


ORIGINAL ARTICLE

Women's representation in clinical trials of patients with chronic kidney disease

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ABSTRACT

Background. Sex and gender differences in chronic kidney disease (CKD), including epidemiology and response to treatment, remain poorly understood. This study aimed to investigate how women are represented in CKD clinical trials and whether sex- and gender-disaggregated outcomes were reported.

Methods. Clinical trials on CKD were identified from ClinicalTrials.gov. Randomised, phase 3/4 trials with ≥ 100 participants were selected to quantify women's representation among participants by computing the participation:prevalence ratio (PPR) and investigating whether sex-disaggregated analyses had been performed.

Results. In total, 192 CKD trials registered on ClinicalTrials.gov and published between 1995 and 2022 were included. Overall, women accounted for 66 875 (45%) of the 147 136 participants. Women's participation in clinical trials was lower than their representation in the underlying CKD population globally (55%). The PPR was 0.75 (95% confidence interval 0.72–0.78), with no significant variation irrespective of mean age, CKD stage, dialysis, location, type of intervention or funding agency. A total of 39 (20%) trials reported sex-disaggregated efficacy outcomes and none reported sex-disaggregated safety outcomes.

Conclusion. Women's participation in CKD clinical trials was lower than their representation in the underlying CKD population. Sex-disaggregated efficacy and safety outcomes were rarely reported. Improving women's enrolment into clinical trials is crucial to enable sex- and gender-disaggregated analysis and thus identify potential differences in treatment response between women and men.

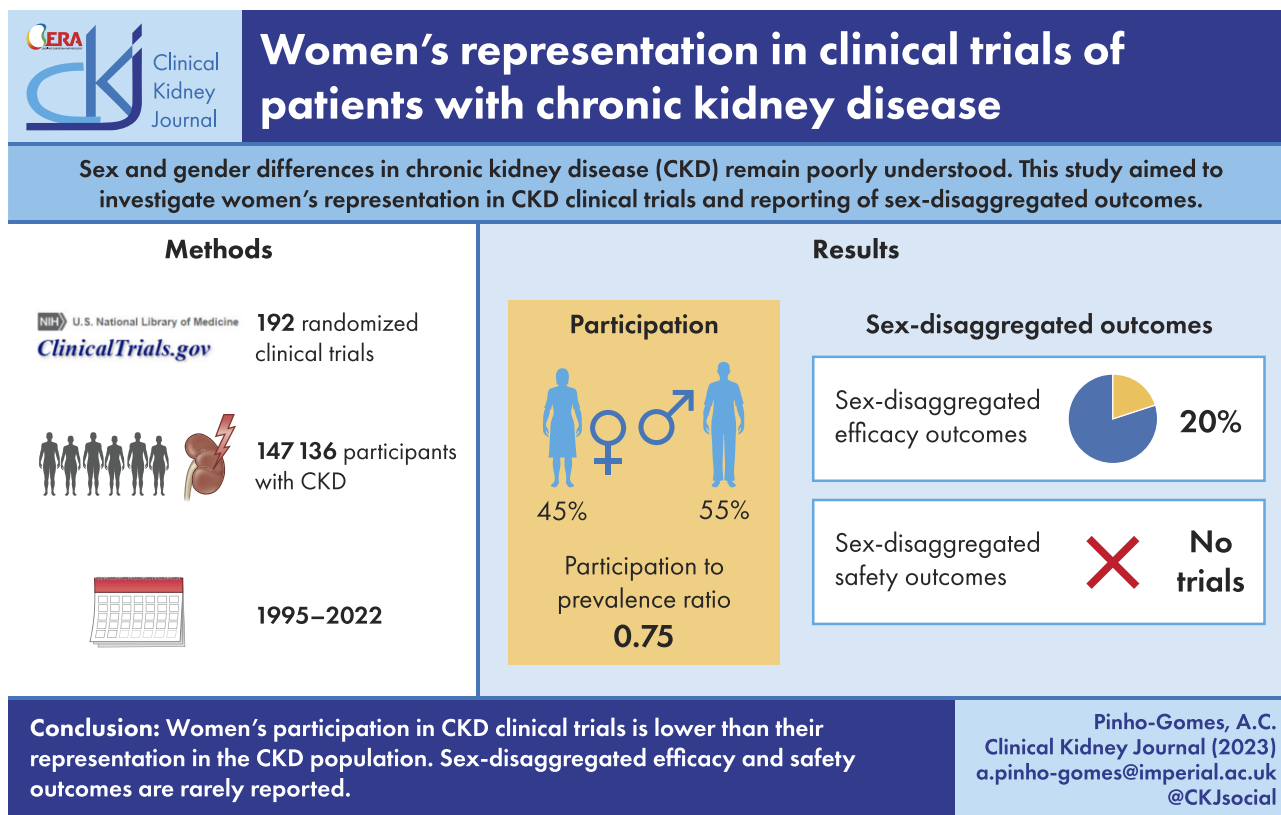
LAY SUMMARY

Using a sample of 192 trials of patients with chronic kidney disease (CKD) published between 1995 and 2022, this study showed that women's participation in those trials was lower than their representation in the population of patients with CKD worldwide. Only one in five trials reported efficacy outcomes separately for women and men and no trial reported safety outcomes separately for women and men. The underrepresentation of women in clinical trials and lack of sex-specific analyses prevents understanding whether there are important differences in response to treatments for CKD between women and men.

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GRAPHICAL ABSTRACT



Keywords: chronic kidney disease, randomised clinical trials, sex-disaggregated analysis, women's representation

INTRODUCTION

Chronic kidney disease (CKD) was estimated to have a global prevalence of 9.4% in 2019, although with wide variations between countries [1]. Although women have an overall higher prevalence of CKD than men, sex differences also vary between countries [2]. Hence, while the reported prevalence of CKD among women in France, Thailand, Portugal and Turkey is 2-fold higher than in men, perhaps due to the longer life expectancy of women, in Japan and Singapore the prevalence of CKD is higher in men than women [2], possibly due to CKD overdiagnosis with the use of estimated glomerular filtration rate equations [3]. However, more men than women undergo renal replacement therapy, not only because of faster CKD progression in men, but also because elderly women are more likely to prefer conservative care [4, 5]. Mortality is higher among men at all levels of pre-dialysis CKD, whereas mortality among individuals on renal replacement therapy is similar for women [6].

Although recent studies have suggested that women with CKD may not benefit as much as men from some new drugs, such as sodium–glucose co-transporter 2 (SGLT2) inhibitors [7, 8], in general there is a dearth of knowledge regarding potential sex differences in CKD. This is due to a lack of sex-disaggregated analysis in CKD trials, which itself may be due to underrepresentation of women in such trials. Women's underrepresentation in randomised clinical trials has been consistently reported for many diseases, such as cardiovascular and cerebrovascular diseases [9–11]. However, evidence from CKD tri-

als is lacking. A small study showed that in contemporary trials examining SGLT2 inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists and non-steroidal mineralocorticoid receptor antagonists, women were significantly underrepresented compared with men [12]. However, that study provides very limited insights into women's representation, as it included only eight trials that were published in the *New England Journal of Medicine*.

Therefore the aims of this study were to estimate the representation of women among participants in CKD trials and determine whether sex-disaggregated analyses were performed, and if so, whether sex differences in safety and/or efficacy were reported.

MATERIALS AND METHODS

Data source and search strategy

We applied the same methods as described in a previous paper [13]. We searched for clinical trials registered on ClinicalTrials.gov, a web-based registry of human clinical studies conducted around the world provided by the US National Library of Medicine and managed by the National Institutes of Health (NIH). The search terms were 'chronic kidney disease (CKD)' as disease condition, 'interventional studies (clinical trials)' as study type and 'completed' or 'terminated' as recruitment status. Searches were limited to trials with adults ≥ 18 years of age. No date restrictions were applied.

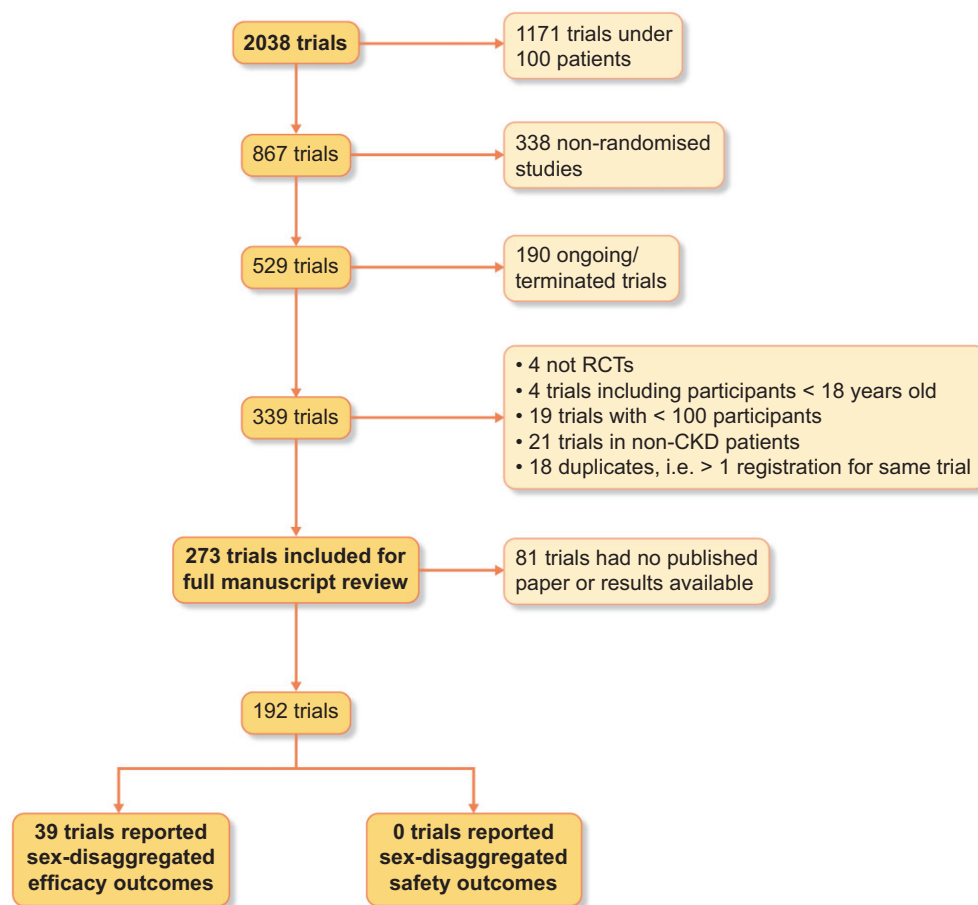


Figure 1: Flowchart summarising the selection of trials for the overall analysis and analysis of women's representation.

Once the trials were identified on the ClinicalTrials.gov webpage, full manuscripts were searched on PubMed using the national clinical trial identifier assigned to the trial, trial registered name and acronym and primary investigator's name. If no matching publication was found, the Google Scholar, Embase and Scopus databases were searched using the national clinical trial identifier, trial registered name and acronym and primary investigator's name. When published reports could not be identified, the principal investigator was contacted whenever an e-mail address was available, but no answers were received. All searches were performed in duplicate.

Selection criteria

The following inclusion criteria were applied: trials that included participants of both genders, trials with at least 100 participants, phase 3 or 4 trials and trials whose interventions were on patients (rather than healthcare professionals or caregivers). Trials were excluded if conducted in patients <18 years of age or not related to treatment of CKD. Trials for which a publication could not be retrieved or that had no results available on ClinicalTrials.gov were also excluded.

Data extraction

Data were extracted by three authors (A.C.-P.G., C.H. and C.C.). As a check on reproducibility, data were extracted in duplicate for 10% of the trials examined by each author. Disagreements

were resolved by consensus. The variables extracted were national clinical trial number, completion date, trial location(s) (i.e. country, continent or worldwide if across several continents), intervention type (i.e. pharmacological, behavioural, radiation, dietary supplement, procedure, device or other), stage of disease [categorised as non-end-stage renal disease (ESRD) versus ESRD and dialysis versus non-dialysis], funding agency (i.e. industry versus other), mean age of participants, total sample size, proportion of women, reporting of sex-disaggregated outcomes, observed differences in efficacy and/or safety and year of publication of results.

Data analyses

To investigate the extent of women's representation among participants in trials, we calculated the participation:prevalence ratio (PPR), the percentage of women among trial participants divided by the percentage of women in the underlying disease population [14]. A PPR close to 1 indicates that the sex composition of the trial is that of the disease population [15]. The percentage of women with CKD in the population was obtained from prevalence estimates from the Global Burden of Disease [16]. Where trials were conducted in a single country location, country-specific prevalence estimates were used. Where trials were conducted across multiple countries, regional or worldwide (if more than one region) prevalence estimates were assigned to the respective trials.

Table 1: Baseline trial characteristics.

| Characteristic | Trials, n (%) in category ^a | Participants, n (%) in category) | Female participants, n (%) of participants |
|--------------------|---|-------------------------------------|---|
| Total | 192 | 147 136 | 66 875 (45.4) |
| Age (years) | | | |
| <61 | 94 (49.0) | 92 799 (63.1) | 43 648 (44.3) |
| ≥61 | 94 (49.0) | 50 267 (40.6) | 21 443 (40.6) |
| Dialysis | | | |
| Yes | 81 (42.2) | 79 441 (54.0) | 39 559 (46.5) |
| No | 107 (55.7) | 54 850 (37.3) | 22 343 (39.7) |
| ESRD | | | |
| Yes | 100 (52.1) | 94 315 (64.1) | 44 909 (44.2) |
| No | 89 (46.4) | 49 636 (33.7) | 20 615 (40.8) |
| Intervention | | | |
| Behavioural | 16 (8.3) | 6338 (4.4) | 2546 (43.9) |
| Biological | 5 (2.6) | 2622 (1.8) | 1265 (47.4) |
| Device | 14 (7.3) | 6746 (4.6) | 3455 (49.8) |
| Dietary supplement | 5 (2.6) | 1916 (1.3) | 794 (1.3) |
| Drug | 127 (66.1) | 88 319 (60.8) | 36 440 (42.4) |
| Procedure | 10 (5.2) | 4336 (3.0) | 1482 (31.6) |
| Other | 15 (7.8) | 35 013 (24.1) | 19 856 (43.1) |
| Continent | | | |
| Americas | 79 (41.1) | 41 222 (28.0) | 18 921 (44.4) |
| Asia | 32 (16.7) | 14 847 (10.1) | 5995 (41.2) |
| Europe | 23 (12.0) | 29 932 (20.3) | 16 938 (36.7) |
| Worldwide | 58 (30.2) | 61 135 (41.5) | 25 021 (43.3) |
| Funding | | | |
| Industry | 71 (37.0) | 58 573 (39.8) | 29 442 (40.6) |
| Other | 121 (63.0) | 88 563 (60.2) | 37 433 (43.7) |

^aFor certain categories, the percentages do not add up to 100%, as the remaining are 'missing'.

Subgroup analyses were conducted according to intervention (drug versus other), stage of disease (non-ESRD versus ESRD), sponsor type (industry versus other), intervention (pharmacological versus other), continent (Americas, Asia, Europe and worldwide), age (mean age <61 years versus ≥61 years). To assess whether the PPR varied by study sample size, we calculated a sample size weighted mean (SSWM) of the PPR across all trials. The SSWM was calculated by multiplying the trial PPR by the trial sample size and dividing by the sum of participants in all trials included in this study. The sum of this quantity is the SSWM. Bootstrap methods were used to obtain 95% confidence intervals (CIs) for the mean PPR and SSWM of the PPR, using the percentile method with 100 000 iterations. Trends over time were displayed for mean PPR between 1995 and 2022. All data analyses were performed in R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 192 trials were eligible for inclusion in the analysis of women's representation after applying our search criteria (Fig. 1). These trials included a total of 147 136 participants with a mean age of 61.4 years (Table 1). A total of 127 (66.5%) trials investigated pharmacological treatments and 70 (36.6%) trials were funded by industry. The trials were conducted in 26 different countries and 58 trials were international (Supplementary Table S1).

Women's representation

Women accounted for 66 875 of the 147 136 participants (45.4%). The percentage of women in individual trials varied widely, from

1.7% to 98.5%, with a mean of 42.6% [standard deviation (SD) 12.4] and a median of 41.4% [interquartile range (IQR) 36.7–49.1].

Overall, women were represented in clinical trials at a lower percentage relative to their percentage in the underlying CKD population, in which women account for 55.1% of cases globally. There was a large variation in the PPR across trials, which ranged from 0.03 to 1.68, with a mean PPR of 0.75 (95% CI 0.72–0.78) and a median of 0.75 (IQR 0.66–0.85). The SSWM, which gives more weight to larger trials, was 0.81 (95% CI 0.53–1.25), similar to the PPR but with a wider CI.

The PPR was lower for trials conducted in Europe [0.65 (95% CI 0.60–0.69)] than elsewhere (Fig. 2 and Supplementary Table S2). Women's underrepresentation was broadly similar irrespective of the mean age of patients, whether trials were conducted in patients with kidney failure (with or without dialysis) or those undergoing dialysis, the type of intervention and the funding agency. There was no evidence that women's representation increased between 1995 and 2022, the period covered by the included trials (Fig. 3).

Sex-disaggregated analyses

Only 39 (20%) of the 192 trials reported sex-disaggregated efficacy outcomes, and none reported adverse events stratified by sex. This includes reports in the main manuscript, either quantitatively or qualitatively, in supplementary appendices or published separately as post hoc studies. The mean sample size for these 39 trials was 1834 patients [median 804 (IQR 350–2659)]. Only 1 of the 39 trials reported differences in efficacy between women and men. In that trial (NCT00004285), the risk of death among women was 19 percentage points lower in the high-dose

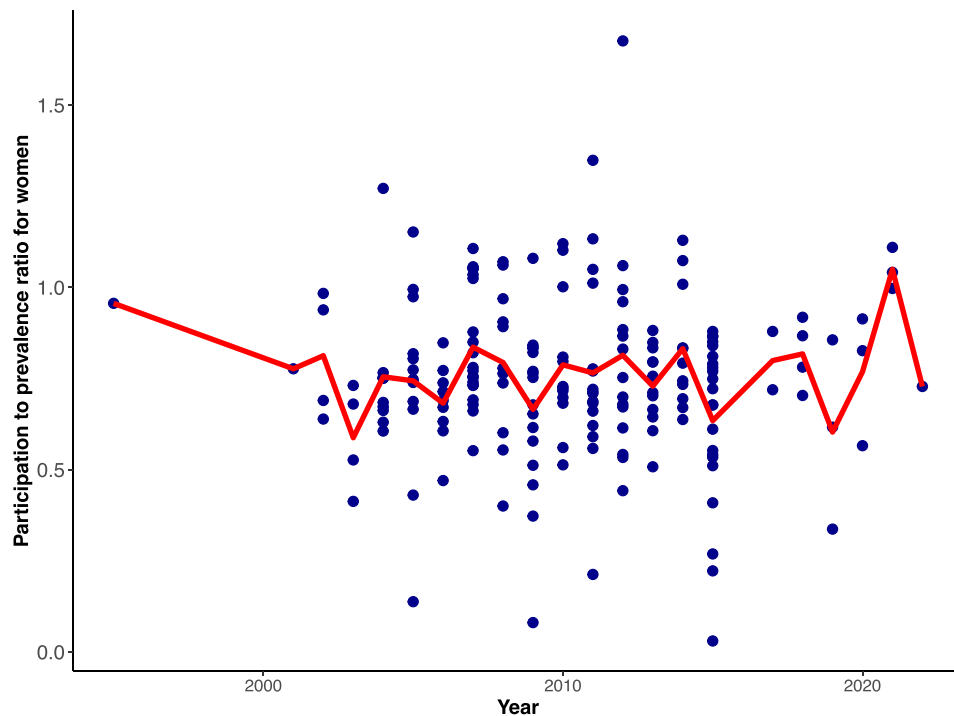


Figure 2: Subgroup analysis of PPR for women. The size of the box is proportional to the number of studies in each category.

dialysis group than in the standard-dose group, but the risk of death among men was 16 percentage points higher than in the standard-dose group [17].

DISCUSSION

In 192 CKD trials registered on ClinicalTrials.gov and published between 1995 and 2022, women accounted for 66 875 (45.4%) of the total 147 136 participants. Women's participation was considerably lower than their representation in the global CKD population (55%). The mean ratio of trial to population participation of women was 0.75, with a tight CI and no significant variation irrespective of mean age, type of intervention, CKD stage, receipt of dialysis or funding agency. Women's representation appeared to be lower in trials conducted in Europe than in other continents. A mere 20% of the trials reported sex-disaggregated efficacy outcomes and none reported sex-disaggregated safety outcomes.

Women's representation in clinical trials

Women have been shown to be underrepresented in clinical trials in many diseases, including cardiovascular disease, stroke and dementia [10, 11, 18, 19]. Our study extended these findings to CKD, where evidence was lacking. In addition, by estimating the PPR, it illustrated the extent of women's underrepresentation compared with their representation in the CKD population. Women comprised $\approx 45\%$ of participants in CKD trials, which could arguably be considered close to parity. However, this, in isolation, underestimates women's underrepresentation, as it fails to account for the higher prevalence of CKD among women than men. This is even more concerning as the soaring rates of obesity, which disproportionately affects women, are set to

further widen the discrepancy in the incidence of CKD between women and men [20]. The corollary is that trials are not enrolling the people who are most commonly suffering from CKD, thus not generating the much-needed evidence to support their treatment. This is compounded by the fact that women experience many challenges in accessing care due to social norms and roles of caregiving responsibilities, disempowerment, lack of support, stereotyping by clinicians and entrenched social and economic disadvantage [21]. Although some may argue that women already seem to have a lower risk of progressing to ESRD and a lower risk of death from CKD [22], their outcomes may be worse than they could otherwise be if they did not face barriers to being enrolled into clinical trials and accessing the care they need.

Sex-disaggregated outcomes

There is no dearth of evidence on sex differences in the development and progression of CKD and there is also emerging evidence on potential sex differences in treatment response [2]. For instance, SGLT2 inhibitors appear to afford a significantly lower reduction in major adverse cardiovascular events for women than men, while GLP-1 receptor agonists seem to confer a similar risk reduction irrespective of gender [7]. However, it remains to be established whether these results reflect a true gender difference or are related to inadequate statistical power due to underrepresentation of women, as they accounted for only about one-third of the participants. Thus it is concerning that only 39 of 192 trials reported efficacy outcomes disaggregated by sex and none of the trials reported safety outcomes stratified by sex. It is biologically plausible that, as for efficacy outcomes, sex differences exist in the type and/or severity of adverse events [23]. A comprehensive review of the US Food and Drug Administration Adverse Event Reporting System (FAERS) identified sex

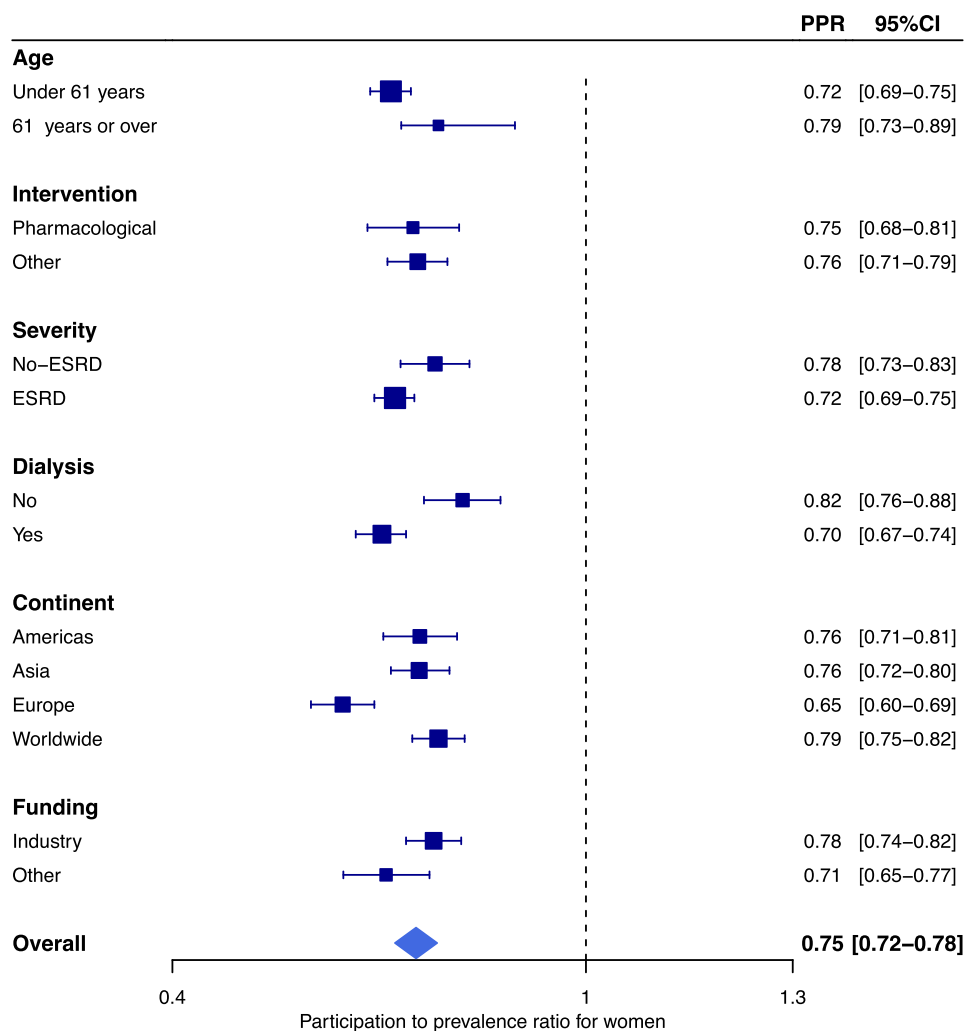


Figure 3: Women's representation in CKD trials, relative to prevalence, between 2010 and 2021. Dots represent the PPR for each trial plotted by year of publication of primary trial results. The line represents the mean PPR per year.

differences in adverse events for 307 of 668 drugs of the 20 most common treatment regimens in the USA [24]. This is in keeping with further evidence suggesting that sex differences in pharmacokinetics and pharmacodynamics underpin, at least partially, the increased risk of adverse events observed in women compared with men [25, 26]. Thus it is critical that not only efficacy, but also safety outcomes are reported disaggregated by sex, which requires that women are adequately represented in clinical trials to enable subgroup analyses for both common and rare events.

Considering the lack of improvement in women's representation over the years that we observed, and is in keeping with previous studies [19], it is germane to ask what strategies could promote women's participation in trials and systematic reporting of sex-disaggregated analyses. First, all scientific journals could require trials include both sexes in adequate numbers and address sex and gender differences in order to be considered for publication [27]. Importantly, sex-stratified analysis should be planned in trial protocols and included in power calculations. Second, frameworks to integrate health equity considerations into the design of clinical trials should be implemented in re-

search to promote recruitment of women [28, 29]. This may involve avoiding women-specific exclusion criteria (i.e. women of child-bearing age) as well as more nuanced criteria that may preferentially select men due to sex differences in how diseases manifest and progress [30]. Third, addressing barriers that may disproportionately affect women is paramount, such as logistic or communication barriers. For instance, evidence suggests that women and men may make decisions differently and thus the same enrolment process may yield different enrolment rates by sex [31, 32]. In addition, greater flexibility in study structures and processes to cater to the different preferences and needs of women and men may promote gender equality among participants in clinical trials [33].

Limitations

This study has several limitations. First, our only source of data was ClinicalTrials.gov. However, most journals require that trials are registered in an open platform to be published, and this is the most commonly used platform. Therefore, we expect our findings to be representative of the overall landscape of CKD

trials. Second, we could not obtain full manuscripts for all the trials eligible for inclusion in the analysis of women's representation, even though we searched the largest databases of index publications (PubMed, Google Scholar, Embase and Scopus). However, we do not expect that these trials would have had a material impact on our findings, as the reason for them not being published is unlikely to be related to women's representation. Third, the background population prevalence used to derive the PPR may not have been representative of the actual prevalence in the study population, particularly for trials that enrolled participants worldwide and older trials, as we used the most recent data on prevalence provided by the Global Burden of Disease. However, any errors in prevalence estimates by population or time are unlikely to vary by sex, and it is the women to men relative prevalence that informs the PPR. Fourth, we used overall prevalence of CKD, and there may be differences according to underlying aetiology within and between countries and regions. Fifth, although we searched for any currently published articles for each trial, it is possible that some may eventually publish secondary analyses with sex-stratified outcomes. Finally, we were unable to ascertain whether sex disaggregation of results was prespecified in the protocol.

CONCLUSION

Women's representation in CKD clinical trials is lower than their representation in the overall CKD population, with no evidence of improvement over time. Only one in five trials reported sex-disaggregated efficacy outcomes and none reported safety outcomes stratified by sex. Identification of variation by sex in the effects of interventions that are often novel and costly will be impossible unless women are proportionately represented in clinical trials, thus perpetuating women's disadvantage in health and care.

SUPPLEMENTARY DATA

Supplementary data are available at [ckj](#) online.

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None declared.

AUTHORS' CONTRIBUTIONS

ACPG and CH designed this study. ACPG, CC and CH extracted the data. ACPG analysed the data and drafted the manuscript. All authors reviewed the manuscript.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared upon reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

M.W. has recently been a consultant for Amgen and Freeline. The other authors declare no conflicts of interest.

(See related article by Mallamaci and Tripepi. Shedding a light on sex disparity in clinical trials in CKD patients. *Clin Kidney J* (2023) 16: 1369–1371.)

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