

VIEWPOINT

Reporting Sex, Gender, or Both in Clinical Research?

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Virtually every clinical research report includes basic demographic characteristics about the study participants, such as age, and how many participants were male/men or female/women. Some research articles refer to this latter variable as sex, others refer to it as gender. As one of the first pieces of data reported, the importance of including sex appears undisputed. But what does the sex-gender category really entail, and how should it be reported?

With emerging evidence that both sex and gender have an effect, for instance, on how an individual selects, responds to, metabolizes, and adheres to a particular drug regimen,¹ there is an ethical and scientific imperative to report to whom research results apply. This Viewpoint explains the contexts in which sex and gender are relevant and provides suggestions for improving reporting of this characteristic.

Terminology

Two common questions asked by clinical researchers are (1) Should the sex or gender of the study participants be reported? and (2) What is the correct term for

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designating males and females or men and women? The answers depend on whether biological or psychosocial factors are under study. Sex and gender are not mutually exclusive. They are integrally related and influence health in different ways. According to the National Institutes of Health (NIH)² and the Canadian Institutes of Health Research (CIHR),³ sex is considered a biological component, defined via the genetic complement of chromosomes, including cellular and molecular differences.⁴ Karyotype at birth is nearly equal for 46XX and 46XY. Sex is reflected physiologically by the gonads, sex hormones, external genitalia, and internal reproductive organs. The terms male and female should be used when describing the sex of human participants or other sex-related biological or physiological factors. Descriptions of differences between males and females should carefully refer to "sex differences" rather than "gender differences."

Gender comprises the social, environmental, cultural, and behavioral factors and choices that influence a person's self-identity and health.^{3,4} Gender includes gender identity (how individuals and groups perceive

and present themselves), gender norms (unspoken rules in the family, workplace, institutional, or global culture that influence individual attitudes and behaviors), and gender relations (the power relations between individuals of different gender identities).⁵ At present, there are no agreed-upon, validated tools for assessing gender. A 2-step approach to questioning has been proposed, whereby participants are asked both their sex assigned at birth and their current gender identity.⁶ Authors should consider appropriate use of the words sex and gender to avoid confusing both terms.⁴

Transparency

NIH policies to enhance reproducibility through rigor and transparency require that researchers address and report relevant biological variables, such as sex, in human and vertebrate animal studies.² The Sex and Gender Equity in Research (SAGER) guidelines reinforce that authors should provide an explanation in the methods section whether the sex of human research participants was defined based on self-report or was assigned following external or internal examination of body characteristics or through genetic testing or other means.⁴ When sex is based on self-report, it will be incorrect in a very small percentage of individuals because some individuals will not be 46XX or 46XY. However, in most research studies, it is not possible to conduct detailed genetic evaluation to determine the genetic make-up of all participants.

Authors reporting the results of clinical trials should analyze and report data separately for male and female study participants.^{3,4} Three compelling reasons drive the recommendation to stratify and report outcome data by sex, gender, or both. One reason is to avoid drawing incorrect conclusions. When results for male and female participants are combined, the average of aggregated male and female participants' results may mask differences between them. The effects of an intervention in one sex might be greater than in the other; toxicity might differ; symptom profiles might differ; or one sex might experience more adverse effects.¹ Failing to account for gender can also lead to spurious results. For example, gender, independent of sex, predicts poor outcomes after acute coronary syndrome.⁷

Another reason to report data by sex, gender, or both is to facilitate meta-analysis. When no differences exist, and even when studies are underpowered, the raw data should be presented to allow for meta-analysis by sex, gender, or both and can inform sample size calculations for future studies. A third reason is to reduce waste in research. Repeating a trial because previous

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Table. Suggested Approach for Reporting Demographic Characteristics of Study Participants and Outcome by Sex and Gender (N = 59)

| Demographic Characteristics | |
|-------------------------------|---------|
| Total No. | 59 |
| Age range, y | 18-90 |
| Sex, No. ^a | |
| Male participant | 27 |
| Female participant | 32 |
| Gender, No. ^b | |
| Men | 26 |
| Women | 33 |
| Outcome, No. (%) ^c | 50 (85) |
| Males | 20 (40) |
| Females | 30 (60) |
| Outcome, No. (%) ^d | |
| Male | 20 (74) |
| Female | 30 (94) |

^a Ascertained by genotyping of blood sample.

^b Ascertained by self-report.

^c The number (%) occurring in males and females of the total outcomes (n = 50).

^d Number (%) of outcomes occurring within the subgroups of males (20/27) and females (30/32).

relevant studies did not disaggregate study participants and report results by sex, by gender, or both is unethical. Following this logic, all tables and figures in the results section of a manuscript should clearly identify the magnitude of effect according to sex, gender, or both.

The Table shows an example of how to specify and report sex and gender in a clinical research article.

The Bigger Picture

Practical issues regarding how to structure demographic data lead to bigger questions about what to study and why. For example,

how do sex and gender affect health, separately and collectively? Is the basis of the pathology attributable to genes, sex hormones, gender-related environmental exposures, or some combination of these factors? As questions concerning sex and gender are refined, new methods will need to be developed, including new ways to ascertain data about these variables and statistically analyze them.³

Many journals, including *JAMA*, are requiring more transparency and rigor in reporting of such data. According to the *JAMA* Instructions for Authors: "Report the sex distribution of study participants or samples in the Methods section, including studies of humans, tissues, cells, or animals. If only one sex is reported, or included in the study, explain why the other sex is not reported or included, except for studies of diseases/disorders that only affect males (eg, prostate disease) or females (eg, ovarian disease)." To meet this standard, researchers are encouraged to access available resources including websites for the Gendered Innovations in Science, Health, and Medicine, Engineering, and Environment project at Stanford University,⁸ the NIH Office of Research in Women's Health,² and the CIHR Institute of Gender and Health.³

Conclusion and Recommendations

Sex is recognized implicitly as an important factor in clinical research. More work is needed to standardize the way sex and gender are reported and elucidate the way these characteristics function independently and together to influence health and health care. The following recommendations for reporting in research articles may improve understanding and comparability across studies, and help deliver truly personalized medicine: (1) use the terms *sex* when reporting biological factors and *gender* when reporting gender identity or psychosocial or cultural factors; (2) disaggregate demographic and all outcome data by sex, gender, or both; (3) report the methods used to obtain information on sex, gender, or both; and (4) note all limitations of these methods.

ARTICLE INFORMATION

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