in response to a variety of potassium channel-blocking drugs.



Sex refers to the classification of living things, generally as male or female according to their reproductive organs and functions assigned by chromosomal complement.

Gender refers to a person's self-representation as male or female, or how that person is responded to by social institutions based on the individual's gender presentation. Gender is rooted in biology and shaped by environment and experience.



Men and women differ in brain organization for language. Men (left image) rely on the left inferior frontal gyrus to carry out language tasks, such as determining if two nonsense words rhyme. Women (right image) use both the left and the right inferior gyri to carry out the same task. Interestingly, men and women perform the task equally accurately and equally rapidly. This may protect women who suffer a left-sided stroke from experiencing decrements in their language performance. Shaywitz et al. (1995) *Nature* 373:607–609.

Differences in the prevalence and severity of a broad range of diseases, disorders, and conditions exist between the sexes.

Recent research has shed some light on these puzzles. In the case of stroke, for example, functional magnetic resonance imaging has shown that females rely on both sides of the brain for certain aspects of language, whereas males predominantly rely on the left hemisphere.

Differences in the prevalence and severity of a broad range of diseases, disorders, and conditions exist between the sexes. Investigators are now positioned to move to the next level of study, where the mechanisms and origins of sex differences can be explored.

Two questions at the core of these explorations are: 1) How can information on sex differences be translated into preventative, diagnostic, and therapeutic practice? and 2) How can the new knowledge about and understanding of biological sex differences and similarities most effectively be used to positively affect patient outcomes and improve health and health care?

The Institute of Medicine formed a committee to evaluate and consider the current understanding of sex differences and determinants at the biological level and to identify current and potential barriers to the conduct of research in this area. The committee's report, *Ex-*

ploring the Biological Contributions to Human Health: Does Sex Matter? contains findings and recommendations to facilitate scientific endeavors in this area, take advantage of new opportunities in basic and applied research, and fill identified research gaps.

Recurring Themes

Three common recurring messages emerged from the committee's review.

- **Sex matters.** Sex, that is, being male or female, is an important basic human variable that should be considered when designing and analyzing studies in all areas and at all levels of biomedical and health-related research. Differences in health and illness are influenced by individual genetic and physiological constitutions, as well as by an individual's interaction with environmental and experiential factors. The incidence and severity of diseases vary between the sexes and may be related to differences in exposures, routes of entry and the processing of a foreign agent, and cellular responses.

- **The study of sex differences is evolving into a mature science.** There is now sufficient knowledge of the biological basis of sex differences to validate the scientific study of sex differences and to allow the generation of hypotheses. The next step is to move from the descriptive to the experimental and establish the conditions that must be in place to facilitate and encourage the scientific study of the mechanisms and origins of sex differences.

- **Barriers to the advancement of knowledge about sex differences in health and illness exist and must be eliminated.** Scientists conducting research on sex differences are confronted with an array of barriers to progress, including ethical, financial, sociological, and scientific factors.

Every Cell Has a Sex

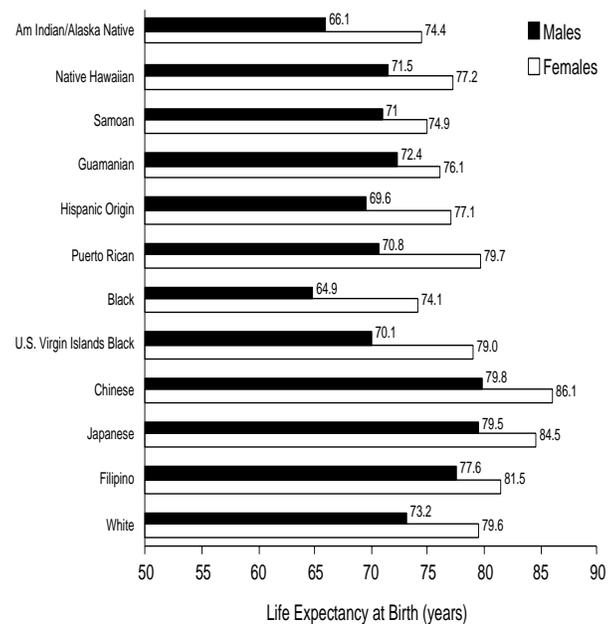
Rapid advances in molecular biology have revealed the genetic and molecular basis of a number of sex-based differences in health and human disease, some of which are attributed to sexual genotype—XX in the female and XY in the male. Genes on the sex chromosomes can be expressed differently between males and females, because of the presence of either single or double copies of the gene and because of the phenomena of differing meiotic effects, X-chromosome inactivation, and genetic imprinting. The inheritance of either a male or female genotype is further influenced by the source (maternal or paternal) of the X chromosome. The relative roles of the sex chromosome genes and their expression explains X-linked disease and is likely to illuminate the reasons for heterogeneous expression of some diseases within and between the sexes.

These findings argue that there are multiple, ubiquitous differences in the basic cellular biochemistry of males and females that can affect an individual's health. Many of these differences do not necessarily arise as a result of differences in the hormonal regime to which males and females are exposed but are a direct result of the genetic differences between the two sexes. Further research should be conducted to determine the functions and effects of X-chromosome- and Y-chromosome-linked genes in somatic cells as well as germ-line cells, determine how genetic sex differences influence other levels of biological organization (cell, organ, organ system, organism), including susceptibility to disease, and develop systems that can identify and distinguish between the effects of genes and the effects of hormones.

Sex Begins in the Womb

Sex differences of importance to health and human disease occur throughout the life span, although their specific expression varies at different stages of life. Some differences originate in events occurring in the intrauterine environment, where developmental processes differentially organize tissues for later activation in the male or female. In the prenatal period, sex determination and differentiation occur in a series of sequential processes governed by genetic and environmental factors. During the prepubertal period, behavioral and hormonal changes manifest the secondary sexual characteristics that reinforce the

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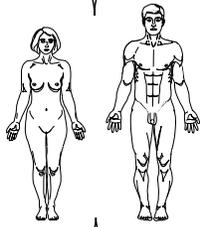
Although actual life expectancy differs among ethnic groups, the consistency in the observation of an advantage for females across ethnic groups is striking. Source: NCHS and NIH. Data are from 1989 to 1994.

External Agents

Physical: Sounds, light, heat, vibrations, gravity, radiation
Chemical: Drugs, food and supplements, environmental compounds
Infectious: Bacteria, mycobacteria, viruses, fungi, parasites

Entry

Gastrointestinal tract, respiratory tract, skin, eyes, urogenital tract, parenteral routes, transplacental



Responses

Genetic, molecular, cellular, organ, organ system, whole organism (dependent or independent of environment)

Factors That Affect Responses

Genotype, growth and development, life stage, hormone cycles, pregnancy, chronobiology, prior exposures and responses, current health status

sexual identity of the individual through adolescence and into adulthood. Hormonal events occurring in puberty lay a framework for biological differences that persist through life and contribute to variable onset and progression of disease in males and females. It is important to study sex differences at all stages of the life cycle, relying on animal models of disease and including sex as a variable in basic and clinical research designs.

Sex Affects Behavior and Perception

Basic genetic and physiological differences, in combination with environmental factors, result in behavioral and cognitive differences between males and females. Sexual differences in the brain, sex-typed behavior and gender identity, and sex differences in cognitive ability should be studied at all points in the lifespan. Hormones play a role in behavioral and cognitive sexual dimorphism, but are not solely responsible. In addition, sex differences in perception of pain have important clinical implications. Research is needed on the natural variations between and within the sexes in behavior, cognition, and perception, with expanded investigation of sex differences in brain organization and function.

Sex Affects Health

Males and females have different patterns of illness and different life spans, raising questions about the relative roles of biology and environment in these disparities. Dissimilar exposures, susceptibilities, and responses to initiating agents, and differences in energy storage and metabolism result in variable responses to pharmacologic agents and the initiation and manifestation of diseases such as obesity, autoimmune disorders, and coronary heart disease, to name a few. Understanding the bases of these sex-based differences are important to developing new approaches to prevention, diagnosis, and treatment.

The Future of Research on Biological Sex Differences

Being male or female is an important fundamental variable that should be considered when designing and analyzing basic and clinical research. Historically, the terms *sex* and *gender* have been loosely, and sometimes inappropriately, used in reporting research results, a situation that should be remedied through further clarification. Conducting studies that account for sex differences might require innovative designs, methods, and model systems, all of which might require additional resources. Studies relying on biological materials would benefit from a determination and disclosure of the sex of origin of the material, and clinical researchers should attempt to identify the endocrine status of research subjects. Longitudinal studies should be designed to allow analysis of data by sex. Once studies are conducted, data regarding sex differences, or the lack thereof, should

“Sex does matter. It matters in ways that we did not expect. Undoubtedly, it also matters in ways that we have not begun to imagine.”
Mary-Lou Pardue,
Ph.D. Chair

be readily available in the scientific literature. Interdisciplinary efforts are needed to conduct research on sex differences.

There is a lack of awareness that the consequences of genetics and physiology may be amenable to change. The committee noted that, historically, studies on race, ethnicity, age, nationality, religion, and sex have sometimes led to discriminatory practices. The committee believes, therefore, that these historical practices should be taken into consideration so that they will not be repeated. The past should not limit the future of research but should serve as a guide to its use. Ethical research on the biology of sex differences is essential to the advancement of human health and should not be constrained.

In the report, the committee expresses its expectation that the public, scientific, and policy communities will agree that the understanding of sex differences in health and illness merits serious scientific inquiry in all aspects of biomedical and health-related research. Until the question of sex is routinely asked and the results—positive or negative—are routinely reported, many opportunities to obtain a better understanding of the pathogenesis of disease and to advance human health will surely be missed.

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Summary of Barriers to Progress in Research on Sex Differences

Terminology

- There is inconsistent and often confusing use of the terms *sex* and *gender* in the scientific literature and popular press.

Research Tools and Resources

- The conduct of research on sex differences and longitudinal research may require more complex studies and additional resources.
- Information on sex differences can be difficult to glean from the published literature.
- Useful information on the sex of origin of cell and tissue culture material is often lacking in the literature.
- There is a lack of data from longitudinal studies encompassing different diseases, disorders, and conditions across the life span.
- There is a lack of consideration of hormonal variability.

Interdisciplinary and Collaborative Research

- The application of federal regulations is not uniform.
- Opportunities for interdisciplinary collaboration have been underused.

Non-Health-Related Implications of Research on Sex Differences in Health

- There is a lack of awareness that the consequences of genetics and physiology may be amenable to change.
- The finding of sex differences can lead to discriminatory practices.

Summary of Major Recommendations

- **Promote research on sex at the cellular level.**
- **Study sex differences from womb to tomb.**
- **Mine cross-species information.**
- **Investigate natural variations.**
- **Expand research on sex differences in brain organization and function.**
- **Monitor sex differences and similarities in all human disease.**
- **Clarify use of the terms *sex* and *gender*.**
- **Support and conduct additional research on sex differences.**
- **Make sex-specific data more readily available.**
- **Determine and disclose the sex of origin of biological research materials.**
- **Conduct and construct longitudinal studies so that the results can be analyzed by sex.**
- **Identify the endocrine status of research subjects (an important variable that should be considered when possible in analyses).**
- **Encourage and support interdisciplinary research on sex differences.**
- **Reduce the potential for discrimination based on identified sex differences.**

For More Information...

Copies of *Exploring the Biological Contributions to Human Health: Does Sex Matter?* are available for sale from the National Academy Press; call (800) 624-6242 or (202) 334-3313 (in the Washington metropolitan area), or visit the NAP home page at www.nap.edu. The full text of this report is available at <http://www.nap.edu/catalog/10028.html>

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