

Sex, gender and the mechanisms of disease

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Medical research did not always include women as participants or investigate the influence of sex and gender on health. This has now changed, and research is beginning to uncover ways in which sex as a biological variable (SABV) affects health. The social environment's effect on our biology also is increasingly being acknowledged, along with data indicating that these effects vary by gender. Thus, both biological sex and gendered experience can play a role in the physiological mechanisms of disease.

A newly published paper in the journal *Cell* asserts that despite the challenges in navigating the paradigm shift required to study the effects of sex and gender as well as the biological and social determinants of health, the future of science is to study how all these factors intersect.

Co-authors Nina Stachenfeld, Ph.D., fellow at the John B. Pierce Laboratory, and senior research scientist in obstetrics, gynecology, and [reproductive sciences](#) at Yale School of Medicine and Carolyn M. Mazure, Ph.D., Director of Women's Health Research at Yale, Norma Weinberg Spungen and Joan Lebson Bildner Professor in Women's Health Research and Professor of Psychiatry and Psychology, call on laboratory researchers to incorporate SABV into their studies and to consider how gender-sensitive experience affects disease processes. This is important because much of laboratory science forms the foundation for future study of human biology and behavior.

In the commentary, Drs. Mazure and Stachenfeld recount the reasons behind the historical exclusion of females as subjects in most studies not centered on [reproductive biology](#) and the regulatory changes in the mid-1990s that led to the requirement of NIH applications to include [women](#) in clinical trials. It was only in 2016 that the NIH required laboratory studies of vertebrate animals to include females and analyze

data by sex.

"Sex differences in the biology of health have not been a target of study to the detriment of both women and men," the authors write. "Such exclusion eliminated, or at least greatly reduced, the option of comparing the biology of males and females and created a knowledge gap on the health of women that has only begun to be remedied in relatively recent years."

Despite these recent developments, the authors point out that analyses of sex or the gendered effects of the social environment on the biology of human health are not present in most published study results. This has been the case even as women and men experience meaningful differences in health effects across a large range of diseases. For example, women are more likely to develop Alzheimer's disease, autoimmune disorders, and higher rates of depression after puberty. Men are more likely to develop liver cancer than women, even when controlling for alcohol consumption, and rates of COVID-19 and similar for women and men, but men are more likely to die from COVID-19.

Cardiovascular disease—the greatest cause of mortality in women and men—and specifically heart attack and hypertension are used by the authors to illustrate how sex differences and gender-based experience matter in understanding disorders. For example, men generally experience heart attacks due to obstruction of one or more of the major coronary arteries. Yet, heart attacks can occur due to small vessel disease. Of those who suffer this type of [heart attack](#), the majority are women.

In addition, the authors write, men are more likely to develop high blood pressure than women, but women have a higher risk of stroke over the course of their lifetimes and beginning at a lower threshold of blood pressure. Moreover, race and ethnicity as social constructs play a

significant role. For example, non-Hispanic Black men and women experience [high blood pressure](#) out of proportion with their share of the population, and Black women are more likely to experience the condition earlier than White women.

The authors cite significant health-related sex differences in cellular pathways and other mechanisms underlying aspects of cardiovascular disease. They call for the inclusion of SABV and improved study designs in consultation with statistical and methodological experts to produce more practical sex-and-gender-related analyses. They also call on [scientific journals](#) to require the reporting of sex-and-gender analyses in discussions of study results.

"Surmounting the hurdles encountered in exploring SABV will enhance rigor and reproducibility and increase the precision of our discoveries," the authors write. "Incorporating the intersection of sex, gender, and social variables into our scientific inquiry [of the biological mechanisms of disease] will advance the relevance and practical benefit of research."

More information: Nina S. Stachenfeld et al, Precision medicine requires understanding how both sex and gender influence health, *Cell* (2022). [DOI: 10.1016/j.cell.2022.04.012](https://doi.org/10.1016/j.cell.2022.04.012)

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