



UNCOVERING HOW
SEX DIFFERENCES
AFFECT HEALTH

BY JENNIFER B. WELLS
Women's Health and Gender Biology

photo: Kevin Curtis/Photo Researchers, Inc.

In science, sex matters. It matters in prevention, in treatment, and in research. Astonishingly, only about 10–15 years ago, scientists often ignored the impact of sex—which refers to the biology of being male or female, that is, having XX versus XY chromosomes.

Scientists assumed that if something was valid for men, the same would hold true for women. And studying females meant having to account for changes in the body during the menstrual cycle. Politically, there was the notion that sex differences could be interpreted in a way that reflected poorly on women. Thus, with limited research funding available, the environment to investigate sex differences in healthcare was not encouraging.

As a result, research on women was limited to reproductive disorders. The consequences—women's health suffered. Treatments for women were based on studies performed on men. For example, women are the most common pain sufferers, while the model for basic pain research is the male rat. Medication for cardiovascular disease, the number-one killer of women in the United States, is based on studies of men. However, it turns out that even the recommendation of an aspirin a day to lower the risk for heart attacks only works for men.

Today, physicians and scientists have redefined the field of women's health. A growing body of evidence demonstrates that gender and sex affect every system in the body. (Gender refers to the roles and behaviors that a society considers appropriate for being a man or a woman.) Women are twice as likely to be diagnosed with depression and Alzheimer's disease. They have a greater risk for anxiety disorders, autoimmune diseases, and arthritis, to name a few, while men are more prone to have autism and substance abuse disorders. Even in the same disease, the progression and the response to treatment are different for women and men.

The mechanisms that explain sex differences in diseases are still unclear. But leading the way with research in this area is Brigham and Women's Hospital (BWH) and its Connors Center's Research Advisory Council to the Biomedical Research Institute (BRI), whose chair and co-chair are Jill Goldstein, PhD, and Julie Buring, ScD, respectively. Goldstein, a professor of psychiatry and medicine, serves as the director of research for the Connors-BRI Center for Research on Women's Health & Gender Biology. During the past 20 years, her clinical neuroscience laboratory has focused on investigating sex differences in psychiatric disorders.

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To understand the causes of these psychiatric illnesses, her lab team studies genes, hormones, and the brain. Moreover, they use a lifespan perspective. "Although these [psychiatric disorders] are primarily adult onset diseases, they have fetal developmental causes that have implications for sex differences," says Goldstein.

EARLY ORIGINS LINK HEART DISEASE AND DEPRESSION

Goldstein's group is involved in a series of studies that explore how fetal antecedents—risk factors for diseases that develop during pregnancy—relate to sex differences in psychiatric disorders. One such study investigates shared fetal antecedents of depression and risk for cardiovascular disease. These diseases have a high comorbidity, meaning if you have one, you're likely to have the other. Given that depression and cardiovascular disease are two of the leading causes of disability and mortality worldwide, there is a critical need to understand how they are linked.

"This is a huge public health problem," says Goldstein. "Both of these disorders have sex differences. Even though they are mainly adult onset diseases, we believe that these disorders have shared fetal antecedents that may help us understand their comorbidity in adulthood."



Jill Goldstein, PhD, a professor of psychiatry and medicine, serves as the director of research for the Connors-BRI Center for Research on Women's Health & Gender Biology. During the past 20 years, her clinical neuroscience laboratory has focused on investigating sex differences in psychiatric disorders. She shows a picture of the hypothalamus, which plays an important role in depression and heart regulation.

“Jill Goldstein is at the forefront of combining a basic science, a clinical, and a developmental approach to address important issues concerning women’s mental health and its relationship to other aspects of health, in a manner that can open the door for new clinical advances,” comments David Silbersweig, MD, chairman of the Department of Psychiatry and Institute for Neurosciences. “For example, her work looking at fetal antecedents of risk for depression and cardiovascular disease in women promises to illuminate two major areas of women’s health at their intersection, laying the foundation for early intervention and improved treatment outcomes.”

LESSONS FROM LANDMARK STUDY

Data for the heart disease/depression study comes from the National Collaborative Perinatal Project, conducted from 1959 through 1964 at twelve sites in the United States, including two in New England—at BWH and at Brown University. Nationally, more than 60,000 women and their children participated; in New England alone, more than 16,000 families participated.

The National Collaborative Perinatal Project started as a way to learn more about pregnancy complications and adverse child development associated with neurologic diseases in children. Researchers gathered information on the mother’s health, the family’s health, and their living conditions. Once the children were born, the researchers followed their development until they were seven years old. This landmark study substantially contributed to the idea that what happens during pregnancy and the first few years of life has a great effect on development. And as a result, the federal government funded medical programs that help pregnant women and their children obtain better care.

As part of a series of follow-up studies, researchers have located, recruited, and evaluated the children in the original project, who are now adults in their forties. Goldstein’s team has followed the New England cohort, which is a group of people born in the same time period, for about 20 years. The goal is to discover how events in people’s early years affect their adult health.

In the cardiovascular/depression study, Goldstein’s team is looking at same-sex siblings in which one had fetal growth restriction—a birth weight that is small for gestational age—or was exposed to preeclampsia, a condition defined by high blood pressure and excess protein in the urine. Both of these risk factors produce an inflammatory response in the mother, and have consequences for depression and heart regulation. The study will identify how these consequences are different for women and men.

“This project is quite an undertaking—to find people 40 years later and get them excited about making an important contribution to science,” adds Goldstein. “We are lucky to have a unique opportunity to investigate fetal risk factors for adult onset diseases in human studies.”

Goldstein calls her team a “village of collaborators.” Researchers collect data, analyze prenatal and adult blood results, conduct clinical interviews and neuropsychological tasks, and perform stress tests and brain imaging.

“We are so excited about the potential scope and wide-ranging benefits of this project, and I can think of no one more qualified than Jill Goldstein to lead us forward,” comments Paula Johnson, MD, MPH, BWH’s executive director of the Connors Center for Women’s Health and Gender Biology, and chief of the Division of Women’s Health. “It will be one of the most important undertakings of the Connors Center for Women’s Health and Gender Biology in the coming years.”

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MINING ITS OWN GOLD

During the next few years, BWH will be creating its own research “gold mine” by developing a family cohort that follows the mother and the partner, as well as the children. With 8,000–10,000 births annually and a longstanding commitment to research, BWH is one of the only hospitals in the world that has the capacity and infrastructure to develop such a comprehensive study. The data from parents and their children, including stored blood for analyzing DNA, will provide an unprecedented resource for studying diseases that have early origins and affect women and men differently.

Thanks to scientists like Goldstein and her team, we know that small differences in men and women’s brains have big implications for health later in life. And understanding what happens during pregnancy is the first step to developing sex-specific approaches to treat and prevent these diseases. ●