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# Sex Inequities in Clinical Trials and Trial Leadership



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Despite decades of progress, sex inequities in medicine and research remain pervasive. Much work has focused on biases against women in clinical medicine and in sex differences in health outcomes for men and women.[1,2] More recently, a spotlight has been shone on the underrepresentation of women in clinical trials.

In this issue, Lodhi *et al.*[3] performed a systematic review of sex inequities in clinical trial leadership and sex representation in trials. The authors screened 11 high impact factor medical, surgical, and nephrology journals from 2011 to 2021. The top 5 medical journals, top 4 nephrology journals, and top 2 transplant journals were chosen. They identified 395 phase 3 randomized controlled trials. Women comprised 28% of first authors, 19% of last authors, and 22% of corresponding authors. There were no improvements in representation of women in leadership positions over time. Female lead authors were less likely to be funded by industry or to lead international trials. Women were also less likely to be published in the highest impact journals, accounting for only 6% to 24% of first, lead, or corresponding author positions in the New England Journal of Medicine, Lancet, or Journal of the American Medical Association.

The authors also found that women with chronic kidney disease (CKD) were underrepresented in kidney trial participation. Women make up at least 50% of pre-CKD 5 populations, with the Global Burden of Disease study estimating women had an age-standardized prevalence of CKD 1.3 times higher than men.[4] Despite this, women comprised ∼39% of trial populations with no change over the 10 years.[3] This mirrors a recent review of the landmark SGLT2i/MRA/GLP1a trials with kidney outcomes, which found that women were underrecruited, accounting for 35% of trial populations (Table 1).[5] This represented a population prevalence ratio (PPR) of 0.67, where a ratio of 1 means women are equally represented. This is similar to cardiology trials (population prevalence ratio, ∼0.7) but markedly worse than oncology trials (population prevalence ratio, 0.9).[6,7]

In medical trials, and nephrology trials specifically, sex has often been ignored. This has led to a lack of sex balance in trials and a dearth of sex-specific analyses. In the systematic review by Lodhi *et al.*,[3] only 13% of trials reported a sex stratified subgroup analysis. We would suggest that information from these subgroup analyses represent a major lost opportunity in the era of "precision medicine." Although women comprise at least 50% of CKD populations, they do have many differing characteristics to men, which may impact both recruitment, and possibly response to therapies. In general population and CKD cohorts, women had a lower initial estimated glomerular filtration rate than men, but men were more likely to die and to progress to kidney replacement therapy.[8,9] Renal tubular structure and function are different in men and women, likely due in part to the effect of sex chromosomes and sex hormones (Supplementary reference S1). Differences in body size and composition, kidney size (and presumably nephron endowment) and renal hemodynamics also appear to play a role in differing outcomes.[S1,S2] Major life events such as the onset of menarche, pregnancy, breastfeeding, and menopause affect the female body, with associated changes in function and disease risk. The failure to recruit women proportionately, and the failure to include sex-stratified analyses, leads to a knowledge gap in differences in both health outcomes and safety data for men and women. The lack of representation of women also extends to phase 1 trials and preclinical research, further contributing to our knowledge gaps, though this is not the focus of the current article, nor the systematic review on which it is based.[S3]

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**Table 1.** Sex representation in recent ground-breaking kidney trials

| Trial | Number of Women | Trial Population | % Women |
|---|---|---|---|
| Dapa-CKD | 1425 | 4304 | 33 |
| Empa-Kidney | 2192 | 6609 | 33 |
| Credence | 1494 | 4401 | 34 |
| Scored | 4754 | 10584 | 45 |
| Amplitude-O | 1344 | 4076 | 33 |
| Fidelio | 1691 | 5674 | 30 |
| Figaro | 2247 | 7352 | 31 |
| Total of all trials | 15147 | 43000 | 35 |

Data from.[5]

The failure to adequately include women in clinical trials leads to incomplete knowledge about harms and benefits. Drugs and interventions may well have differing harms in men and women. Thus, if there is insufficient enrolment of women in trials, we may miss harm signals. Furthermore, because there are differences in risks of CKD progression and death between men and women, the risk-benefit balance for some drugs may also be impacted. Differences in biology may affect pharmacokinetics, pharmacodynamics, and effect; while differences in social environments may impact both drug acceptability and drug adherence. The exclusion of women of "childbearing potential" excludes yet another group of women from trials, recognizing that the age range impacted is vast: from 14 to 50 years. These factors combine to exclude women from participating in research that may improve their health and allow clinicians and researchers to gain insights. All of these impact our ability to practice evidenced-based or evidence informed medicine for women.

To achieve sex equity in clinical trials, we need to design trials in ways that encourage the involvement of women. This includes women in leadership roles designing and implementing the trials. The lived experience of women can inform female-friendly trial design and though sex equity is the responsibility of all, women may be more likely to advocate for increased female participation. There are multiple approaches we can take to maximize female enrolment. A study of willingness to participate in cardiovascular trials found that women had more trust in clinicians than men, but perceived a higher risk from trial participation.[S4] We need to ensure that participant information forms have sufficient information to explain and contextualize risks and this is explained to women and men. We should expect sex-stratified analyses, including of harms, for all trials. Reducing the time-burden of trials on participants would be welcomed by all. Women would benefit the most because they are more likely to have caregiver roles, with associated time constraints. We should also extend trials to underrepresented populations such as children. Adolescents could be enrolled in the majority of nephrology trials, with benefit to both girls and boys. Research should focus on women's issues, for example pregnancy care in CKD, postpregnancy CKD risk and changes in primary kidney outcomes and secondary complications such as cardiovascular disease around menopause.

Research dissemination is also a crucial target for improving gender equity. Clinical guidelines must be frank about the limitations of evidence for women and men and consider the impact of sex, and other factors such as age and socioeconomic status, in the interpretation of recommendations. The current version of the Kidney Disease: Improving Global Outcomes CKD Evaluation and Management Guidelines champions this approach, advocating for a life-course assessment in all aspects of CKD assessment and care. If half of the kidney community is not adequately represented in our clinical trials, then how are we to inform care?

Together as nephrology community, we must act together in a multiplicity of ways to improve representation of women in clinical trials, so that we may improve the care we deliver every day in our clinics, to all of our patients.

## DISCLOSURE

All the authors declared no conflicting interests.

## SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

**Supplementary references.**

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