

## Sex, gender and nephrology: time for a paradigm shift

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The global burden of chronic kidney disease (CKD) has reached epidemic proportions and is becoming a major public health problem in many countries. Inextricably linked to this expansion emerges the question of marked gender-based disparity in disease prevalence. Population-based studies indicate that females exhibit a greater likelihood of CKD diagnosis when compared to males. Furthermore, men and women differ concerning the underlying pathophysiology of CKD and its complications, present different symptoms and signs, respond differently to therapy and cope with the disease distinctly. Nevertheless, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines still propose a "one-size-fits-all" approach in terms of delivery of care. A review by Brar and Markell recently highlighted that recommendations for medical care of patients with CKD or end-stage kidney disease (ESKD) are not sex or gender-specific, even though there are important physiological differences between men and women.

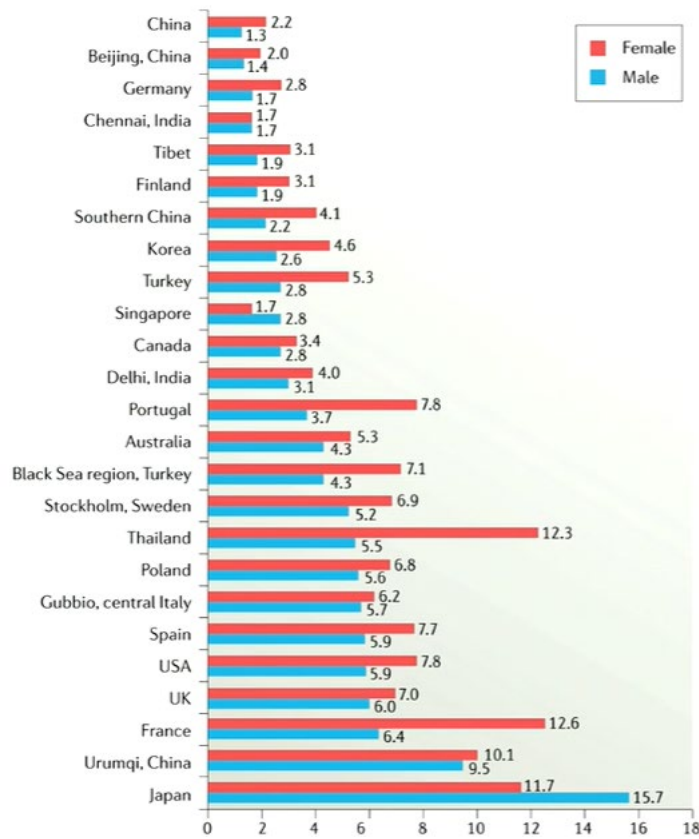


Figure 1. Prevalence of CKD stages G3 to G5 by country

### Differences in terms and medical practice

The terms "sex" and "gender" are not interchangeable. "Sex" refers to biological factors such as genetics, physiology, immunology, and anatomy, while "gender" pertains to socially framed roles.

Gender can be deconstructed into four dimensions: gender roles, gender identity, gender relations, and institutionalized gender. Gender roles are generally attributed to individuals based on their gender identity. On the other hand, gender identity refers to an individual's inner sense of self. The term "transgender" encompasses a wide range of individuals whose current gender identity differs from the sex they were assigned at birth.

Within nephrology, there are notable differences between sex and gender that impact patient outcomes. A study by Ryta et al. examined incident peritoneal dialysis (PD) patients and assessed their haemoglobin (Hb) levels. Among prevalent PD patients, Hb concentration was significantly lower in women, despite higher doses of erythropoiesis-stimulating agents (ESA) and significantly higher Kt/V. In incident PD patients, this association was present throughout the observation period, while the ESA dose in women was significantly higher at every time point. Sex-based differences also exist related to bone fractures. Naylor et al. observed that, despite the overall increase in the risk of fractures with declining renal function, women demonstrated a higher incidence of fractures than men. Carrero et al. analysed the relative risk of death related to dialysis initiation among patients from nine European countries. The results showed that women who initiate dialysis under 45 years of age have a higher mortality rate compared to men. Notably, contrary to the findings in the general population, younger women initiating dialysis were at high risk for cardiovascular mortality. In contrast, among dialysis patients over the age of 45, men demonstrate higher mortality, especially from cardiovascular disease. Nevertheless, despite these prominent sex-related differences in mortality and cause of death, recommendations for the care of dialysis patients remain uniform regardless of gender.

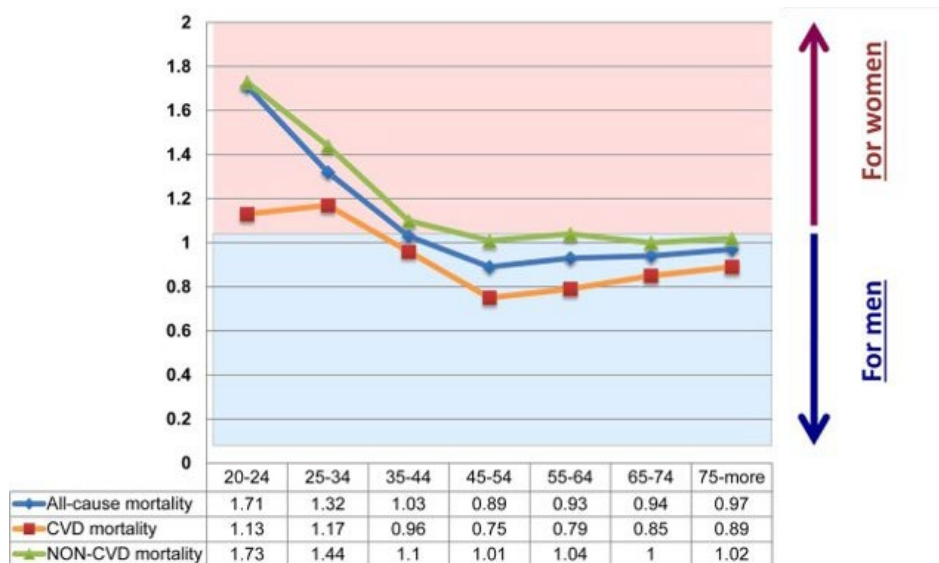


Figure 2. Relative mortality risk in women vs men initiating dialysis

Gender disparities also exist related to access and outcomes of kidney transplantation. Boucquemont et al. investigated whether adherence to prescribed therapy contributes to the higher incidence of graft failure observed in girls and young women compared to boys and young men among kidney transplant recipients. Adherence was comparable among participants of different sex aged 11 to 16 years. However, among transplanted patients aged 17 to 24 years, women demonstrated significantly greater odds of higher medication adherence scores than men, both in terms of taking adherence and

timing adherence. Thus, worse transplant outcomes among women cannot be attributed to poor medication adherence.

### The changing environment

The question of sex and gender has become a prominent driver of change in many aspects, such as different industries, politics and medicine. The recent surge of different hormonal therapies prompted the need to optimize care for transgender and gender-diverse individuals. Also, there has been an increase in nephrology studies and commentaries focusing on providing gender-affirming care to avoid possible delays in diagnosis, dialysis initiation and transplantation. In their review, Collister et al. observed that gender-affirming hormone therapy with testosterone, estradiol, and anti-androgen therapies changed body composition and lean body mass which influenced creatinine generation and the performance of estimated glomerular filtration rate (eGFR) equations in transgender persons. Therefore, confirmation of eGFR by measured GFR is reasonable when an accurate insight into GFR is needed for clinical decision-making. Gender-affirming hormone therapy is necessary for developing secondary sexual characteristics that align with gender identity.

The research group led by Sarah K. Fadich looked at serum creatinine levels in transgender men and women initiating gender-affirming hormone therapy. The results showed a clinically significant increase in serum creatinine levels in the testosterone group, while no changes were observed in the oestrogen group. However, it is currently unclear whether the changes or lack of changes in serum creatinine levels with initiation of hormonal therapy only reflect changes in muscle mass or body distribution, or whether they indicate changes in kidney function.

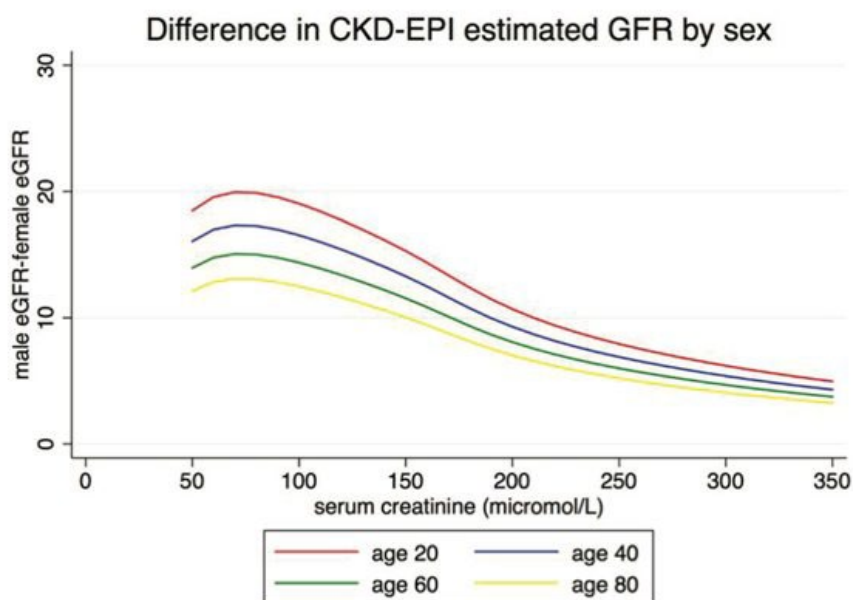


Figure 3. Differences in estimated glomerular filtration rate by sex

Eckenrode et al. studied the prevalence of kidney disease in transgender patients and found a lower prevalence of acute kidney injury (AKI) and CKD in transgender individuals receiving gender-affirming hormonal therapy compared with those not receiving this treatment, particularly among transgender women, who had the highest prevalence of AKI. Since the study involved otherwise health-impaired

individuals and given the high prevalence of AKI and CKD in this entire cohort, further investigation is needed to ensure that transgender patients receive robust and equitable care.

### **Key points**

1. Sex and biological factors play an important role in health outcomes, but so do social, cultural or gender factors as well.
2. Healthcare providers should address gender differences in medical care. Clinical trials and research studies should include diverse populations across genders and other intersectional factors, including age, race/ethnicity, geographical location and socioeconomic position.
3. The inclusion of gender differences in future medical care is essential for promoting health equity and reducing disparities.

### Further reading

- (1) GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2020;395(10225):709-733. doi:10.1016/S0140-6736(20)30045-3
- (2) Carrero JJ, Thomas F, Nagy K, et al. Global Prevalence of Protein-Energy Wasting in Kidney Disease: A Meta-analysis of Contemporary Observational Studies From the International Society of Renal Nutrition and Metabolism. *J Ren Nutr*. 2018;28(6):380-392. doi:10.1053/j.jrn.2018.08.006
- (3) Brar A, Markell M. Impact of gender and gender disparities in patients with kidney disease. *Curr Opin Nephrol Hypertens*. 2019;28(2):178-182. doi:10.1097/MNH.0000000000000482.
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- (10) Eckenrode HE, Gutierrez OM, Osis G, Agarwal A, Curtis LM. Kidney Disease Prevalence in Transgender Individuals. *Clin J Am Soc Nephrol*. 2022;17(2):280-282. doi: 10.2215/CJN.04660421.