Chronic Kidney Disease 2

Advances in understanding the impact of sex on kidney health and disease

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Biological differences exist between males and females in kidney structure and function, leading to sex heterogeneity in the presentation and outcomes of chronic kidney disease (CKD) and response to novel therapeutics. However, treatment guidelines ignore sex-specific differences. This Series paper provides an integrated discussion of the complexity of sex differences in the context of kidney health and disease, from biology through clinical characteristics, treatment, evidence generation, and reporting. Throughout, we consider the effect of genetics, epigenetic regulation, and the role of sex hormones. We highlight substantial opportunities that exist for policy makers, scientific organisations, journal editors, funders, and individuals to change the current paradigm. Strategic and systematic acknowledgment, exploration, and reporting of these differences is needed in future research to continue to advance our understanding of pathophysiology, diagnostics, and novel therapeutics for CKD.

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Introduction

Chronic kidney disease (CKD) is a common and growing public health concern globally and associated with substantial morbidity and mortality.[1] Recent advances in understanding CKD pathophysiology and diagnostics, discussed in the first paper of this Series,[2] have yielded important therapeutic developments and improved clinical outcomes, which are discussed in the third Series paper;[3] however, inadequate appreciation of the biological sex differences that exist between females and males in kidney structure and function limit the generalisability of these key scientific advances.

Beyond biological and medical differences, gender roles, social factors, legislation and policy, and exposure to sex-based and gender-based discrimination contribute substantially to sex differences in CKD care and outcomes, with substantial variation by geographical location and health-care setting. These topics have been considered previously[4] and are not discussed in detail here. In this Series paper, we seek to provide an integrated overview of our understanding of sex differences in kidney health and disease, and what implications they may have for CKD therapeutics and clinical outcomes. We indicate opportunities for future evidence generation and the varied roles of policy makers through to individuals in changing the current paradigm.

Sex determination and its influence on CKD

Biological sex in humans is determined by genetic and epigenetic factors. The presence of a Y-chromosome in males triggers the development of testes and the production of male sex hormones; the absence of a Y-chromosome in females triggers ovarian development and production of female sex hormones. Sex hormones are essential components for the development and maintenance of human reproduction and promote the development of a range of secondary sexual characteristics through epigenetic regulation,[5] which we now understand to have important implications for sex differences in the development and outcomes of CKD.[5] In a comprehensive, sex-stratified, cross-ancestry meta-analysis studying genetic variants on the X chromosome, six of 23 genetic variants associated with kidney function showed sex bias, with gene expression driven by differential exposure to sex hormones.[6] Emerging evidence shows a role for epigenetic "memory" in acute kidney injury (AKI)-to-CKD progression and diabetic kidney disease: past episodes of hypoxia, inflammation, or hyperglycaemia can lead to changes in DNA methylation, histone modifications, or chromatin structure and continue to influence gene expression

Search strategy and selection criteria

We searched PubMed for articles published in English from database inception updated to Dec 15, 2025, using the following terms and related keywords: "chronic kidney disease" OR "CKD" OR "kidney disease" OR "renal disease" in combination with "sex" OR "gender" OR "women" OR "female" OR "reproductive" OR "fertility" OR "pregnancy" OR "conception" OR "contraception" OR "menopause" OR "puberty" OR "menarche" OR "hormone replacement therapy" OR "HRT" OR "pharmacokinetics". Priority was given to systematic reviews, meta-analyses, and consensus statements published within the past 5 years, supplemented with seminal articles and original research published within the same 5-year window. The search was done by JSL with input from all authors. We reviewed articles resulting from these searches and their references and selected those relevant to sex differences in chronic kidney disease biology or therapeutics. The selection of articles was proposed by JSL and reviewed by all coauthors, with disagreements resolved through consensus via email discussion.

Key messages

- Sex differences in kidney structure, function, propensity to inflammation, immune dysfunction, and disease are results of physiology, serving to optimise reproduction, but which create meaningful differences in the presentation, progression, and risks of chronic kidney disease (CKD)
- During pregnancy, females with CKD face higher rates of pre-eclampsia, acute kidney injury (AKI), preterm delivery, and maternal mortality; pregnancy-related AKI, hypertensive disorders, and immune dysfunction substantially raise long-term risks of CKD and kidney failure for both mothers and their offspring
- Sex differences exist in drug absorption, metabolism, and clearance, which commonly lead to higher drug concentrations and more adverse reactions in females; trials rarely report sex-disaggregated safety and efficacy data and treatment guidelines largely ignore sex-specific differences
- Females remain under-represented in preclinical and clinical research, limiting understanding of sex-specific mechanisms
- Systematic integration of sex differences into CKD education programmes across preclinical, clinical, and pharmaceutical sciences, and throughout research, diagnostics, therapeutics, and policy, is required to improve CKD outcomes

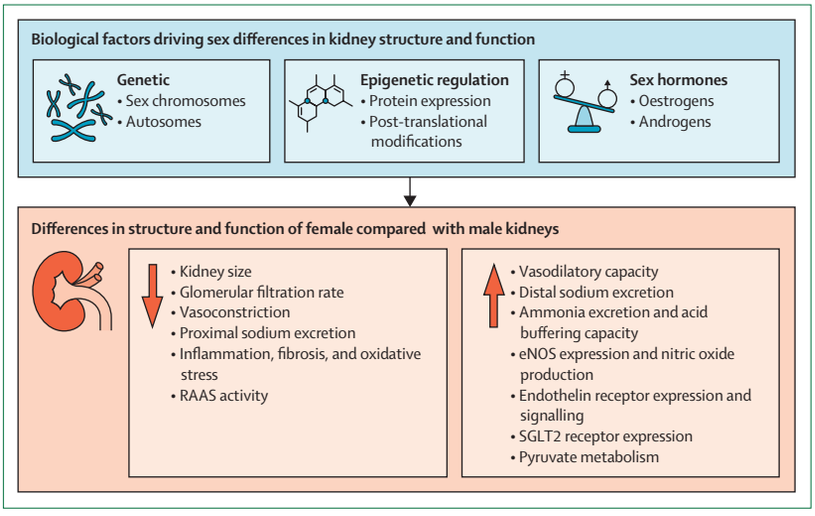

Figure 1: **Biological sex differences in kidney structure and function**
eNOS=endothelial nitric oxide synthase. RAAS=renal–angiotensin–aldosterone system.

even after the original trigger has resolved.[7] Comprehensive, cell-specific, genome-wide epigenetic profiling in human kidneys is scarce, making it difficult to distinguish which epigenetic changes truly drive CKD versus those that simply accompany injury, and the mechanisms of long-lasting epigenetic memory and interaction between transcription factors and epigenetic machinery remain uncertain.[7]

Sex differences in kidney structure and functions

Through a combination of animal and human studies, understanding has evolved that female kidneys are structurally and functionally different from male kidneys (figure 1):[8] these differences are established at birth and are necessary adaptations to maintain fertility and to cope with the physiological stresses of pregnancy and lactation. Here, we summarise some of the key differences, and their implications for disease expression.

Female kidneys are smaller, with reduced glomerular size and total glomerular volume compared with male kidneys.[9] Females have evidence of lower vasoconstriction and greater vasodilatory capacity than males,[10] leading to hyperfiltration without increases in intraglomerular pressure and supporting the increased blood volume and renal blood flow seen during pregnancy. Studies in patients receiving gender-affirming hormone therapy show increased renal plasma flow in response to oestrogen but not testosterone, and emphasise the protective role of oestrogen, and the deleterious effects of testosterone, on tubular and glomerular function.[11]

Fractional sodium excretion varies by sex. In animal models, sodium excretion is typically lower in proximal and higher in distal segments in female than in males, relating to sex differences in abundance or activity of renal transporters along the nephron,[12,13] where receptor expression is primarily regulated by androgens (in the proximal nephron) and oestrogens (in the distal nephron).[12] Consequences for overall sodium excretion varies by species: female rats excrete a saline load twice as fast as males,[12] whereas there is no apparent difference in diuretic and natriuretic response in female compared with male mice. These differences are thought to be mediated by relatively lower expression of aquaporin 1 in the proximal tubule in female compared with male rats, with higher expression of aquaporin 1 in female compared with male mice.[12]

Acid–base homeostasis is maintained through different renal ammonia metabolism and transport mechanisms, leading to higher ammonia excretion and better buffering capacity in females.[14] Females express higher levels of endothelial nitric oxide synthase and nitric oxide, which have a range of physiological effects on kidney health and disease, including increased glomerular filtration, improved endothelial function, increased inhibition of angiotensin 2, and reduced inflammation and oxidative stress.[15] In experimental models of CKD caused by chronic nitric oxide inhibition, there is less severe albuminuria, glomerular ischaemia, and glomerulosclerosis in female rats: an effect that could be explained by a protective effect of oestrogen, deleterious effects of testosterone, or differential reaction to renal–angiotensin–aldosterone system (RAAS) activation.[16] Females have been shown to exhibit lower susceptibility to AKI, with less inflammation and interstitial fibrosis than in males:[8,17]

a protective effect that appears to be lost with ageing and reductions in circulating oestrogens.[18]

Females have more efficient energy conservation mechanisms than males. In times of food scarcity, females rely on larger stores of subcutaneous fat to oxidise lipids for energy, preserving glucose for essential activities.[19] This allows females to remain fertile when food is scarce but also predisposes females more than males to development of obesity. Sex hormones and genes further affect insulin-sensitivity, lipid metabolism and storage, and glucose homeostasis,[19] driving sex differences in metabolic response to novel therapeutics for diabetes and obesity (discussed in the third Series paper),[20,3] although still yielding benefits for both sexes for kidney and cardiovascular outcomes.[21,22] Females and males with diabetes have different energy metabolism within the kidneys: females tend to favour more pyruvate metabolism and thus generate fewer oxidative free radicals than males, which lead to higher estimated glomerular filtration rate (eGFR) and lower mortality in females with human diabetic kidney disease.[23]

Expression and activity of renal drug transporters vary by sex. Females have decreased RAAS activity overall, with reduced expression of the counter-regulatory arm of the RAAS system, including angiotensin converting enzyme (ACE)-1, angiotensin 2, and angiotensin receptor 1,[8,24–26] in part explaining the lower propensity towards hypertension and cardiovascular disease seen in women compared with men during reproductive years.[27] Endothelin receptor density, signalling via endothelin-1 and endothelin receptor-B, and expression of sodium–glucose cotransporters are higher in females than in males.[8,24,28] These sex differences in homeostatic mechanisms, receptor expression, and signalling have implications for response to therapeutics.[13,29,30]

Sex differences in CKD and reproductive health

Sex hormones do not have a static effect over time but instead fluctuate throughout the life course with differential implications for kidney health and disease in females and males (figure 2). Conversely, CKD affects changes in sex hormones with implications for reproductive health and other adverse outcomes. In this section, we discuss the bidirectional relationship between CKD and reproductive health in females and males.

Puberty

Measuring kidney function during puberty is challenging. As in adults, direct GFR measurement requires invasive procedures with iohexol and timed blood samples, which might be less acceptable in children and adolescents.[32] Creatinine-based estimates are confounded by age-dependent and sex-hormone dependent changes in muscle mass and growth. Cystatin C is an alternative biomarker, and it typically increases during puberty in males and decreases slightly in females, meaning neither biomarker provides consistently accurate estimates across age and sex.[32]

In young people with CKD, puberty might be delayed,[33] but once reached, sex hormones might affect kidney function in both females and males. In an analysis of a nationwide cohort (Italian Pediatric Registry of Renal Failure project), including children with CKD secondary to kidney hypodysplasia, the onset of puberty was associated with accelerated decline in GFR.[34] Onset of puberty, and therefore GFR decline, occurred at a younger age in females, and decline continued after slowing or cessation of growth, illustrating that the differences were not explained by changes in body mass.[34] The prospective Chronic Kidney Disease in children study, including 540 children with eGFR between 30 and 75 mL/min per 1·73 m², evaluated the

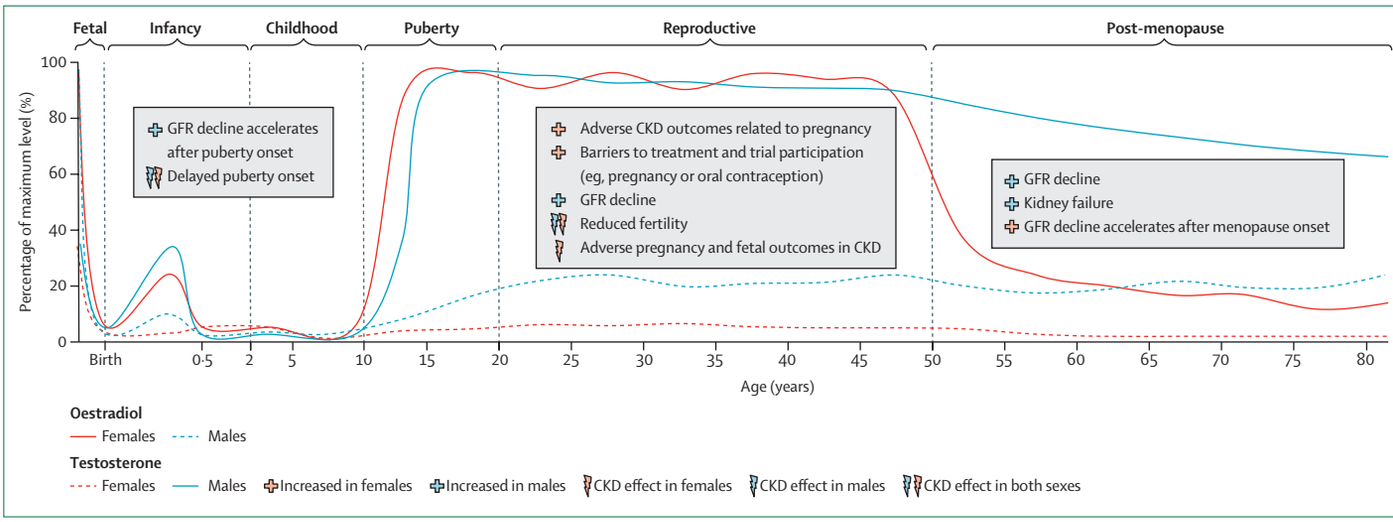

Figure 2: **Sex differences in the bi-directional relationship between reproductive life cycle and CKD**
Adapted from Ober et al[31] by permission of Springer Nature. CKD=chronic kidney disease. GFR=glomerular filtration rate.

association between pubertal onset and change in GFR in children with CKD using creatinine-based and cystatin C-based equations and change in iohexol-based measured GFR. Using luteinising hormone as a marker of puberty onset, decline in GFR associated with puberty was evident in both sexes, but faster in boys than in girls, and consistent across estimated and measured GFR.[35] The role of pubertal sex hormones on kidney function changes in females and males is not yet well understood.

Fertility

CKD adversely affects female and male fertility through shared but sex-modulated pathways, including reduced testosterone and raised prolactin levels, but with differential effects on fertility, cardiovascular risk, and quality of life. Inflammation is a key driver of reduced fertility (as well as CKD progression and cardiovascular disease)[2] in both females and males with CKD. In females, fertility is adversely affected through disruption to normal menstruation, including anovulation and amenorrhoea (mediated by disruption to the hypothalamic–pituitary–gonadal axis), reduced levels of anti-Mullerian hormone (reflecting ovarian reserve), and premature menopause.[36–39] In males, adverse effects on fertility are mediated through erectile dysfunction, impaired spermatogenesis, reduced sperm quality, and hypogonadism.[39] Fertility can be further reduced by treatments used in CKD, such as cyclophosphamide, which is used in the treatment of a range of glomerular diseases and causes direct ovarian and testicular toxicities.[39] Fertility improves with restoration of kidney function (eg, through kidney transplantation) in both females and males, although the mechanisms are incompletely understood.[39–41]

Contraception

Sex differences in approaches to contraception have implications for use of therapeutics in females with CKD: highly effective contraception was mandated for female participation in many landmark trials for CKD management, without parallels in males,[42–44] limiting potential for female participation and uncertainty regarding treatment safety for women of reproductive age. Effective contraception is advised for females taking teratogenic immunosuppression (eg, for glomerular disease), and hormonal contraception poses theoretical risks of CKD progression, worsening hypertension and thromboembolic disease, although with little evidence to support these concerns.[45]

Pregnancy

Pre-existing CKD increases the risk of adverse pregnancy outcomes, and pregnancy might have adverse consequences for CKD outcomes. Observational data suggest that 3–6% of females of reproductive age have pre-existing CKD,[46] although this statistic might be up to 50% higher in low-income and middle-income countries (LMICs).[47] CKD is a risk factor for adverse pregnancy complications: for the mother, these include pre-eclampsia, AKI (particularly in LMICs and vulnerable or marginalised populations in high-income countries [HICs]), and maternal mortality; for the fetus, these include preterm delivery, low birthweight, stillbirth and intrauterine death.[48–50] Independent of reduced GFR, females with proteinuria and hypertension have higher risks of adverse pregnancy outcomes than do females with no evidence of CKD.[49,51] Pre-existing CKD also complicates care during pregnancy and lactation; guidance to avoid medications with known or potential teratogenic effects (eg, antihypertensive or immunosuppression regimens)[52] potentially increases the risk of deteriorating disease control,[48] leading to adverse long-term consequences, including CKD progression and kidney failure.[39] The effects of maternal CKD on future CKD in the offspring, and whether these effects are differentially affected according to the sex of the offspring, remain largely unquantified.

Pregnancy complications have consequences for adverse kidney outcomes. Pre-eclampsia is considered the most common glomerular disease in pregnancy; however, it is uncertain whether pre-eclampsia unmasks pre-existing, undiagnosed glomerular disease or contributes to the pathogenesis of glomerular disease diagnosed later in life.[48] In a systematic review and meta-analysis of 23 observational studies (5769 891 participants), pre-eclampsia and gestational hypertension were associated with increased risk of CKD and kidney failure.[53] Preterm delivery, with or without pre-eclampsia, was also associated with 2–5 times the risk of kidney failure.[53] Diagnosed or undiagnosed AKI in pregnancy is associated with acute requirement for haemodialysis in 16–37% of females and a higher likelihood of developing CKD, including kidney failure and cardiovascular disease, in later life.[50] More pregnancies now occur at advanced maternal ages, which might increase the prevalence of CKD in pregnancy,[54] with a potential deleterious effect on outcomes.

Pregnancy induces important immunological changes with implications for long-term kidney health. HLA sensitisation remains unavoidable when the maternal and fetal circulations are co-exposed, and this sensitisation is exacerbated if blood transfusion is required for bleeding complications.[55] The end results of HLA sensitisation include longer wait for kidney transplantation, increased post-transfusion complications, greater exposure to immunosuppression and its adverse effects, and a higher rate of graft rejection than females without pregnancy-induced HLA sensitisation, particularly when the graft is received from the father or offspring.[55]

Immune adaptations occur during pregnancy to balance protection of the fetus with defence against

pathogens, and account for a higher likelihood of immune disease flare (particularly lupus nephritis)[48] and the increased risk of CKD, diabetes, and cardiovascular disease in later life.[56] Moreover, maternal immune activation increases the likelihood of immune, neurodevelopmental, metabolic, and cardiovascular disorders in the offspring.[57]

Menopause

Ageing is associated with a decline in GFR in both females and males, but differences in the rate of decline appear to be mediated by sex hormones, with oestrogens adopting a protective role and androgens a deleterious effect. On average, GFR is lower but declines more slowly and linearly in females, whereas a steeper, curvilinear decline is observed in males, particularly at older ages.[58,59] In the Renal Iohexol Clearance Survey, these sex differences appear to be unrelated to health status.[58] In females, GFR declines more quickly following the onset of menopause,[8] suggesting a protective role of endogenous oestrogens in maintaining kidney health. In the National Health and Nutrition Examination Survey (n=4945), early (<45 years) natural and surgical menopause were associated with a higher risk of CKD compared with those with menopause aged 45 years and older.

Hormone replacement therapy

The role of exogenous hormones (hormone replacement therapy [HRT]) for prevention of CKD and other chronic diseases is controversial. From a systematic review and meta-analysis of trials and observational studies of HRT, there are some data to support a role for HRT in reducing albuminuria.[60] A large observational study from South Korea suggested that use of HRT in females with CKD might be associated with lower risks of kidney failure and cardiovascular disease;[61] however, randomised evidence is scarce.[62] Although there might be benefits in preventing chronic conditions associated with CKD development (such as diabetes and possibly myocardial infarction), some forms of HRT (particularly oral oestrogens or combined oral oestrogen–progestin therapies) appear also to cause harm, with increased risk of stroke, dementia, and certain cancers.[63–65] For cardiovascular disease, including stroke, these harms might be lower or non-existent with transdermal oestrogen preparations.[63]

Sex differences in CKD epidemiology, diagnosis, management, and outcomes

Sex differences in CKD epidemiology

In most regions with available data, prevalence of CKD stage G3–5 is reported more in females than in males,[66] and CKD stage G1–2 (albuminuria without reduced eGFR criteria) is typically reported more in males.[66] These are unsurprising findings given that CKD diagnostic thresholds for eGFR and albuminuria are not sex-specific.[67] Both measures are typically lower in most females than in males,[58] as creatinine generation and excretion is lower in females,[2] which can lower the albumin to creatinine ratio for the same level of urinary albumin. Adding complexity, the potential for misdiagnosis or overestimation of albuminuria due to menstruation remains uncertain and under-studied.

Sex differences in CKD aetiology

Globally, the most important risk factors for CKD are high fasting plasma glucose, high BMI, and high systolic blood pressure (discussed in the first Series paper).[1,2] CKD is seen commonly alongside other cardiovascular and metabolic conditions in the cardiovascular–kidney–metabolic (CKM) syndrome:[68] a spectrum of related conditions thought to be caused by inflammation arising from excess of dysfunctional adipose tissue (discussed in the third Series paper).[69,3] CKM syndrome is generally more common and associated with higher mortality in males than in females, however, for a given higher CKM stage, the relative risk of cardiovascular and all-cause mortality is greater in females than in males.[70,71] Furthermore, albuminuria and eGFR based on cystatin C are stronger risk markers of adverse outcomes in females than in males,[2,72–74] a finding that has also been shown for cardiac troponin.[75,76]

Infectious, inflammatory, and autoimmune conditions present differently in males and females.[5] Primary glomerulonephritis (including IgA nephropathy, membranous nephropathy, minimal change disease, and focal segmental glomerulosclerosis) is more common in males than females. The mechanisms for this male preponderance are poorly understood and challenging to study, with added complexity from known geographical and ethnic variations in prevalence of glomerular disease.[77] IgA nephropathy (the most common glomerular disease in males)[78] is often cited as the most common glomerular disease worldwide, but an international survey of 29 nephropathology centres including 42 603 glomerular disease samples indicated that the most common glomerular disease in females is lupus nephritis.[78] Males with lupus nephritis were thought to have more severe disease and worse cardiovascular and renal outcomes,[79–81] but an international analysis of four trials and seven cohort studies of lupus nephritis showed that, beyond the lower eGFR observed in males, females and males displayed similar disease severity, response to treatment, and kidney outcomes.[82] Supporting a role for endogenous oestrogens in the pathophysiology, sex differences in systemic lupus erythematosus (not restricted to those with lupus nephritis) are far less striking in prepubertal children and older individuals.[83]

Illustration of the dynamic regulation of the immune system by sex hormones was provided in a 2024 study published in *Nature*, where immunological changes were observed after gender-affirming testosterone therapy in transgender men.[84] Although endogenous oestrogens

can have both stimulatory and inhibitory effects on the immune response,[85] type 1 and type 2 interferon signalling and humoral responses are generally greater in females than in males.[86] Accordingly, females are more prone to developing autoimmune diseases (such as lupus) but tend to have less severe infection outcomes and respond better to vaccination.[85] By contrast, androgens exert inhibitory actions on the activity of immune cell populations, with lower likelihood of autoimmune diseases.[85]

Sex differences in propensity to infection were apparent during the COVID-19 pandemic. An analysis of an international, multicentre, prospective observational database showed that males were more likely to develop critical illness, more frequently required interventions and had lower survival than females.[87] CKD was a risk factor for severe adverse outcomes in both females and males, although there have been conflicting reports regarding whether the relative effect of CKD on adverse outcomes is more pronounced in females or males.[88] Although sex differences in response to COVID vaccination are not well studied,[89] animal models indicate that the stronger immune response to vaccination observed in young females is no longer apparent in older animals,[90] suggesting a potential influence of changing hormonal profiles with increasing age on vaccine response.

Diagnosis, monitoring, and treatment delivery

Women are likely to receive fewer diagnostic tests than men, even when presenting with similar symptoms. In nationally representative analyses of data from Sweden and Australia, women were less likely to receive testing or monitoring for CKD, referral to specialists, and cardiovascular risk management.[91,92] Where biochemical data support a diagnosis, women are less likely to be coded as having CKD, and less likely to receive guideline-directed therapy, including statins, ACE inhibitors, and SGLT2 inhibitors (discussed in the third Series paper).[91,93,94,3] Differences in health-seeking behaviour (related to gender roles, social factors, or biological differences in symptom experience)[66,95] and higher rates of polypharmacy and treatment-related adverse events observed in females than in males, likely contribute to disparities in CKD treatment and outcomes.

There is a major missed opportunity for CKD screening during pregnancy. In HICs, pregnant females all have antenatal screening, but are not typically screened for CKD despite a major impact on pregnancy outcomes. Abnormalities identified during pregnancy (eg, proteinuria) are often inappropriately attributed to other causes, such as urinary tract infections, or assumed to be related to pre-eclampsia, and these abnormalities do not typically trigger appropriate follow-up. These observations in HICs with accessible health care are important, as the delays in diagnosis and treatment likely contribute to worse outcomes seen in females than in males, which could be exacerbated further in LMICs.[96]

Treatment response

Sex differences in the absorption, distribution, bioavailability, metabolism, and excretion of drugs might result in sexual dimorphism in pharmacological treatment responses (panel). Given body size differences between females and males, weight-based adjustment might partially address this issue, although insufficient data are available to confirm this. However, most drugs continue to be prescribed and administered at a single dose for females and males.

Body composition directly affects a drug's volume of distribution. Healthy females typically have smaller organ size and lower lean tissue mass, but a higher percentage of body fat than males.[102–104] Sex differences in body composition among individuals with comorbid conditions, such as type 2 diabetes,[104] might be amplified: higher body fat percentage can enhance drug accumulation, leading to longer half-lives and delayed washout for lipophilic drugs.[105] These differences are relevant for all the major drug classes currently used in the treatment of CKD and its complications, including statins,[106] ACE inhibitors,[107] angiotensin receptor blockers,[108] beta blockers,[109] SGLT2 inhibitors,[110] and steroidal and non-steroidal mineralocorticoid receptor antagonists.[111–113] Although female and male patients might expect to derive similar benefits from many of these treatments,[21,22] females might expect to see benefits at lower doses. In a prospective study of 1308 males and 402 females with heart failure with reduced ejection fraction, females showed approximately 30% lower risk for the primary outcome when receiving only 50% of the optimised male dose of ACE inhibitors, angiotensin receptor blockers, or beta blockers.[114] Given data describing increase in adverse drug reactions in females, sex-specific dosing advice might help to avoid treatment-associated adverse events and drug discontinuation, and maintain treatment benefits in females.[115]

Several differences in the gastrointestinal tract further influence pharmacokinetics. Females have a lower fluid volume in the stomach and small intestine, reducing drug dissolution; higher gastric pH, influencing absorption and bioavailability of pH-sensitive drugs; longer gastric emptying time in the premenopausal phase, increasing lag time for oral drug absorption; longer colonic transit time, potentially increasing drug absorption time and oral bioavailability, particularly for sustained-release drug forms; and differential expression of intestinal receptors and membrane transports, with variable effects of bioavailability.[116] Furthermore, sex hormones influence variation in the gut microbiome, resulting in differences between male and females, and in premenopausal and postmenopausal phases.[117,118] Variation in the gut microbiome is associated with differences in the development of chronic disease (including CKD, cardiovascular disease, diabetes, and hypertension)[119–122] and directly and indirectly (through alterations to bile acid profiles)[123] influencing response to treatment.[124]

Panel: Effects of sex and gender on the most common drugs

Pharmacokinetics[29,97,98]

Absorption (assuming oral administration)

- Higher gastric pH, which decreases weak acid absorption and increases weak base absorption, with evidence for an increased effect during pregnancy
- Increased gastrointestinal transit time, prolonging the absorption window and increasing overall absorption, with evidence for an increased effect during pregnancy

Distribution

- Lower body weight, smaller organ size, lower lean tissue mass, and higher fat mass
- Lower plasma volume and lower blood flow rate, with evidence for an increased effect during pregnancy
- Higher unbound drug fraction, with evidence for an increased effect during pregnancy
- Hydrophilic drugs have a lower volume of distribution, higher peak plasma levels, and a shorter duration of action
- Lipophilic drugs have a higher volume of distribution, lower peak plasma levels, and a longer duration of action

Metabolism (cytochrome P450 system)

- Higher CYP3A4 activity, with evidence for an increased effect during pregnancy
- Lower CYP2D6 activity, with evidence for an increased effect during pregnancy
- Lower CYP1A2 activity, with evidence for a decreased effect during pregnancy
- Females might have higher or lower exposure to drugs and their metabolites than males

Excretion

- Lower glomerular filtration rate, with evidence for an increased effect during pregnancy
- Altered active secretion in proximal tubule
- Reduced drug elimination and longer half-lives

Evidence for sex differences in pharmacokinetics for therapeutics used in chronic kidney disease (CKD)

- Loop diuretics (torasemide): higher peak serum concentration, area under curve (AUC), clearance time, and half-life
- Endothelin receptor antagonists (atrasentan): higher AUC and peak serum concentration
- Angiotensin receptor blockers (losartan): higher AUC and peak serum concentration
- Direct renin inhibitors (aliskiren): higher AUC and peak serum concentration

Pharmacodynamics[22,29,30,98–100]

Effects of sex hormones on receptor expression, binding, and signal transduction, leading to a different outcome from same delivered treatment

Evidence for sex differences in pharmacodynamics for therapeutics used in CKD

- Angiotensin converting enzyme inhibitors (class level): similar effects at half dose used in males
- Angiotensin receptor blockers (losartan and irbesartan): differential effect on kidney failure and cardiovascular outcomes
- SGLT2 inhibitors (class level): higher adverse event rate in females but similar effects on glycated haemoglobin (HbA1c) and cardiovascular events
- GLP1-receptor agonists (class level): greater weight loss and higher adverse event rate in females but similar effects on HbA1c and cardiovascular events
- Diuretics (torasemide): more frequent electrolyte disturbance including hospitalisations
- Endothelin receptor antagonists (atrasentan): more effective kidney failure reduction but higher heart failure events
- Direct renin inhibitors (aliskerin): higher rate of diarrhoea

Drug–drug interactions[101]

Females take more unique medications than males, including non-prescription drugs, herbal remedies and hormonal therapies for contraception and menopause, which can lead to changes to pharmacokinetics or pharmacodynamics

Evidence for sex differences in drug–drug interactions for therapeutics used in CKD

GLP1-receptor agonists (tirzepatide): causes reduced peak serum concentration and AUC for oral contraceptives

Sex differences in drug elimination exist, mediated by various mechanisms. There are sex differences in the expression and activity of hepatic metabolising enzymes. Renal drug transporters differ in their expression and response to sex hormones in males and females,[12] manipulating drug efficacy and safety and influencing drug–drug interactions. Renal clearance is reduced in females, in whom the average GFR is around 8 mL/min per 1·73 m² lower than in males.[58,125]

Although data are sparse, hormonal variation that occurs throughout the menstrual cycle, during pregnancy, breastfeeding, and with concomitant oral contraceptive use might result in alterations to renal clearance, gastrointestinal transit, haemodynamic accommodations, and others. For example, renal clearance is thought to be highest during the luteal phase of the menstrual cycle,[125] but the effect of this finding on pharmacokinetics has been understudied. These fluctuating hormonal effects, without parallels in males, could substantially affect drug concentrations, efficacy, and adverse events.[126]

An assessment of US Food and Drug Administration-approved drugs—although only a minority of drugs had accessible pharmacokinetic data for analysis—showed that 88% (76/86) of evaluated drugs showed a female sex-bias in pharmacokinetics, with higher area under the curve, higher peak concentrations, and longer clearance rates than observed in males.[98] Among drugs where there was a female-bias in pharmacokinetic values, 96% were

associated with a higher incidence of adverse drug reactions in females. These included, but were not limited to, allergy, bleeding, fracture, cardiovascular disease, hospitalisation, and death. Conversely, in 8% (7/86) of drugs where pharmacokinetic values were biased towards males, only 29% were also associated with male-biased adverse drug reactions.[98]

Sex differences in drug handling vary throughout the life course and might diminish or enhance in association with ageing, hormonal cycles, and development of comorbid or multimorbid disease, all factors that are commonly observed or disrupted with coexisting CKD. The effects of polypharmacy further enhance complexity: females are more likely to experience polypharmacy and use more unique medications than males.[127] These facts remain underappreciated in clinical practice and trial design, thus limiting our knowledge about best practices of drug prescribing.

Evidence generation and reporting: sex disparities and consequences

Lack of appreciation of sex differences in clinical practice stems from suboptimal exploration of sex differences during preclinical and clinical research. In this section, we describe to what extent modelling of sex differences has been incorporated into evidence generation and where scientific advances can support better appreciation of these nuances.

Preclinical models of CKD

Preclinical models offer potential to understand sex differences in kidney health and disease in more controlled environments than in clinical studies,[128] and have been shown previously to facilitate insights into sex differences in human research.[129] Traditional models of kidney disease with applications for therapeutic development and testing have included two dimensional cell culture systems, static three dimensional (3D) culture models, and animal models.[128]

In cell experiments, holistic exploration of sex differences requires that the sex of the cells, the serum source, and the extracellular matrix environment must be considered and aligned; however, the sex of cells is not commonly reported in primary cell cultures, and the sex of the extracellular environment is almost never considered.[130,131] In an assessment of cell experiments published in the *American Journal of Physiology Cell Physiology*, there was an improvement in reporting the sex of cells used between 2013 and 2018, but there continues to be a male bias, and results are rarely sex-stratified.[132] In kidney cell experiments, around a third of cells had no sex recorded (Cellosaurus database),[133] and two-thirds of cells for which sex could ultimately be determined were male.[128] Notably, female cell lines were not available across either human or non-human cells for the distal convoluted tubule, distal tubule, mesangial cells, or the thick ascending limb of the loop of Henle.[128] Conversely, only one female embryonic kidney cell line was identified, without a male comparator.[128]

In-vitro cell experiments are currently the most used for drug screening and modelling nephrotoxicity. In a systematic review of in-vitro studies of nephrotoxicity, proximal tubule cells (only two of 24 known cell lines are female)[128] were studied in more than 84% of studies,[134] followed by glomerular cells in 7% of studies[134] (for which only one of nine cell lines is female).[128] Inadequate consideration of sex in in-vitro models risks missing important differences in nephrotoxic drug effects. For example, female rats were shown to be less likely to develop severe cisplatin-induced nephrotoxicity than males, mediated in part by differential intratubular expression of cytochrome P450.[135]

In animal studies, female sex most commonly has a protective (but occasionally a neutral or harmful) effect against injury, with lower levels of oxidative stress, inflammation, and fibrosis across a range of CKD models in diverse animal strains.[8] However, sex differences are underexplored in animal models of CKD, through under-representation of females and a scarcity of sex-stratified reporting.[136–138] This stems from a widely held belief that, because of the reproductive cycle, female animals display substantial variability in response and thus should not be routinely included.[139,140] However, unstaged female animals display no more variation in diverse traits, such as hormone profiles, metabolism, gene expression, and electrophysiology, than do males; indeed, variation might even be lower in female animals. Notably, when housed together, the reproductive cycles of females synchronise,[141] leading to a homogeneous cohort of female animals: a phenomenon that is similarly described in humans.[142] Furthermore, where hormones might play a role in the outcome of interest, the study of a homogeneous cohort of female animals could be valuable.

Clinical studies

More than 30 years later after the US National Institutes of Health (NIH) set out guidance for inclusion of females in research, females remain under-represented in clinical trials.[143] In a review of 192 CKD trials, fewer than 45% of trial participants were female (with participation-to-prevalence ratio of 0·75)[144] and this number dropped further to 33% when examining recent SGLT2 inhibitor trials.[145] Sex-stratified efficacy outcomes were rarely reported, and sex-disaggregated safety outcomes were not reported for any trial.[144]

The assumption that trial data can equally be applied to females and males introduces potential for harm. In the SONAR trial, a fixed dose of atrasentan—an endothelin receptor antagonist—resulted in higher plasma drug levels and greater kidney protection among female participants, but at the expense of more heart failure events,[29] highlighting whether the risk–benefit balance was enough to justify treatment in females. A

meta-analysis of Angiotensin II Antagonist Losartan Study and Irbesartan type 2 Diabetic Nephropathy Trial showed that angiotensin receptor blockers had similar beneficial effects for reducing adverse kidney outcomes in both sexes but reduced cardiovascular events only in males.[30] In the REGENCY trial (obinutuzumab in proliferative lupus nephritis), the trial met its primary endpoint for efficacy with a relatively small effect in the combined group; however, outcomes were substantially better in females (n=229) treated with obinutuzumab, but better without treatment in males (n=42), strengthening the case for use of obinutuzumab in females with active lupus nephritis.[146]

Trials for complications of CKD have commonly ignored biological dimorphism by sex, unintentionally increasing the likelihood that females are excluded from participation. For example, fixed minimum eGFR thresholds for participation can disproportionately exclude females because eGFR in females is, on average, lower than in males. Similarly, several trials have focused on improving laboratory parameters to a single target value. The best example exists for haemoglobin, where observed values are lower in females than males across all stages of CKD, yet several major trials in anaemia management had single enrolment and treatment thresholds for the whole population.[147] Unsurprisingly, in an international study of dialysis practice across 12 countries, erythropoiesis-stimulating agents were more frequently prescribed for females (91·1%) than for males (85·4%),[147] a factor that has been associated with increased risk of morbidity and mortality.[147] In the absence of consistent reporting of sex-stratified safety data from randomised studies, it is not possible to ascertain whether the risk–benefit balance falls in favour of, or against, higher erythropoiesis-stimulating agent doses in females.[147,148]

Opportunities and recommendations

Scientific and medical organisations have called for increased attention to sex and diversity in experimental design (see our key recommendations in the table).[149–152] Codified in public law in 1993, the NIH established the Advisory Committee on Research on Women's Health and produced recommendations about inclusivity of sex across all aspects of research: basic, clinical, and implementation.[149] Formal guidance for the reporting of sex and gender issues in study design, analysis plans, results reporting, and interpretation were formalised in the Sex and Gender Equity in Research guidelines in 2016,[150] to which many research funders and journals have subscribed. In 2022, the Medical Research Council mandated the inclusion of animals of both sexes, and

	Policy ororganisational level (eg, government, research funders, or journals or editorial boards)	Collaboration level (eg, research consortia and clinical trial organisations)	Individual physician level
Improve awareness of the biological relevance of sex differences in kidney health and disease	Highlight sex (in policy documents and national campaigns) as an important and characterisable factor that influences health and disease; inclusion of sex differences in educational curricula for biological, clinical, and pharmaceutical sciences	Provide education on sex differences in kidney health and disease; promote interdisciplinary research (eg, basic science, social science, statisticians, epidemiologists, and clinicians); mandate engagement with educational resources for relevant personnel	Engage with educational materials to understand the relevance of sex differences in research and practice; engage with local students, colleagues, and mentors to share education on sex differences
Improve representation of female cells, animals, and human participants in research	Subscribe to and enforce guidance for consideration of sex and gender in study design, analysis plans, results reporting, and interpretation (ie, Sex and Gender Equity in Research guidelines 2016)[150]	Consider experimental design to facilitate inclusion of both sexes in animal research (see guidance from National Centre for the Replacement, Refinement and Reduction of Animals in Research)[152] unless single sex study is strongly justified; consider stage of life cycle in research design (prepuberty or postpuberty, pregnancy, and premenopause or postmenopause); design pragmatic clinical trial protocols that promote female participation; consider support for caregivers in clinical trial design; targeted increases in proportion of female participants invited to trial screening	Be mindful of sex disparities when approaching potential participants for clinical studies
Improve reporting of sex differences in research	Formal integration of sex and gender considerations in funding policy and application processes; mandatory reporting of the sex of cells, tissues, and animals and human participants; mandatory reporting of sex-disaggregated efficacy and safety data in research outputs to facilitate later meta-analysis	Two-step data collection for sex at birth and current gender identity; normalise the measurement and reporting of reproductive health and sex hormone levels in clinical studies; integrate sex (and gender) into statistical analysis plans—eg, include sex as an explicit biological variable and assess interaction with other variables; reanalysis of existing efficacy and safety data through a sex lens (requires sharing of raw data and publication of sex-disaggregated data)	Be mindful of sex considerations when designing, analysing, reporting, reviewing, and interpreting research
Reduce sex disparities in treatment of CKD	Generate guidance documents to reduce sex and gender disparities in provision of CKD care (eg, Association for Diagnostics & Laboratory Medicine/ National Kidney Foundation guidance to improve equity in CKD care 2023)[153]	Engage with actionable advice to reduce sex-disparities and gender-disparities in CKD care; use advances in digital health-care technologies and artificial intelligence to identify diagnosis and treatment gaps	Audit of local practice to identify sex discrepancies in the identification or treatment of CKD; identify local barriers to providing sex-equitable CKD care; develop local strategies to overcome barriers to providing equitable CKD care

CKD=chronic kidney disease.

***Table*: Opportunities and recommendations to improve understanding of sex differences in kidney health and disease**

meticulous reporting of the sex of animals and cell lines, in all grant applications involving preclinical studies.[151]

In preclinical research, the National Centre for the Replacement, Refinement and Reduction of Animals in Research offers an experimental design assistant to facilitate the design of experiments incorporating both sexes.[152] Appropriate consideration of sex differences does not necessarily require much larger sample sizes: there is negligible loss of statistical power if factorial analysis methods are used.[152,154] Advances in preclinical science offer enhanced potential to understand sex differences in kidney disease and therapeutics with better translational potential than traditional models.[128,155] 3D kidney organoids can be developed from adult stem cells derived from male or female-specific stem cell lineages, and evidence from non-kidney (uterus) organoids shows the potential to develop organoid models that can respond to the dynamic effects of reproductive hormones.[156] Kidney-on-a-chip describes microfluidic culture devices that mimic the function and complexity of human kidney segments and allow the study of kidney health and therapeutics under controlled laboratory settings:[155] devices have been developed for the glomerulus, proximal tubule, distal tubule, and collecting duct.[155,157,158] Although there are still challenges relating to reproducibility due to experimental and between-laboratory variation, these developments offer future potential to model the full nephron,[159] offer personalised disease and drug testing,[160] and to study the dynamic effects of the menstrual cycle and pregnancy-like endocrine exposures.[161]

In clinical trials in CKD, recognising multiple potential barriers to female participation provides opportunity to overcome them (figure 3). In meta-analyses of individual participant-level data in trials across chronic medical conditions, females appeared only slightly less likely to proceed beyond trial screening than males,[162] but once randomised, were equally likely to complete trial participation as males.[163] The implication is that enhancing the proportion of females invited to participate in trials might yield important improvements in representation. Where evidence of therapeutic safety and effect on CKD outcomes is particularly sparse (eg, in breastfeeding females), dedicated exploration is required.

Influencing funders and regulators to include sex and gender as part of funding policies and grant proposal processes can have a major impact. Over the past 10 years, the Canadian Institutes of Health Research (CIHR) formally integrated sex and gender into all grant applications, and specific resources were developed to support both applicants and evaluators. Mandatory reporting of how sex and gender was to be addressed within the study was introduced on application forms and on all subsequent reporting to CIHR. Following this, integration of sex as an important explanatory variable rose from 22% to 83%, and gender from 12% to 33%.[164]

Following existing Sex and Gender Equity in Research guidance, journal editors could insist on sex-disaggregated data (where relevant) as an important way to actualise the recommendations,[150] but this is not yet happening consistently. If a study is underpowered to detect sex-specific differences, there should be overt recognition that this is an important limitation of the data. When a difference is exposed, explanations as to the cause of that difference (environmental, biological, behavioural, or other) should be sought. Rapid developments in artificial intelligence and machine learning offer efficient means to reanalyse existing metadata to identify sex differences and simulate the potential for sex heterogeneity in outcomes. However, these techniques cannot be used safely if appropriate data are not collected and shared: training and executing these models on existing, unrepresentative data risks perpetuating known biases.[165]

Better research starts with improved education, including developing an understanding of sex

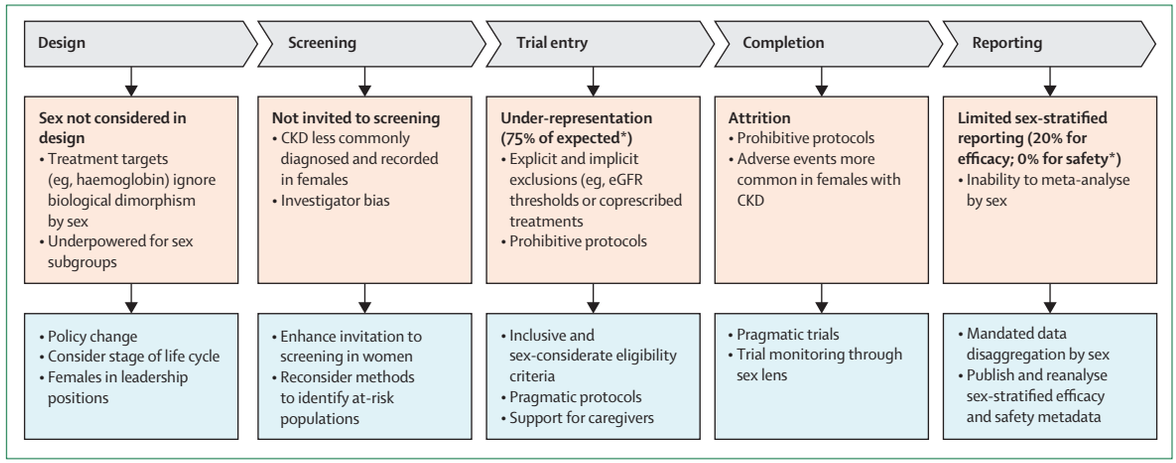

***Figure 3*: Issues affecting clinical evidence base for CKD in females**
CKD=chronic kidney disease. eGFR=estimated glomerular filtration rate. *In a systematic review and meta-analysis of 192 CKD trials.[144]

heterogeneity as a key curriculum component for teaching programmes across foundational and clinical sciences. Our hope is that this Series paper contributes to an increased awareness of the relevance of sex differences to kidney health and disease and inspires health-care practitioners and researchers alike to be aware and mindful of sex heterogeneity in their daily work (table). Until improvements in sex-stratified research and guidance are consistently delivered, clinical care can be improved by data-driven, sex-stratified assessments of CKD diagnostic and prescribing practices, including pro-active case-finding in high-risk situations such as pregnancy, and in creating targeted approaches to reducing sex-based disparities where these exist. These actions, even conducted at local level, could go some way to improving CKD care and outcomes in females.

Conclusion

Sex differences in kidney structure, function, and propensity to disease are necessary and expected results of physiology that have evolved to optimise reproduction. Substantial gains have been made in our appreciation of the sex differences in kidney health and disease. Strategic and systematic acknowledgment, exploration, and reporting of these differences is required in future research, or we risk derailing substantial efforts to advance our understanding of pathophysiology and novel therapeutics for CKD, which are discussed in detail in the first and third Series papers.[2,3]

To continue to develop an understanding of sex heterogeneity in kidney health and disease, a concerted effort is required by all. Policy makers, scientific organisations, journal editors, and funders can insist on appropriate consideration of the potential for sex differences in policy initiatives, new research ventures, and research dissemination. Individuals can take ownership of considering the potential for sex differences when designing, reporting, and reviewing research. To make a sizeable impact, sex heterogeneity must be acknowledged in education programmes across preclinical, clinical, and pharmaceutical sciences. With increasing use of artificial intelligence and machine learning, unrepresentative data, the absence of sex-stratified data, or the absence of data exploring sex differences will potentially bias future research and breakthroughs. Disentangling the influence of gender on sex disparities requires dedicated study. These fundamental issues must be addressed to ensure that our knowledge of CKD continues to expand in a responsible and safe manner.

Contributors

JSL and AL conceptualised the Series theme and this Series paper and invited the authors. All authors conceptualised this paper and agreed upon the structure. All authors contributed to writing—first draft in subsections of the paper. Subsections were collated into a full first draft by JSL. All authors contributed to writing—review and editing. Figures were conceptualised and created by JSL. Each iteration of the paper was reviewed and discussed by all authors who all helped in drafting the response to the reviewers, revision, and approval of the final manuscript.

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