

Sex, gender and clinical research: have you considered the possibilities?

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There is compelling evidence for the integration of sex and gender considerations in today's clinical research. Indeed, it is hard to think of a disease state or clinical outcome that is not influenced by sex or gender. Considering sex differences, for example, has led to new understandings of multiple sclerosis [1], cardiovascular disease [2], substance misuse [3], arthritis [4] and pain [5]. Gender is increasingly recognized as an important determinant of clinical encounters and outcomes. For example, physicians have been found to recommend different treatments for the same condition depending on whether the patient is male or female [6].

The evidence is clear - sex and gender matter when it comes to health outcomes and opportunities for care. Although distinct influences of sex and gender have emerged, many researchers continue to use the terms interchangeably. At the Canadian Institutes of Health Research (CIHR), Institute of Gender and Health, we differentiate between these concepts. We use the term 'sex' to refer to "a set of biological attributes in humans and animals. It is primarily associated with physical and physiological features including chromosomes, gene expression, hormone levels and function, and reproductive/sexual anatomy. Sex is usually categorized as female or male but there is variation in the biological attributes that comprise sex and how those attributes are expressed" [7]. 'Gender', on the other hand, refers to "the socially constructed roles, behaviors, expressions and identities of girls, women, boys, men, and gender diverse people. It influences how people perceive themselves and each other, how they act and

interact, and the distribution of power and resources in society. Gender is usually conceptualized as a binary (girl/woman and boy/man) yet there is considerable diversity in how individuals and groups understand, experience, and express it" [7]. Differentiating between sex and gender helps researchers to be more precise about whether they are examining social or biological mechanisms, or a mixture of both.

In many ways it is surprising that an argument still needs to be made of the importance of sex and gender in clinical research. The fact remains, however, that considerable clinical research is conducted wherein the mechanisms by which sex and gender influence health remain unexplored. For example, a recent study found that despite substantial efforts in past years to recruit women into cardiovascular clinical trials, women remain woefully under-represented [8]. Even when women are included in trials, the majority of researchers fail to consider sex and gender differences (i.e., do not stratify their analyses), do not report negative findings (i.e., are biased toward statistical significance), or are unable to determine whether the absence of differences are likely the result of insufficient sample size (i.e., they do not ensure sufficient statistical power, *a priori*) [9].

In recent years, the implications have come to light of not considering sex or gender in clinical trials. For example, in 2013, the US FDA lowered the recommended dose for women taking the sleeping medication, zolpidem, after complaints were made about daytime drowsiness that led to severe consequences, including motor vehicle crashes [10].



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This dosing change did not occur simply because women are smaller than men; women metabolize drugs differently than men because they have a higher percentage of body fat and are exposed to different levels of hormones.

Left to their own devices, many scientists would not concern themselves with the representation of subpopulations in their clinical trials. Recruiting sufficient numbers of eligible participants is difficult enough without the added challenge of achieving a balanced sex ratio. Yet, an underlying principle of clinical research is that patients entering a trial should be reasonably representative of the population that will be later treated by the intervention under study. Excluding subpopulations (e.g., women) can lead to the misapplication of an intervention and can be very costly. In preclinical research, when potential targets for clinical interventions are identified, a paucity of understanding related to the influence of sex is typical. For example, despite the unequivocal evidence related to differences between male and female brains, it has been reported that, in the field of neuroscience, 5.5 male animal models are used for every female model [11]. This practice represents a missed opportunity to ensure that robust clinical models and targets are developed and that a solid foundation for clinical intervention is developed.

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There is growing recognition that sex and gender are key considerations in clinical research and that steps must be made to encourage their meaningful integration. We at CIHR now require that all applicants for research funding indicate whether their proposed research takes sex and gender into account, and provide a rationale for their response. As a result of this policy, we have witnessed an impressive uptake of sex and gender considerations, particularly in the area of clinical research [7]. Other funding agencies are also researching and developing policies promoting – or even requiring – the integration of sex and gender analyses in health research. In 2013, the European

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Commission funded a project with nine national funding agency partners from across Europe. The project, known as Gender-Net, is focused on developing ways to enhance the uptake of sex and gender considerations in research. Similarly, the US NIH have recently announced plans for a policy change that will require researchers to integrate sex considerations in preclinical research [12].

The field of sex, gender, and health has progressed considerably, but there is more work to do. The CIHR Institute of Gender and Health has embarked on an ambitious plan to shape a science agenda that embraces sex and gender and that will in turn unlock new knowledge that supports better health for men, women, girls, boys and gender-diverse people. Strategy 2017 includes three strategic directions: integration, innovation and impact. Our integration goals are focused on facilitating the uptake of sex and gender considerations across the research pipeline - from grant writing to the mechanics of peer review and publishing. It is clear that considering sex and gender in health research is a lever for new insights and innovation. New breakthroughs are occurring in several fields that are now beginning to take a sex and gender perspective, including cognitive degeneration, pain, inflammation, and responses to drugs, to name but a few examples. Our focus on innovation encourages a fresh look at areas of health research that have not adequately taken up sex and gender. Finally, Strategy 2017 aims to increase the impact of sex, gender, and health research by helping to mobilize evidence into health policies and clinical interventions that are safe and effective for everybody.

The future of gender, sex, and clinical research is full of opportunity. Have you considered the possibilities? To learn more about Strategy 2017 see reference [13].

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