The art of medicine

Analysing how sex and gender interact

In recent years prominent UK and US leaders in science and medicine have called for the end of all-male speaking panels, or "manels", and focused admirably on the issue of participation in science. Arguably more important than who does the research, however, is how the research is conducted. Are crucial variables missing? Are basic theoretical frameworks ignoring key components? We posit that it's time to end science in which mankind represents all humankind. It's also time to integrate how sex and gender interact into basic and applied research. How scientific knowledge is produced is fundamentally important.

Historically, medical knowledge of humans has been largely based on men—and predominantly white men. In 1543, Andreas Vesalius published the first widely recognised modern rendering of the human skeleton—a male—in *De Humani Corporis Fabrica* (*On the Fabric of the Human Body*). Since that time, standard references in human medicine have generally highlighted male anatomy and physiology, with the notable exception of reproduction. Clinical trials, for example, have been conducted primarily in men. Basic science is based predominantly on preclinical research on male rodents, whereas the sex of tissues and cells is rarely known or considered.

When sex and gender became a focus of scientific inquiry in the 1960s, gender research focused mostly on women, and was soon expanded to sexual and gender minority persons. Curiously, the scholars who analysed sex and gender were also mostly women. Even today, an analysis of 1·5 million medical papers revealed that women researchers conduct the most sex and gender analyses

But times are changing rapidly. Numerous funding agencies, including the Canadian Institutes of Health Research, the European Commission, and the US National Institutes of Health (NIH), have implemented policies requiring that applicants include sex or gender analysis in their proposed research, where relevant. Peer-reviewed journals have developed editorial guidelines for reporting how data on sex are collected, analysed, and presented. Yet, despite growing awareness that sex and gender interact to determine health outcomes, gender analysis is still largely overlooked. Moreover, both sex and gender intersect with age, race and ethnicity, education, socioeconomic status, and other sociocultural factors. This topic is of such importance that last year the NIH called for proposals exploring the intersection of sex and gender influences on health and disease.

A fascinating example of how sex and gender interact is the experience, reporting, and treatment of pain in western cultures. There is a common misconception that women tolerate more pain than men, despite considerable evidence that women have a lower pain threshold and report a higher intensity and unpleasantness of pain for many modalities—including pressure, heat, cold, chemical and electrical stimulation, and ischaemia—compared with age-matched men. Many physiological factors that impact pain signalling relate to gonadal hormone concentrations. High oestrogen concentrations, for example, may sharpen or lessen pain in mice and humans, depending on concentrations, such that pain tolerance fluctuates over both the rodent oestrous cycle and the human menstrual cycle, and changes with pregnancy and after menopause. Similarly, high testosterone concentrations may reduce pain, irrespective of sex or gender.

Reporting pain, however, is also influenced by social norms. Gender stereotypes typically cast men as strong and resolute; thus, men may be less willing to report pain than women. These stereotypes vary within and across a given culture and by age, reproductive status, and sociocultural factors, including race and ethnicity, gender and sexual orientation, as well as access to health care. The gender of the person assessing the pain, such as researchers or health providers, can also influence pain reporting by men, women, and, presumably, non-binary persons, although research here is lagging. Furthermore, gender stereotypes held by physicians can influence treatments. Women, for example, are more likely to be given non-specific diagnoses, be referred for psychological therapy, and be prescribed more antidepressants than men, who are, in turn, often perceived

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to be more resistant to psychological treatment and in greater need of painkillers.

Sex and gender interactions can underlie even more complicated examples of poor medical care. For example, because three of four people with autoimmune diseases are women, such diseases are often labelled so-called women's diseases and physicians may fail to diagnose a female-predominant autoimmune disorder, such as lupus or rheumatoid arthritis, in a man who presents with symptoms that would be easily recognised in a woman. Consequently, these men may go untreated until their symptoms become even more severe. Conversely, gender-biased medicine can lead to a failure to consider heart disease, stereotypically considered a man's disease, in a woman with an autoimmune disease.

This year we have also seen how sex and gender interact in COVID-19. Although a similar proportion of men and women seem to become infected with severe acute respiratory syndrome coronavirus 2, news stories report a higher proportion of deaths among men in many countries. On the side of biology are potential differences in viral reproduction, the viral receptor, antibody production possibly arising from the expression of genes on the X chromosome, hormonal effects, or other sex-related factors. On the side of gender are factors such as prevalence of smoking (higher in men worldwide), preventive measures such as handwashing (generally lower among men), occupation (women make up a majority of health-care workers), living arrangements, access to and use of health care, testing, and protective equipment. We need to understand how sex and gender interact and how these intersect with other factors such as age, structural racism, and socioeconomic status to develop a more comprehensive strategy to combat COVID-19. Looking at biology without considering broader sociocultural circumstances will not lead to accurate conclusions or useful solutions.

While the study of how sex and gender interact is important to health care and may lead to helpful sex-specific treatments, overemphasising sex differences can raise new problems. Sex assignment at birth is usually based on external genitalia, which generally show marked sexual dimorphism. In most organs that exhibit some sexual dimorphism, however, form and function largely overlap, with size being the primary difference.

One area where problems arise is in studies of the human brain. Despite the fact that human brains overlap robustly, a "male" versus "female" brain has been touted since at least the 18th century. The notion that men's brains are more "lateralised" compared to women's has led to a cascading array of purported sex differences in cognitive function, such as greater mathematical and spatial ability in men and greater verbal ability in women. There are differences in human brains. Men do, in general, have larger brains than women; yet, after accounting for brain volume relative to body size, there is little difference between human male and female brains. Furthermore, there is an over 85% overlap in how the left and right brain hemispheres are "connected" in men and women, meaning that men's and women's brains are much more alike than different. Similarly, differences in cognitive abilities across genders are very small to non-existent for almost all domains, including mathematical ability. Here, too, sex and gender interact. Gender norms, which influence diet, physical activity, and other factors, also affect the degree of overlap versus dichotomy of most organs, including the brain. For the brain, experience and education, which are influenced by gender norms, have crucial roles in development, from cradle to grave. Importantly, the belief in "male" versus "female" brains might lead to delayed diagnoses and misdiagnoses of psychiatric problems in the unexpected sex or gender. These include delayed treatment in girls with autism or boys with eating disorders, overdiagnosis of depression in middle-aged women, and underdiagnosis of anxiety and depression in men. Like any organ system, it is important to study sex differences in the brain to better manage disease. Nonetheless, the facts are that sex differences here are small, and that human brains are more similar than different. The interplay between social gender norms and neuroplasticity, which recognises an adaptive rather than a "hardwired" brain, has not been adequately studied.

As these examples highlight, understanding how sex and gender interact—and intersect with other biological and sociocultural factors—enhances the quality of science, health, and medicine and contributes to global human health. The problem is that too few researchers know how to do sex and gender analyses. Sex and gender continue to be conflated in biomedical literature, and gender still does not receive the attention it should. Some progress is being made—eg, in 2015 the Charité–Universitätsmedizin Berlin, in Germany, integrated sex and gender analysis across 6 years of medical training and the US Sex and Gender Health Education Summits in 2015, 2018, and 2020 have helped advance this agenda in medicine, nursing, dentistry, pharmacy, and allied health. Yet researchers and universities need to step up to foster excellence in scientific techniques in this area and to integrate them into the medical curriculum. The study of the interaction of sex and gender is fascinating—and also crucial to the health and wellbeing of humankind.

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