WOMEN'S HEALTH

The power—and complexity—of policy to drive advances in women's health

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As international investments in women's health increase, funders are adopting sex and gender policies and regulators are requiring disaggregated data, actions which impact research design.

It is now well recognized that the inadequate inclusion and consideration of female participants in medical research have led to health inequities, from preclinical studies in cells and animals through to human clinical trials. Examples abound of treatments that were never adequately tested in women and were either: inappropriate [lower limb prostheses (*1*)], ineffective [lecanamab (*2*), an Alzheimer's treatment], non-beneficial [implantable cardioverter defibrillators (*3*)], or detrimental [thalidomide, an anti-nausea and morning sickness drug (*4*)]. All of which have a cost, both financial and, more importantly, to patient health.

Over the past two decades, research funders from several high-income countries have introduced policies and statements regarding the incorporation of sex and gender in research (*5*). High-profile sex and gender policies have been adopted by the Canadian Institutes for Health Research (2006), Horizon Europe (2014), and the US National Institutes of Health (2016). Policies are soon to be rolled out in the UK in partnership with the Medical Science Sex and Gender Equity (MESSAGE) project, with a policy having been adopted by the Medical Research Council in 2023. In Australia, a 2024 statement by the National Health and Medical Research Council strongly encourages all research to consider sex, gender, and variations in sex characteristics and sexual orientation.

Such policies are intended to reduce the sex- and gender-based health inequities experienced by women and other marginalized sex and gender groups, as well as to produce scientific knowledge that is more accurate, representative, and reproducible. These initiatives encourage or require researchers to demonstrate how they have considered or accounted for sex and gender (when relevant) in their research. "Consideration" and "accounting for" are, by design, terms with wide scope for interpretation. Naturally, this has led to the question (by funding applicants and grant evaluators alike), "How do we know we're doing it right?"

As a start, consideration forces the scientist to be clear about how to define and operationalize sex and gender. These terms are high-level categories used to describe a constellation of characteristics or constructs, each of which exhibit natural variation within the population, may change across the lifespan, and, in the case of gender, are influenced by culture. Sex characteristics may include chromosomes, hormones, or sex organs. Gender comprises identity, behavior, experiences, social norms, and/or power dynamics. When referring to sex, the terms "male" and "female" are typically used, whereas the terms "girl/women" and "boy/man" are typically used when referring to gender. Moreover, traditional binary definitions of sex and gender are being revisited. People with variations in sex characteristics (intersex), or those who are trans, non-binary, or with other identities and experiences underscore the breadth of sex and gender modalities (*6*).

INCLUSION AND CONSIDERATION

It is often thought that sex and gender can be adequately accounted for through improved inclusion of female as well as male cells, animals, or humans in the sample. Coincident with the introduction of North American sex and gender research policies, for example, a range of scientific disciplines have seen an almost threefold increase in the proportion of mixed-sex studies relative to studies conducted in only one sex (*7*).

Of course, to reduce knowledge gaps in women's health, inclusion of women in research is a prerequisite. But, while a good start, the inclusion of women in research alone will not shift the needle on women's health inequities to the required extent. At a minimum, data need to be analyzed and disaggregated according to sex and gender. Moreover, it is important to recognize that inclusion is not synonymous with consideration. Inclusion can be satisfied by merely inserting women into the current research landscape—one in which the questions asked, and the methods used to address these questions, are shaped by an assumption that the male body is the default.

Consideration, by definition, requires deeper thought about how sex- and gender-specific variables may influence the outcomes measured. When it is recognized that health conditions are more prevalent in women, or manifest differently in women, the underlying mechanisms of these differences must be interrogated. Such differences can be driven by a combination of, or interactions between, one or more of the many characteristics subsumed by sex and gender, and the environment in which they exist. Relying on a male prototype or a singular interpretation of what it means to be a woman hampers developing an understanding of the mechanisms that underpin sex and gender differences. This understanding is critical to ensure women receive personalized and optimized health care. Notably, cisgender men's health and experience of health care is also shaped by their sex and gender, so accounting for these variables benefits all people (*8*).

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Consideration of sex and gender also shapes the very nature of the questions asked. Women must be invited into the research process as co-designers, and should drive research generation, so that areas of health that women perceive as most important are addressed. It is past time to expand the narrative of women's health beyond the perception that it is solely about fertility or reproductive health. When science is expanded to consider women, variables that could never be examined in male models of health and disease become available for exploration, including, but not limited to, the impact of X chromosome inactivation, where one of the X chromosomes is silenced, and X inactivation escape, where a proportion of genes from the inactivated X chromosome escape this silencing. Similarly, one may ask how changes in the hormonal milieu associated with the menstrual cycle, pregnancy, contraception, and menopause impact health trajectories over the lifespan, or even vaccine dose and safety.

These examples speak to the notion that including women in health research depends on consideration of other variables, such as age, because an 18-year-old woman and her health needs are not the same as those of a 60-year-old woman. As such, advances in women's health will depend on additional policies beyond existing sex and gender policies. The US Inclusion across the Lifespan Policy is meant to ensure that heterogeneity in women across their lives is adequately accounted for in research. Targeted investments from government, such as the White House Initiative on Women's Health Research, and directives to industry from the Innovation Equity Forum's Women's Health Innovation Opportunity Map 2023 to advance women's global health research and development, will serve to fill the gaps in historically under-researched areas like endometriosis or menopause.

Research will need to adhere to policies that mandate inclusion of historically marginalized or systemically excluded women from Indigenous peoples, LGBTQIA+ communities or ethnic and racial minorities. For example, when thinking about sex and gender from an Indigenous perspective, the complex role of coloniality and the extractive nature of western scientific discovery in contributing to sex- and gender-based inequities must be considered. Within this context, pursuit of sex and gender research that prioritizes euro-centric science has the power to decontextualize and distort Indigenous paradigms that have existed for millennia and resist cultural or linguistic translation. Such approaches fail to address inter-group variations in women's health outcomes.

THE SCIENTIFIC METHOD STILL APPLIES

Accounting for sex and gender in research, with all this nuance and complexity, is no small feat. Indeed, the challenge, complexity, and imperative that attract some scientists to the study of sex and gender differences can confuse or repel many others, even those who acknowledge the value of rectifying sex and gender imbalances in research. In many ways, this reaction is puzzling. After all, scientists are well equipped to manage complexity and are drawn to a challenge. Scientists know how to break down complex problems into smaller ones. Relevant variables are examined systematically. There is freedom to pursue different questions, different possible mechanisms, while recognizing that no single study can address every question nor every possible mechanism since science is cumulative and collaborative. The scientific method still applies to advances in women's health and the consideration of sex and gender. It is for these reasons that successful sex and gender policy initiatives around the world are not overly prescriptive—because the right way to consider sex and gender will differ according to the problem under investigation and the context in which the questions are asked. These policies are not trying to stymie intellectual freedom. Rather, policies are in place to help overcome historical and ongoing biases in scientific models and practices to ensure that appropriate health care is provided regardless of sex or gender.

Successful sex and gender policy initiatives by research funders in Canada, the US, and Europe as key exemplars, have several common elements (*5*). First, adherence to mandates is assessed by requiring researchers to explain how they have accounted for sex and gender in the funding application, and requiring assessors to evaluate and, in some cases score, these responses in the peer review process. Second, mandates are balanced with incentives, such as priority funding schemes for women's health research. Third, educational resources and training programs provide opportunities for capacity building amongst research applicants and peer reviewers to ensure that sex and gender are appropriately integrated into all stages of the research pipeline. These initiatives have led to improved treatments both for conditions that exclusively impact women (e.g., menopause) and those that disproportionately impact women (e.g., autoimmune disease) (*9*).

Yet, some reactions to and criticisms of sex and gender research policies give the impression that women's health and sex- and gender-based research are sometimes judged by different standards to that of other research. For example, concerns about the financial costs or practicalities of including women and female samples in research (*10*) ignore the fact that all research must overcome financial and logistical hurdles, not to mention the economic consequences of systematically excluding one sex or genders from research. Another concern is that the outcomes of sex- and gender-based research could be misrepresented in media and perpetuate stereotypes and discrimination, such as the notion that all differences detected between men and women are "hard-wired" rather than driven through enculturation processes (*11*). This is a valid concern yet is also a risk shared by many areas of health research (*12*) and certainly pales in comparison to the risks that come with the knowledge gaps arising from the exclusion of females and women from studies.

Another area of controversy relates to whether sex and gender should be examined categorically by comparing outcomes between females versus males or by focusing on specific sex- and gender-related variables, such as hormone levels, chromosomes, or alignment with gender norms (*12*, *13*). This debate has arisen in part from the valid desire to ensure that already marginalized sex and gender groups such as people with innate variations in sex characteristics, trans, and non-binary, do not get left behind as we improve the representation of cisgender women in research. This debate is also fueled by the demonstration that there is often large cross-over in the distribution of data from females and males, or women and men, despite significant sex differences in the average outcome. The latter argument calls into question the value of using sex or gender as categories of interest in research, and by extension, embedding these constructs in research policy.

These criticisms lead to questions by granting agencies, researchers, and peer evaluators about whether the policies are getting it right or whether policies to advance women's health are causing more harm than good. While the merits and pitfalls to the different policies and approaches are vigorously debated, one would contend that debates about how to conduct women's health research are preferable to a complete lack of scientific discourse on the topic. Such debates must not fuel apathy toward changing the status quo to correct sex and gender biases in health and medical research. Rather, flexibility within sex- and gender-research policies should be considered an advantage as circumstances will exist when it is relevant to compare different sexes and/or genders (*12*). Other times, it will make more sense to investigate certain sex-specific characteristics such as differences in cycling hormone levels, pregnant versus not pregnant status, and cycling women versus those using various forms of hormonal contraception versus women who are post-menopausal (*13*). Equally, the health needs and knowledge gaps of trans, intersex, and non-binary people must not be ignored, and must be met by proactive recruitment methods, data disaggregation, and further incentivization by priority funding calls. Ultimately, the debate around the right way to consider sex and gender in women's health research will be driven by scientific rigor and inclusion. The answer to conducting the best sex and gender science is not static. The expectation is that policies and programs designed to advance research into women's health will evolve and adapt just as remarkably as the diverse women they seek to support.

REFERENCES

1. K. Lehavot, J. P. Young, R. M. Thomas, R. M. Williams, A. P. Turner, D. C. Norvell, J. M. Czerniecki, A. Korpak, A. J. Littman, Voices of women veterans with lower limb prostheses: A qualitative study. *J. Gen. Intern. Med.* **37**, 799–805 (2022).
2. R. F. Buckley, J. Gong, M. Woodward, A call to action to address sex differences in Alzheimer disease clinical trials. *JAMA Neurol.* **80**, 769–770 (2023).
3. S. Barra, R. Providência, S. Boveda, K. Narayanan, M. Virdee, E. Marijon, S. Agarwal, Do women benefit equally as men from the primary prevention implantable cardioverter-defibrillator? *Europace* **20**, 897–901 (2018).
4. M. R. Waggoner, A. D. Lyerly, Clinical trials in pregnancy and the "shadows of thalidomide": Revisiting the legacy of Frances Kelsey. *Contemp. Clin. Trials* **119**, 106806 (2022).
5. J. White, C. Tannenbaum, I. Klinge, L. Schiebinger, J. Clayton, The integration of sex and gender considerations into biomedical research: Lessons from international funding agencies. *J. Clin. Endocrinol. Metab.* **106**, 3034–3048 (2021).
6. F. Ashley, S. Brightly-Brown, G. N. Rider, Beyond the trans/cis binary: Introducing new terms will enrich gender research. *Nature* **630**, 293–295 (2024).
7. N. C. Woitowich, A. Beery, T. Woodruff, A 10-year follow-up study of sex inclusion in the biological sciences. *eLife* **9**, e56344 (2020).
8. S. Haupt, C. Carcel, R. Norton, Neglecting sex and gender in research is a public-health risk. *Nature* **629**, 527–530 (2024).
9. J. A. Clayton, D. W. Bianchi, R. Hodes, T. A. Schwetz, M. Bertagnolli, Recent developments in women's health research at the US National Institutes of Health. *JAMA* 10.1001/jama.2024.25878 (2025).
10. R. D. Fields, NIH policy: Mandate goes too far. *Nature* **510**, 340 (2014); https://doi.org/10.1038/510340a
11. L. Eliot, S. S. Richardson, Sex in context: Limitations of animal studies for addressing human sex/gender neurobehavioral health disparities. *J. Neurosci.* **36**, 11823–11830 (2016).
12. A. P. Arnold, S. L. Klein, M. M. McCarthy, J. S. Mogil, Male-female comparisons are powerful in biomedical research—Don't abandon them. *Nature* **629**, 37–40 (2024).
13. M. Pape, M. Miyagi, S. A. Ritz, M. Boulicault, S. S. Richardson, D. L. Maney, Sex contextualism in laboratory research: Enhancing rigor and precision in the study of sex-related variables. *Cell* **187**, 1316–1326 (2024).

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