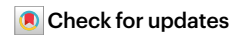


Consideration of sex differences is necessary to achieve health equity



Improved understanding of the impact of sex and gender-related factors on human health and disease and the inclusion of people of all genders in research studies is necessary to reduce health inequities and enable a more personalized approach to patient care.

Sex differences exist in all physiological systems and impact every aspect of human health and disease. Gender-related factors also affect disease epidemiology and outcomes. Failure to consider sex and gender in research and clinical care contributes to health inequities and, in particular, poor understanding of women's health. In this Focus issue, we present six articles that highlight the importance of sex differences in nephrology and physiology.

[Jager and co-authors](#) review differences in the epidemiology, management and outcomes of kidney disease in men and women. Men have a higher prevalence of albuminuria and experience faster progression to kidney failure than women, whereas women have a higher prevalence of chronic kidney disease (CKD) stages 3–5 than men but are less likely to be diagnosed with CKD, referred to a nephrologist and waitlisted for kidney transplantation. The authors suggest that a more sex-specific approach to the development of clinical guidelines could lead to more equitable management of CKD. Importantly, further research is needed to investigate the epidemiology and burden of kidney disease in transgender, nonbinary and gender-diverse individuals.

Rodent studies have shown that the abundance of renal fluid and electrolyte transporters differs in males and females, likely contributing to sex differences in kidney function and pathophysiology. [McDonough and co-authors](#) review these differences, their physiological consequences and the impact of sex on transporter regulation by hormones, diet and acid load. They highlight the need for further research into the changes that occur in the female kidney during development, pregnancy, lactation, menopause and ageing. A knowledge gap also exists regarding the bidirectional relationship between menopause and CKD, which is discussed in a Comment article by [Dines and Garovic](#). Improved understanding of this relationship could have important clinical implications for women with CKD, particularly those with potentially reversible functional menopause.

Sex differences in immunity also affect disease epidemiology, pathogenesis and outcomes. [Klein and co-authors](#) review sex differences in immune responses, the mechanisms that underlie these differences and their consequences for kidney disease, hypertension, autoimmune diseases, infectious diseases and transplant rejection.

Differences in gender roles and behaviours may also impact immunity, but little is known about the effects of these factors on the immune system.

Sexual dimorphism likely arose during evolution in response to differing selection pressures on males and females. In his Review, [Mauvais-Jarvis](#) explains that female mammals have evolved more efficient and adaptive mechanisms to store and conserve energy than males. These mechanisms of starvation resistance enable females to remain fertile during times of energy deficit, but also predispose women to the development of obesity. Furthermore, sex differences in energy partitioning, adipose tissue and glucose homeostasis underlie differing responses to anti-diabetic and anti-obesity drugs in men and women.

Despite the importance of sex in all aspects of biology, historically, most preclinical research used male animals and women were excluded from clinical studies, partly as a result of concerns regarding increased variability in results owing to hormonal cyclicity, as well as the potential teratogenic effects of pharmacological interventions¹. Although initiatives such as the NIH policy on sex as a biological variable have improved the inclusion of women in clinical trials, efforts to improve the use of female cells and models in preclinical studies have been less successful². In her Comment article, [Ahmed](#) explains that failure to consider the impact of sex and gender-related factors in basic and clinical research limits the generalizability of results and potentially leads to adverse health outcomes.

Improved understanding of the impact of sex and gender in research and clinical care is important to reduce health disparities, enable personalized medicine and potentially improve treatment outcomes in patients of all genders. To achieve this goal, researchers must ensure that their preclinical and clinical studies incorporate consideration of sex and gender-related factors at every stage from planning to publication. Editors also have a role in ensuring that sex and gender are reported in studies published in their journals³. At *Nature Reviews Nephrology*, we are committed to ensuring that our articles contain discussion of sex differences and highlight knowledge gaps where such data are not available, with the aim of raising awareness and stimulating further research.

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