

Submitted by the Endocrine Society to the National Academies Ad Hoc Committee on the Assessment of NIH Research on Women's Health

March 20, 2024

The Endocrine Society is enthusiastic about the opportunity to contribute to the Assessment of NIH Research on Women's Health and we sincerely appreciate the Committee's work on this important project. Founded in 1916, the Endocrine Society is the world's oldest, largest, and most active organization devoted to research on hormones and the clinical practice of endocrinology. Our membership of over 18,000 includes many NIH-funded scientists who are advancing women's health through biomedical research. Our members' expertise helps us understand, treat, and cure many conditions that only affect women such as polycystic ovarian syndrome, fibroids, endometriosis, and menopause; and those that disproportionately impact women or that affect women differently such as thyroid disease, osteoporosis, diabetes, and infertility. We also count among our members basic scientists who study estrogen and progesterone receptors and central mechanisms that control reproduction. Collectively, we are dedicated to improving women's health across the life course through the discovery and application of scientific advancements to patient care. Our comments address topics that span the missions and objectives of all Institutes and Centers (ICs) at NIH, and our belief that a comprehensive approach to Women's Health requires strategic planning, coordination, and investment across all ICs. In our comments, we define women's health as pertaining to individuals that identify as women, and/or have female reproductive organs, and/or produce or use gonadal hormones commonly associated with the female sex, from in utero development to death.

### **A Definition of Women's Health Should Reflect a Life Course Approach**

While we appreciate that a woman's reproductive-age years are a critical window in the context of public health (e.g., persistently high maternal morbidity and mortality), we urge the Committee and by extension the NIH to consider the entire life course, from development *in utero* through advanced age, when assessing funding strategies. Peripubertal girls and peri- and postmenopausal women face unique and important health issues and disparities; advancing health and gender equity through research investments therefore requires the inclusion of girls and women of all ages. We note that hormonal status may influence health and disease in myriad ways, including as the fundamental drivers of different disease and treatment outcomes between men and women. Because the relative levels of estrogen and other ovarian hormones change at different points in a woman's life (e.g., infancy, pre-puberty, puberty, pre-, peri- and post-menopause), designing inclusive research strategies for women at all life stages will improve outcomes and help us better understand the role of gonadal hormones in disease as well as healthy aging. The inclusion of *in utero* development is also critical to the definition of women's health, as maternal environmental exposures, and other factors such as adverse pregnancy outcomes may influence health in ways that manifest throughout life, often with sex-specific effects.



## **Gender and Biological Sex are Both Essential Components of Women's Health**

A comprehensive assessment of women's health should reflect the role of biological sex in health, and also consider gender influences in health outcomes<sup>1</sup>. We commend the NIH for establishing the Sex as a Biological Variable policy; however, NIH structures, systems, and review processes should be strengthened to ensure that this policy is implemented in funded research, as intended.

Researchers who are interested in identifying and studying sex differences through their research should be encouraged, and grant reviewers with expertise should be identified to provide useful evaluations and feedback to prospective grantees so that they are empowered to identify potential sex specific effects. This includes appreciating when it may be unreasonable to expect sufficient data to identify and completely characterize sex differences with rigorous statistical power, e.g., when preliminary data has yet to indicate the potential for a sexually dimorphic effect. When possible, NIH should require disaggregated, sex-specific analysis of male and female research participants at all levels of biological complexity. Designation of reproductive phase that includes pre-puberty, puberty, pregnancy and menopause, and identification of use of exogenous hormones including contraception and hormone therapy for menopause symptoms would improve refinement of clinical trial inclusion/exclusion criteria and interpretation of clinical outcomes.

Gender is also essential to defining women's health, and clinical research should capture information about a person's biological sex as well as their self-reported gender to ensure that we can better understand when sex and gender are not interchangeable, how sex and gender may diverge under biological and social influences, and avoid a strictly binary approach to sex and gender health. We note that persistent structural gender biases in society may create challenges as the Committee considers recommendations about relative funding levels for different areas of women's health research. For instance, males are predominantly studied in neurotrauma research because neurotrauma is a male dominated injury, but women may experience mild or repetitive traumatic brain injury that often goes unreported and un-recognized leading to poor endocrine, neurocognitive, and neuropsychological outcomes. Furthermore, while we must be mindful of the leading causes of death in women, it may not be appropriate to make funding recommendations based solely on relative rates of injury or disease.

## **Researchers Should be Encouraged to Study Women's Health**

We emphasize the importance of diversity, equity, and inclusion, including representation of women, across the biomedical research enterprise and at leadership levels. We note the success of cohort programs such as the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) and the Women's Reproductive Health Research (WRHR) program in developing peer and mentor networks to advance the careers of underrepresented groups in research. The Committee should explore ways that NIH could expand these programs to encourage research in more fields of

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<sup>1</sup> Bhargava et al., *Endocr Rev.* 2021 May 25;42(3):219-258. doi: 10.1210/edrev/bnaa034.



biomedical research, especially where the Committee identifies gaps and opportunities. Additionally, NIH training systems could be improved by identifying where flexibility is needed (e.g., K to R transition) and propose mechanisms for talented and committed women's health researchers to extend their fellowship through a competitive renewal such that they maintain momentum in their careers.

### **Additional Knowledge Gaps and Barriers**

Women's health has suffered due to historical underinvestment and persistent bias that favored the study of male research subjects. Consequently, it may be appropriate to reevaluate clinical targets and goals that were originally based on studies done predominantly in men. Replication studies may be required with more rigorous sex-specific analysis, and we suggest the Committee consider this when making funding recommendations. In addition to a more equitable approach to clinical research that rigorously evaluates historical data in fields such as cardiovascular disease, diabetes, cancer, and other topics, innovative approaches to basic research merit consideration for additional investment. This may include:

- Developing organoids or other reliable in vitro assays that represent female sex cells, tissues or organs
- Studying sex as a driver of differences in cellular biology
- Convening geneticists and endocrinologists to study how hormones and genetics intersect in healthy aging and disease
- Designing studies to understand the basis of disparate health outcomes in minoritized people
- Leveraging data from large randomized controlled trials and large clinical datasets to move from the nebulous construct of "female risk enhancers" (e.g., CVD risk) to rigorous studies to defining sex- and gender differences and to explore underlying mechanisms of disease and disability

In conclusion, the Endocrine Society appreciates the challenge facing the Committee as you seek to fulfill your charge. These challenges are magnified by various current policy and political debates related to access to care and reproductive health. We look forward to further contributions to your work and advancing our shared goals of improving the health of women. Thank you for taking on this important responsibility, and do not hesitate to reach out to Joe Laakso, PhD, Director of Science Policy at [jlaakso@endocrine.org](mailto:jlaakso@endocrine.org) if you have any questions or require clarification of any aspect of our comments.