



Women's Health Research at Yale

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DEFINITIONS OF SEX AND GENDER

Sex: The classification of living things, generally as male or female according to their reproductive organs and functions assigned by chromosomal complement, mostly consisting of XY for males and XX for females.

Gender: 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.

Source: The Institute of Medicine

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SeXX Matters: Examining the Origins of Depression and Heart Disease

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Like many who came of age during or after the feminist wave of the 1960s and 70s, Dr. Jill Goldstein believes in equality. But, she notes, that's not the same as believing there are no differences between the sexes.

"For many years, the study of sex differences in biology was tuned into the politics of sex and gender," said Goldstein, Professor of Psychiatry and Medicine at Harvard Medical School and the Helen T. Moerschner Endowed MGH Research Institute Chair in Women's Health at Massachusetts General Hospital. "Yes, people should be treated equally. But sex and gender exist and matter."

In a Grand Rounds presentation in May sponsored by the Women's Behavioral Health Division of Yale School of Medicine's Department of Psychiatry, Dr. Goldstein explored how sex differences — some beginning during fetal development — contribute to dissimilarities observed in the co-occurrence of major depression and heart disease that carry across the lifespan.

“Jill has been at the vanguard of understanding women's health using interdisciplinary team science – integrating brain imaging, psychophysiology, neuroendocrinology, genetics, and markers of immune function in studies of genes, hormones, and the brain,” said Dr. Carolyn M. Mazure, Director of Women's Health Research at Yale, of her decision to invite Dr. Goldstein to speak. “Every cell in the body has a sex. And thanks to the leadership of groundbreaking researchers such as Jill Goldstein, we are beginning to understand how sex differences affect interconnected aspects of our health and reverberate throughout our lives.”

Major depression and heart disease are, respectively, the No. 1 and No. 2 primary causes of disability in the world. Women are twice as likely to develop major depression. And despite popular perception that men are more often affected by cardiovascular disease, it is also the top killer of women in the United States and in most middle income countries.

In more than 20 percent of the world's population, these diseases occur simultaneously, known as comorbidity, together affecting women twice as often as men. Experts anticipate this percentage will rise to make comorbid major depression and cardiovascular disease (CVD) the single greatest cause of disability worldwide for women and men by 2020. And people with both diseases are up to five times as likely to die from CVD.

In addition, major depression and heart disease are each independent risk factors for Alzheimer's disease, which affects women more often than men and not only because women tend to live longer.

“There are no effective treatments addressing both CVD and major depression at the same time,” Goldstein said, noting that treatments for these diseases can sometimes interfere with one

another, forcing physicians to prioritize preventing the often more urgently life-threatening risks of heart disease. “It’s a major public health challenge.”

In search of potential solutions to this problem, Dr. Goldstein and her colleagues have looked for the earliest causes of these conditions, all the way back to fetal development.

Goldstein’s research has led her to examine a tiny group of nerve cells on top of the brain stem known as the paraventricular nucleus of the hypothalamus, or PVN. She described it as the key relay station regulating how humans react to and regulate stress, including changes in mood and anxiety levels, fluctuations in blood pressure and heart rate, and hormonal and immune system responses.

“Stress affects every chronic disease we know,” Goldstein said. “And major depression and cardiovascular disease are certainly no exception to this.”

The PVN manages the body’s responses to stress through the vagus nerve, which runs from the brain stem to regulate the heart. Goldstein’s research has shown that when a pregnant woman experiences excessive hormonal or immune responses to stress, the timing of the disruption and the sex of the offspring will affect how that offspring regulates stress in the brain throughout life, and males and females do it differently.

“What’s really important to me is to translate this science into something patients can use.

— DR. JILL GOLDSTEIN

Analyzing data gathered in part through a unique, large study of pregnant women and their offspring followed for more than 50 years, Goldstein’s lab found that depending on the timing of this prenatal stress response, female fetuses will experience more negative consequences than male fetuses to the development of their PVNs and surrounding stress circuitry regions — including

how these important nerve cells grow, interconnect, and die.

These developmental effects are correlated with greater risks for major depression in mid-life and loss of vagus nerve regulation of heart function, which is linked to cardiovascular disease.

“So here in the very early stages of development, the timing of a pregnant woman’s stress and the sex of her fetus can combine to set the course for significant health problems decades into the future,” Goldstein said.

Goldstein views these and her lab’s similar findings as an opportunity to develop sex-dependent treatments targeted at the earliest stages of growth to minimize illnesses later in life or possibly prevent them completely.

“What’s really important to me is to translate this science into something patients can use,” Goldstein said. “And make an impact on their health and healthcare choices that is informed by sex differences in these disorders.”

One promising possibility is a technique called transcutaneous vagus nerve stimulation, in which a non-invasive device created by Goldstein’s Harvard colleague, Dr. Vitaly Napadow, Associate Professor in Radiology, stimulates two points in the ear that connect to a branch of the vagus nerve enhanced by the person’s own physical and chemical responses. Initial findings in their studies of people with major depression have shown that the device effectively lowers anxiety, raises depressive mood, beneficially regulates cardiac function, and lowers blood pressure in people experiencing major depression or chronic elevated blood pressure.

“The device is transcutaneous, that is, stimulation at the level of skin,” Goldstein said. “Which means no surgery and no drugs. And, in pilot studies, we have been achieving a positive acute response.”

To advance these and other practical sex-based initiatives addressing the growing problems of major depression and heart disease, Goldstein founded and now leads The Women, Heart and Brain Global Initiative, a collaborative effort between

Massachusetts General Hospital and the Harvard T.H. Chan School of Public Health.

“In addition to enhancing knowledge among health care providers, I believe it is really important to elevate the public’s awareness of these issues and educate the next generation of scientists and clinicians in a comprehensive way so that sex and gender become fully integrated with health research and care,” Goldstein said. “We need to demonstrate the importance of this approach so that the public will demand it of their physicians and other health care providers.”

Goldstein expressed enthusiasm for how much knowledge has already been accumulated to show the need to fully consider sex and gender in every aspect of medical science and clinical care. And she called for researchers and practitioners to work across departments and fields of expertise to achieve the best possible outcomes for patients.

“We need to continue building these models and demonstrating that they work,” Goldstein said. “Sexx — with two Xs — matters.”

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For questions, please contact [Rick Harrison, Communications Officer at rick.harrison@yale.edu](#) or 203-764-6610.

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This article was submitted by Carissa Violante on August 31, 2018.

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