

Inclusion of Sex as a Biological Variable in Research

An Official Position Statement of the Society for Women's Health Research

Position

Research must take into account sex as a biological variable (SABV) in order to better understand its impact on health and disease. SWHR supports studying, analyzing, and reporting on biological sex differences as standard practice across all research. Exceptions should only occur in scientifically justified cases, such as when a study focuses on a sex-specific condition (e.g., pregnancy) or prior evidence suggests no sex differences exist. SWHR also recommends the following:

- Expanding the exploration of SABV in preclinical and clinical research activities and increasing and improving training of researchers on SABV study design in preclinical and clinical research.
- Improving training for grant reviewers working to ensure regulations related to SABV are properly incorporated within grant proposals submitted to federal agencies.
- Prioritizing SABV within federally funded research by expanding initiatives such as the National Institutes of Health (NIH) Sex & Gender Administrative Supplement Program, which grants supplemental funding as an incentive to add a sex component to an existing research program.
- Requiring researchers not only to include both sexes within their studies, but to utilize research designs allowing sufficient analytical power within sex-disaggregated analyses to return statistically significant outcomes, and further, to publish outcome data from these analyses.

Background

Biological differences between the sexes influence disease development, progression, and response to treatment. Studying biological sex differences and applying what we learn to clinical practice can improve health outcomes for all patients.

Until about 25 years ago, essentially all health research was conducted on male subjects due to the unfounded idea that female subjects will demonstrate significant variability due to their menstrual cycles as well as the fear of causing harm to a potential pregnancy.¹ Scientists also argued that using only one sex would reduce variation in results.

¹ Beery, AK. Inclusion of females does not increase variability in rodent research studies. *Sci Direct*. 2018, 23:143-149. doi:10.1016/j.cobeha.2018.06.016

This exclusion of females in health research wasn't just limited to humans. It extended to research on female animals, cells, and tissue. Researchers assumed that they could simply extrapolate their male-only study results to the entire population, a dangerous precedent that overlooked fundamental differences between the sexes.

Thanks to advocacy by SWHR and other groups, Congress passed the National Institutes of Health Revitalization Act of 1993, mandating the inclusion of women and minorities in NIH-funded clinical trials. In the same year, the Food and Drug Administration (FDA) changed its policies to require the inclusion of women in efficacy studies and in the analysis of data on sex differences. Despite NIH-funded clinical trials being required to use women and men since 1993, data show that only 26% of these trials published in 2015 reported at least one outcome by sex or explicitly included sex as a covariate in statistical analysis.²

In 2016, the NIH enacted a policy requiring grant applicants to consider SABV in NIH-funded research on vertebrate animals and humans. Based on the 2016 policy, if grant applicants seek to study only one sex, they must offer strong justification. The implementation of the NIH Policy on Consideration of Sex as a Biological Variable in NIH-funded Research has been a positive catalyst for advancing SABV within the NIH. However, because the policy only requires that investigators *consider* the role of SABV in research designs, analyses, and reporting — and stops short of requiring it — there is great variability in the testing and reporting on sex differences in NIH-funded research.

Current research shows that ignorance of SABV and the dominance of male subjects in studies persists. Overrepresentation of males in preclinical work occurs across fields, from chronic pain to mental health, from autoimmune disorders to stroke research, and within trials for therapeutics and medication. As compared to a 2009 study,³ recent research indicates that significantly more preclinical articles published in 2019 included two sexes in the sample population. However, little progress has been made in analyzing study results by sex. Among studies that included two sexes as subjects, only 42% included sex-disaggregated analyses, down from 50% of articles in 2009.³

Because of research that incorporates and analyzes SABV, we are beginning to understand why certain conditions, disorders, and diseases occur disproportionately in women and/or affect individuals differently due to their sex. Better incorporation of SABV within research will improve not only women's health, but population health more broadly.

SWHR uses the term "sex" to refer to the classification of living things according to reproductive organs and functions assigned by chromosomal complement, and the term gender to refer to the social, cultural, and environmental influences on the biology of women or men. We use the word "woman" (and the pronouns "she" and "her") to refer to individuals who are assigned female sex at birth. As gender-neutral language continues to evolve in the scientific and medical communities, we will reassess this usage as necessary.

² Geller, SE, Koch, AR, Roesch, P, Filut, A, Hallgren, E, Carnes, M. The more things change, the more they stay the same: A study to evaluate compliance with inclusion and assessment of women and minorities in randomized controlled trials. *Acad Med.* 2019, 93(4): 630-635. doi: 10.1097/ACM.0000000000002027

³ Beery AK, Zucker I. Sex bias in neuroscience and biomedical research. *Neurosci Biobehav Rev.* 2011;35(3):565–572. doi: 10.1016/j.neubiorev.2010.07.002