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The use of 'sex' and 'gender' in medical research

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Abstract

There is a widespread practice of using 'sex' and 'gender' interchangeably. The World Health Organization considers that they are not. It defines sex as a set of chromosome-dependent biological variables that show unique hormone profiles and anatomy. Conversely, gender refers to socially constructed sex attributions with differential roles, behavioral expressions, identity, etc. Researchers and institutions have proposed guidelines to ensure that good science is not compromised by ideologies, media or social pressures, morality, religion or economic interests. Sex differences are immune to any ideology or socio-cultural interest, because they are governed by biologically determined genetic parameters. Considering men and women to be alike is very valuable from a moral or social perspective, but ignoring differences could be wrong and unacceptable from a biomedical perspective. The organization of health and/or research systems that does not consider the different morbidity, evolution or treatment response depending on sex would generate biases and mistakes. To work on medical innovation with a gender perspective should need to take sex differences into account and integrate them properly, recognizing diversity. The controversy is not just about sex or gender, but about sex and gender and how they may influence each other. Maintaining a scientific and academic approach will help both to advance science and enrich laws and/or ideologies.

Keywords

Sex. Gender. Genetic determinants. Social construction.

Introduction

For some years now, the custom has spread both in academic articles and in medical conferences, 'sex' and 'gender' are used indistinctly or even as synonyms. This way of proceeding could have its origin in the use that has been made of the term 'gender' in society in general, promoted by various institutions that sought with it the quest for equality and subject's freedom to make their own decisions on sexuality.

When approaching epidemiology, research, and health care, however, we need to consider if sex and gender are really interchangeable terms. Do they really mean the same thing? The World Health Organization clearly defines these terms differently: 'Sex' refers to a set of biological variables in humans and animals, which are dependent on chromosomes and show differential hormone profiles and particular anatomy. 'Gender' refers to attributions about sex, with socially constructed roles, behavioral expressions, identity, stereotypes, etc[1].

Given the possible ideological and political influences and pressures, and the social confusion generated by the use "in the street" and in the media, researchers[2] and institutions have made specific proposals to preserve good scientific and academic work[3]. It should not depend on ideology, media and

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social pressures, morality, religion, or economic interests[4]. This does not mean that all the aforementioned dimensions are ignored or despised; on the contrary, they should be known and considered adequately[5]. Since sex and gender refer to distinct features, both should be integrated into clinical and research approaches. They are variables that can determine, influence, or bias in a different way when examining conditions in individuals, groups or populations.

The controversy is not just about sex or gender, but about sex and gender and how they may influence each other. The discussion is also about the mechanisms that underlie their interaction. We may or may not agree with people's lifestyles, ways of understanding relationships, behaviors, etc., but if we want to carry out quality clinical care or medical research, it is necessary that we know the reality that we are targeting and examining. Then, using the right terms accurately is mandatory; any interpretation should come later.

Distinction and integration of sex and gender into the medical field

There are differences due to sex that are "immune" to any ideology or cultural influence because they are determined by biological genetic parameters[6]. For example, considering men and women, as people, to be equal in terms of capacities and possibilities of development, there is no doubt that is correct from a moral, social, ethical, political or human rights perspective. However, if the statement is made from a biological perspective, it would dismiss the particularities of each biological sex, so relevant from a biomedical perspective. As example, osteoporosis is far more frequent in women than in men, particularly after menopause, so that screening with densitometry is in general recommended in women but not in men[7]. In contrast, sexual human immunodeficiency virus (HIV) transmission is by far more frequent among men who have sex with men (MSM) than among lesbians[8]. Accordingly, pre-exposure prophylaxis with antiretrovirals is only considered for HIV-negative MSM with multiple sex partners but not for lesbians[8,9].

An article published in "Science"[10] has definitively stated that biological sex influences gene expression in almost every distinct human tissue, determining multiple features, as the response to medications, the density of bones, the percentage of body fat, the formation of atherosclerotic plaques, etc. Even the risk of mental disorders with strong biological background, as autism or Alzheimer's disease, is influenced by sexual differences, so that the former is more common in men and the latter in women[11].

For gender, we assume that men and women are influenced, affected, and/or pressured by the same sociocultural variables. Thus, they can generate bias in the way we understand the person who asks for professional assistance or in the research design. If we look at factors associated with gender attributions in certain jobs, family tasks, sex violence, etc., we recognize that we rarely consider them as covariables or modulators in epidemiology or treatment studies. However, it is clear that gender roles and stereotypes can affect people's health, including considerations such as dominance-submission, power-success, work and/or psychosocial overloads, aesthetic demands of beauty-strength, etc. In such a way, they can influence health organizations or research systems, adopting either more "gyne" or "andro-centric" perspectives; thus, it would generate biases.

Besides distinct meaning, sex and gender may influence each other. Biological determinants may impact on gender attributions and, in turn, gender stereotypes have biological manifestations. As example, in neurodevelopmental disorders, both sex and gender contribute to biological and behavioral variability[12]. Methodological limitations frequently inadequate measure these constructs, limiting the translational potential of such research[13].

The US National Institute of Health remarks the variable "sex" as biological and "gender" as psychosocial (Fig. 1)[14]. In Canada, funding of studies requires that the variables sex and gender be treated as distinct. It recommends using "sex" when referring to biological factors and "gender" when referring to cultural, psychosocial, or attributed identity factors. Then, demographics and any other data should be analyzed by sex or gender or both[15.]

In recent global situations such as the COVID-19 pandemic[16], besides considering biological variables, some gender features may modify disease outcomes, including COVID-19 severity and mortality. This is the case for less hand washing, smoking, and drinking, rejection of social isolation, social obligations, psychological stress, and low socioeconomic status.

Another example can be found in the way cigarette smoking differs by biological sex and the social construct of gender. Women compared to men are targeted differently in tobacco advertising, since they become dependent of tobacco smoking more rapidly, have more difficulty quitting and maintaining tobacco abstinence, may be less sensitive to changes in nicotine concentration

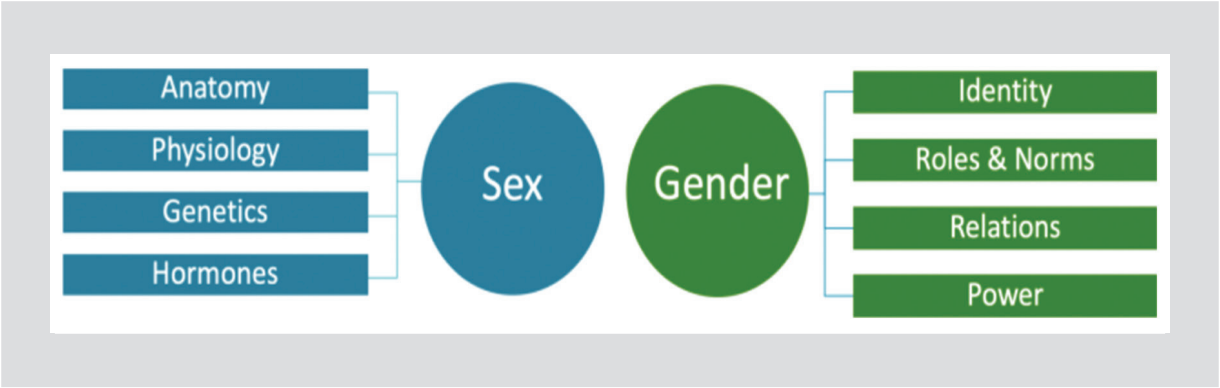

Figure 1. *Dimensions of sex (biological variable) and gender (social and cultural variable) (adapted from reference DHHS[14]).*

and smoke to manage stress, mood, and weight gain. Therefore, it is crucial that health regulators consider these differences when formulating policies and regulatory actions related to tobacco products[17].

In the case of mental health, several authors defend the importance of studying separately and then integrate the variables sex and gender. This is the case for eating disorders[18], domestic violence[19], diagnostic approaches to autism[20], depression[21], addictions, and dual pathology[22]. Anyway, specific evaluations by sex and gender in mental health care are still in very early stages[23].

Sex- and gender-specific barriers may limit research translation in some circumstances, such as women with children of childbearing age being excluded from biomarker studies and drug trials because of teratogenic effects[2]. Understanding psychopathology, and its somatic expression from a gender perspective, can broaden the way and depth with which the reality is approached by each person, acknowledging the richness of variables that may influence how to get sick[24].

Using the variables "sex" and "gender" as distinct dimensions, but at the same time overlapping and related, will allow to: (1) better reflects the reality and improve the validity of results; (2) good clinical practice, by incorporating more personalized responses according to gender particularities (attitudes or sociocultural conditions) and sex features (biology); and (3) provide further opportunities for health prevention. As example, consider the recent news about the cost-effectiveness of genetic tests to anyone at 30-years old[25]. Whereas the value for prevention of Lynch syndrome complications is clear regardless sex, the impact of genetic testing on cardiovascular complications and specially on breast-ovarian cancer is largely sex driven.

It is necessary that science does not allow itself to be dragged by a prevailing sociological current, by the "anything goes" or by the ideology to which we are personally attached. This type of bias can be observed in some guidelines in which the incorporation of the gender variable in research is promoted but partially, without including all people. It is true that for years inequality has prevailed with respect to women. However, it is no less true that men are also made gender attributions with medical implications, and that going now to the extreme of excluding men would only repeat the previous mistakes.

When designing and/or reviewing research studies, we can ask ourselves and hypothesize whether sex-disaggregated data are available or can be generated; whether needs, similarities, specific differences, incidence, or prevalence rates can be identified in women and men, and whether they are due to biological differences, gender inequalities or the influence of social factors, economic or cultural; and indicate whether the study refers to only one sex and why.

It is not easy to measure the gender variable in an absolute way, and we can use open questions and also specific questionnaires regarding attributions, stereotypes, mandates, etc., and the particularities of this population, as proposed by the Canadian Institutes of Health Research[26].

Conclusion

In summary, we suggest a list of items that could help to deal with the right way to use sex and gender in the medical field. This decalogue might serve as a guide to address sex and gender to research, incorporating the richness of these terms without adding confusion.

- Consider the variables sex and gender as diverse; assessing the rates and distribution of diseases accordingly.

- Recognize biological influences (sex) and sexual attributions, roles, and stereotypes (gender) as significant variables in development, diagnosis, treatment, and scientific research.
- Do not reduce health problems only to either biological or only socio-cultural-environmental variables. Consider both and integrate them into clinical care.
- Include equally, or balanced according to objectives and in accordance with ethical criteria, men and women in clinical trials. Collect, analyze, and compare data according to sex and study whether gender attributions – social and individual – can be confounding variables.
- Know, identify and be sensitive to gender-specific variables and biases that may occur in the hypothesis investigation.
- Contextualize the ways of getting sick, preventing or promoting health in men and women by considering social, environmental, political, cultural, religious, economic variables, etc.
- Combine qualitative and quantitative analyses, to produce a greater knowledge of gender and sex factors that may play a role. Address gender biases that may occur in research questions and hypotheses.
- Recognize different and/or specific health problems in men and women without identifying, equating, or denying them. Assess the need to consider good practice and scientific quality to people who are in special personal circumstances because of their sex, sexual identity, sexual orientation, or behaviors. Address the differences in the way each person gets sick that includes the perspective of gender and sex, following a personalized and holistic view.
- Avoid an absolute sexual dichotomy that treats men and women as totally different, as exclusive categories, without common features. Avoid derogatory male or female attribution to health problems.
- Do not reduce health problems only to either biological or socio-cultural-environmental variables.

To work on medical innovation with a gender perspective, it is worth to consider the differences and include them, acknowledge diversity and study it[27]. Keeping scientific and academic criteria independent of changing laws, social or ideological tendencies, will help to both advance science and enrich laws and/or ideologies[28].

As clearly stated in a recent BMJ editorial, 'anyone using data primarily collected for another purpose, including clinical researchers using NHS or census datasets, needs to understand the original purpose and mode of data collection. Ambiguous data collection methods that conflate sex and gender risk erroneous research findings, poor service planning, and lower quality medical practice. Gender and sex should not be used interchangeably. We risk harming patients if we do not understand the difference'[3].

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Conflicts of interest

None.

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