Sex dimorphism in kidney health and disease: mechanistic insights and clinical implication

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Sex is a key variable in the regulation of human physiology and pathology. Many diseases disproportionately affect one sex: autoimmune diseases, such as systemic lupus erythematosus, are more common in women but more severe in men, whereas the incidence of other disorders such as gouty arthritis and malignant cancers is higher in men. Besides the pathophysiology, sex may also influence the efficacy of therapeutics; participants in clinical trials are still predominately men, and the side effects of drugs are more common in women than in men. Sex dimorphism is a prominent feature of kidney physiology and function, and consequently affects the predisposition to many adult kidney diseases. These differences subsequently influence the response to immune stimuli, hormones, and therapies. It is highly likely that these responses differ between the sexes. Therefore, it becomes imperative to consider sex differences in translational science from basic science to preclinical research to clinical research and trials. Under-representation of one sex in preclinical animal studies or clinical trials remains an issue and key reported outcomes of such studies ought to be presented separately. Without this, it remains difficult to tailor the management of kidney disease appropriately and effectively. In this review, we provide mechanistic insights into sex differences in rodents and humans, both in kidney health and disease, highlight the importance of considering sex differences in the design of any preclinical animal or clinical study, and propose guidance on how to optimal design and conduct preclinical animal studies in future research.

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Sex-based differences in common diseases are more widespread than one may assume with significant yet underestimated consequences in immunological responses, health care, clinical outcomes, and response to therapy. It is well recognized that females are more susceptible (80%) to a variety of inflammatory and autoimmune diseases including systemic lupus erythematosus (SLE), multiple sclerosis, and rheumatoid arthritis[1] by contrast to IgG4-related autoimmune disease.[2] In turn, women have a faster clearance of pathogens during infections and a greater vaccine efficacy than males due to a stronger innate and adaptive immune response.[3] Men on the other hand present with worse clinical outcomes and a higher mortality in atherosclerosis-related complications[4,5] and certain infections,[6–8] and are more likely to suffer from acute gouty arthritis.[9] In addition, the Swiss SLE cohort study showed that male patients with SLE have worse cardiovascular and kidney outcomes, and present with a significantly higher risk for coronary artery disease and myocardial infarction.[10] Women mainly develop atherosclerosis and experience acute gout attacks after menopause. This is particularly true if one or more autoimmune diseases, hypertension, obesity, or high blood pressure is present, suggesting immune modulatory properties of sex hormones.[4,5]

Increasingly evidence suggests that there are considerable sex differences in both normal kidney function and the capacity of the kidney to respond to injury.[11] Numerous instances of such effects are evident both in human populations (such as acute kidney injury [AKI][12,13] and chronic kidney disease [CKD][14]) and in commonly used animal models of kidney disease[15–18] (Tables 1 and 2). Broader effects of kidney function, such as age-related decline in glomerular filtration rate (GFR),[85] nephrogenesis,[11,21] low birth weight,[86] structural and cellular changes,[87] predisposition to the development of kidney failure,[88] and responses of the renin-angiotensin system[89] are all influenced by sex. Preclinical animal studies suggest that female rodents show diminished kidney injury, inflammation, and interstitial fibrosis than male rodents in response to AKI. However, data from epidemiologic human studies are less clear and even contradictory to preclinical research studies, certainly in the context of AKI. One reason for these discrepancies may be the unequal sex representation in both preclinical animal and clinical studies, which generally favor the inclusion of men.[90] Conducting studies on only one sex and extrapolating the results to the opposite sex can result in harm, including reduced efficacy or damaging side effects.[91]

In this review, we provide mechanistic insights on sex differences in rodents and in humans, both in kidney health and disease, highlight the relevance of considering sex differences in basic science and preclinical research as well as clinical research and trials (Figure 1), and provide guidance for considering sex differences in the design of any preclinical animal study (Figure 2, Box 1).

Kidney morphologic and functional differences between females and males

Kidney structure and function in rodents. Kidneys from adult male mice are larger and weigh more than those of adult females or orchiectomized males.[19] The sex dimorphism in kidney size is not congenital but programmed by neonatal endogenous androgens.[43] Treatment of newborn male mice with cyproterone acetate and newborn females with testosterone induced female and male patterns of kidney growth, respectively.[19] It appears that neonatal endogenous androgens are required to induce kidney cellular hyperplasia in male mice.[92] Administration of testosterone to adult female mice induced glomerular hypertrophy but not hyperplasia, so that the weight of the kidney remained smaller than in male mice. Moreover, castrated adult rats and those rats with a congenital deficiency of functional testosterone receptors exhibit normal compensatory kidney growth.[93,94] This compensatory kidney growth is growth hormone independent in female rats, whereas the hypertrophic response is growth hormone dependent in male rats.[95]

Sex hormones influence the development of sex specific traits. Recent studies indicate their important roles in regulating the structure and/or function of nearly every tissue and organ in the mammalian body including the kidney, causing sex differences in a variety of characteristics.[87] Sex differences in the normal decline of kidney function due to the natural aging process have been recognized in rodents.[21,96,97] For example, the decline in GFR varies between rat strains, with some showing preserved function, for example, WAG/Rij. Others exhibit severe age-dependent injury, for example, Sprague-Dawley rats, while some have shown a gradual decline, for example, Munich-Wistar rats.[97] In adult male mice, the GFR is higher than in adult female or orchiectomized male mice.[19] However, it is unclear whether the increased GFR in adult male rodents is due to an increase in glomerular size or number of glomeruli, and may potentially contribute to the increased susceptibility of male animals to kidney injury. Several experimental studies failed to find sex-related differences in glomerular size,[19,98,99] whereas others reported increased glomerular size in adult male animals as in female and castrated male animals.[100–102]

One explanation for the increased susceptibility of male animals to kidney injury could be sex-related differences in glomerular hemodynamics. Short-term administration of androgens to oophorectomized female rats increases glomerular size, glomerular ultrafiltration coefficient, whole- and single-nephron GFR, and single-nephron blood flow in the absence of differences in arterial or glomerular capillary pressure.[103] However, prolonged androgen administration plateaued or reversed these changes.[103] It is possible that the increased kidney vascular resistance seen in female rats may protect their glomeruli from hyperfiltration-induced injury by blunting elevations in glomerular capillary pressure associated with various kidney insults.[104] In contrast, another study failed to find any difference in afferent or efferent arteriolar resistances between male and female rats but observed a higher arterial pressure, renal blood flow, glomerular ultrafiltration coefficient, and GFR in male than in female rats.[99] These sex-related differences in kidney function persisted after correction for kidney weight.[99]

Kidney structure and function in humans. Similar to rodents, men have larger kidneys than women. This increased kidney weight seen in men solely depends on their greater body surface area, larger glomerular mass, and greater total glomerular volume than women, whereas no difference in number of glomeruli between men and women was found.[20] It remains unclear whether these structural differences contribute to the greater susceptibility of men to develop kidney failure but larger glomeruli may predispose men to enhanced hyperfiltration-mediated injury at any level of glomerular capillary hypertension.[20] However, this effect may be offset by a greater glomerular mass, which confers increased kidney functional reserve. This would protect men from hyperfiltration-mediated injury after nephron loss, and the larger glomerular mass would mitigate the development of glomerular capillary hypertension.[20] Thus, these data do not support the hypothesis that kidney structural differences explain sex-related differences in the progression of kidney disease.[20]

Table 1 | Mechanisms influenced by sex in the kidney of animals and humans

Pathomechanisms	Male	Female	Ref
Kidney structure and function	• Increased expression of aquaporin 1, Na^+/Pi transporter, and EGFR • Faster age-related GFR decline • Higher glomerular volume, larger kidneys, and glomeruli	• Reduced expression of aquaporin 1, Na^+/Pi transporter, and EGFR • Slower age-related GFR decline due to the beneficial vascular actions of estrogens, estradiol, and NO with lack of damaging androgens • Reduced glomerular volume • Pregnancy	19–24
Renal blood flow	Renal vasoconstriction • Reduced endothelium integrity (endothelin receptor type A expression) • Increased ACE-1, Ang II, and AT1 expression • Increased ET-1 and ETA expression • Reduced angiogenic factors (Ang II and Ang II receptor expression) and vascular permeability • Increased RAAS activity	Renal vasodilation • Enhanced endothelium integrity (endothelin receptor type B expression) • Reduced aquaporin 1, ACE-1, Ang II, and AT1 expression • Increased AT2, ET-1, ETB, ERK/PIK3, and AKT signaling • Increased angiogenic factors (Ang II and Ang II receptor expression) and vascular permeability • Decreased RAAS activity	25–31
Cell death	More cell death • More cell apoptosis and autophagy by increasing transcription factor EB nuclear translocation, expression of FAS ligand, Bax, caspase-3, and JNK signaling • More podocyte loss • Reduced slit diaphragm integrity • Mesangial expansion and glomerular hypertrophy	Less cell death • Less cell apoptosis and autophagy • Less podocyte loss • Increased slit diaphragm integrity • Less mesangial expansion and glomerular hypertrophy	32–34
Oxidative and metabolic stress	More oxidative stress • Reduced eNOS and NO expression • More ROS production and ER stress • Diminished fatty acid oxidation	Less oxidative stress • Higher eNOS and NO expression • Less ROS production and ER stress • More fatty acid oxidation	12,25,35–38
Inflammation and fibrosis	More inflammation and fibrosis • Increased proinflammatory cytokine levels (e.g., TNFα, MCP-1, IFNγ, and CCL-17) • Increased number of innate immune cells (e.g., inflammatory macrophages) • Lower number of adaptive immune cells (e.g., regulatory T cells) • Reduced HIF-1α/VEGF signaling • More glomerulosclerosis development	Less inflammation and fibrosis • Reduced proinflammatory cytokine levels (e.g., TNFα, MCP-1, IFNγ, and CCL-17) • Reduced number of innate immune cells (e.g., inflammatory macrophages) • Higher number of adaptive immune cells (e.g., regulatory T cells) • Enhanced HIF-1α/VEGF signaling • Diminished development of glomerulosclerosis	35,36,39–42
Additional contributing factors	• Reduced expression of kidney transporters (e.g., OATs and SGLTs) but increased fluid and electrolyte handling (e.g., Na^+, K^+, and Cl^- transport) • Reduced mineralocorticoid receptor expression and 11bHSD2 activity • Higher androgen and lower estrogen receptor expression in tubular cells • Testosterone modulates urinary calcium and magnesium clearance, ammonia metabolism and excretion • Higher cortisol metabolism	• Higher expression of kidney transporters (e.g., OATs and SGLTs) but reduced fluid and electrolyte handling (e.g., Na^+, K^+, and Cl^- transport) • Increased mineralocorticoid receptor expression and 11bHSD2 activity • Reduced androgen and higher estrogen receptor expression in tubular cells	32,43–58

ACE-1, angiotensin-converting enzyme; Akt, protein kinase B; Ang II, angiotensin II; AT1, angiotensin receptor 1; AT2, angiotensin receptor 2; CCl-17, chemokine C-C motif ligand 17; Cl, chloride; EGFR, epidermal growth factor receptor; ER, endoplasmatic reticulum; ERK, extracellular signal-regulated kinases; ET-1, endothelin 1; ETB, endothelin receptor B; GFR, glomerular filtration rate; HIF-1α, hypoxia inducible factor 1α; IFN-γ, interferon gamma; MCP-1, monocyte chemoattractant protein 1; Na^+, sodium; NO, nitric oxide; OAT, organic anion transporter; PI3K, phosphatidylinositol 3-kinase; RAS, renin-angiotensin-aldosterone system; Ref, reference; ROS, reactive oxygen species; SGLT, sodium glucose cotransporter; TNF-α, tumor necrosis factor alpha; Treg, regulatory T cells; VEGF, vascular endothelial growth factor.

Table 2 | Preclinical animal studies exploring sex differences in AKI and CKD

Study characteristics	Study context	Etiology	Effect of female sex	Ref
AKI				
C57BL/6 mice	Female and male mice have differential long-term cardiorenal outcomes following a matched degree of ischemia-reperfusion AKI	IRI	Protective	59
C57BL/6	Effect of sex differences on the regulation of IRI-induced inflammation in mice	IRI	Protective	35
C57BL/6 mice	Estrogen administered after cardiac arrest and cardiopulmonary resuscitation ameliorates acute kidney injury in a sex- and age-specific manner	IRI	Protective	60
BALB/c mice	Exaggerated arsenic nephrotoxicity in female mice through estrogen-dependent impairments in the autophagic flux	Sodium arsenite-induced AKI	Harmful	61
C57BL/6J mice	Unique sex- and age-dependent effects in protective pathways in acute kidney injury	Hemeoxygenase-1 induced AKI	Protective	62
C57Bl/6 mice	Sexual dimorphism of acute doxorubicin-induced nephrotoxicity in C57Bl/6 mice	DOX induced AKI	Protective	63
129Sv mice	Sex differences control the susceptibility to ER stress-induced AKI	ER stress induced AKI	Protective	18
C57BL/6 mice	The comparison of inflammatory response after cross-sex-KTX and same-sex-KTX	KTX	Same-sex KTX is protective	64
C57BL/6 mice	The effect of sex on IRI tolerance after KTX	KTX	Protective	65
C57BL/6 mice	Improved kidney ischemia tolerance in females influences kidney transplantation outcomes	IRI and KTX	Protective	65
BALB/c, C57BL/6, SV 129 and C57BL/6 _ SV129 mice	Testosterone is responsible for enhanced susceptibility of males to IRI	IRI	Protective	17
Wistar rats	Sex differences in heat shock protein 72 expression and localization in rats after renal IRI	IRI	Protective	66
Wistar rats	Sexual dimorphism in kidney ischemia-reperfusion injury in rats: possible role of endothelin	IRI	Protective	15
BALB/c mice	Sex differences in the susceptibility to kidney IRI in BALB/c mice	IRI	Protective	67
C57BL/6J mice	Sexual dimorphism in the blood pressure response to angiotensin II in mice after angiotensin-converting enzyme blockade	Angiotensin II stimulation	Protective	68
CKD				
129/SvJ mice	Progression of Alport kidney disease in Col4a3 knock out mice is independent of sex or macrophage depletion by clodronate treatment	Alport kidney disease	Neutral	69
eNOS-/- *db/db* mice	Comparison of diabetic kidney disease between male and female eNOS–/– *db/db* mice	Diabetic kidney disease (type 2)	Neutral	70
CD1 mice	Both sexes develop diabetic kidney disease in the CD1 uninephrectomized streptozotocin mouse model	Diabetic kidney disease (type 1)	Neutral	71
db/db mice	Sex differences in diabetes- and TGF-β1-induced renal damage	Diabetic kidney disease	Harmful	72
UNx db/db C57BLKS mice	Impact of sex on diabetic kidney disease and the renal transcriptome	Diabetic kidney disease	Neutral	73
OVE26 mice	Sex differences in progression of diabetic kidney disease in OVE26 type 1 diabetic mice	Diabetic kidney disease	Harmful	74
WT and nephron-specific Ift88 KO mice	Sex-dependent effects of nephron Ift88 disruption on BP, kidney function, and cystogenesis	Polycystic kidney disease	Ift88 KO is only protective in male mice	75
Han:SPRD rats	Sex hormones and the progression of experimental polycystic kidney disease	Polycystic kidney disease	Protective	76
HO-2 WT, HET and KO mice	Sex-specific effects of hemeoxygenase-2 deficiency on renovascular hypertension	Two-kidney, one-clip Goldblatt hypertension	HET and KO mice exhibited greater cardiac hypertrophy as compared with WT mice only in female mice	77
Sprague-Dawley rats	Sex differences in kidney nuclear receptors and aryl hydrocarbon receptor in 5/6 nephrectomized rats	5/6 nephrectomy	Protective	78

(*Continued on following page*)

Table 2 | (Continued)

Study characteristics	Study context	Etiology	Effect of female sex	Ref
Wistar rats	Sex differences in the progression of experimental CKD Induced by chronic nitric oxide inhibition	L-NAME-induced CKD	Protective	79
Wistar rats	Sex differences in adenine-induced chronic kidney disease and cardiovascular complications in rats	Adenine crystal–induced CKD	Protective	80
C57BL/6 mice	The role of the EGF receptor in sex differences in kidney injury	Dsk5 mutant–induced CKD	Protective	24
MF1 and C57BL/6 mice	Sex differences in kidney ACE2 activity are 17β-estradiol-dependent and sex chromosome-independent	Gonadectomy and 17β-estradiol (E2) treatment	Males have higher renal ACE2 activity	81
C57BL/6 mice	Angiotensin-converting enzyme 2 contributes to sex differences in the development of obesity hypertension in C57BL/6 mice	Obesity	Protective	82
NZB/W mice	Sex-specific effects of LiCl treatment on preservation of kidney function and extended lifespan in murine models of SLE: perspective on insights into the potential basis for survivorship in NZB/W female mice	SLE	LiCl treatment is more effective in female mice	83
C57BL/6J mice	Renoprotective effect of protocatechuic acid is independent of sex-related differences in murine model of UUO-induced kidney injury	UUO	Neutral	84

ACE, angiotensin-converting enzyme; AKI, acute kidney injury; BP, blood pressure; CaP, calcium phosphate; CKD, chronic kidney disease; DKD, diabetic kidney disease; DOX, doxorubicin; EGF, epidermal growth factor; eNOS, endothelial nitric oxide synthase; ER, endoplasmic reticulum; HET, heterozygous; IRI, ischemia-reperfusion injury; LiCl, lithium chloride; L-NAME, N(ω)-nitro-L-arginine methyl ester; KO, knockout; KTX, kidney transplantation; Ref, reference; SLE, systemic lupus erythematous; TGF-β1, transforming growth factor β1; UUO, unilateral ureteral obstruction; WT, wild-type.

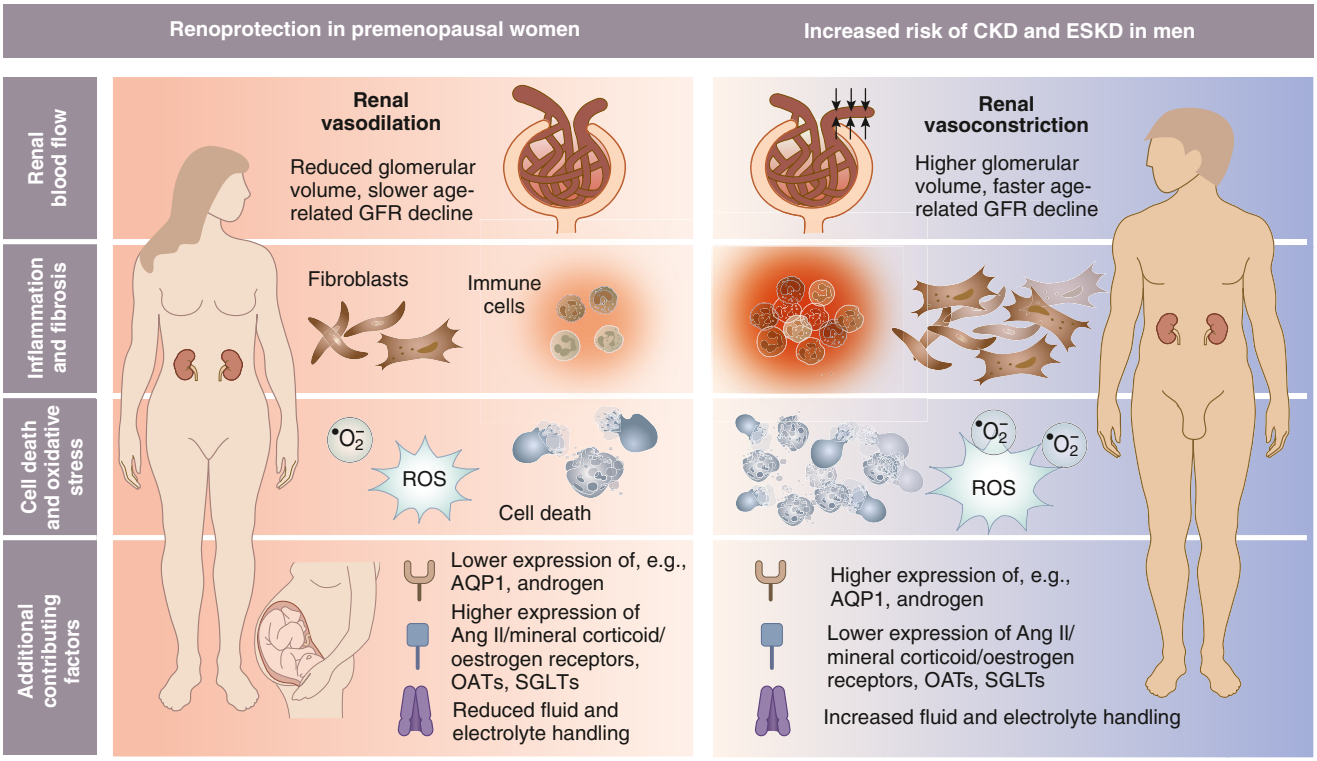

Figure 1 | Mechanisms counterbalancing acute kidney injury (AKI) and chronic kidney disease (CKD) outcomes in premenopausal females and males. Several studies in both animals and humans have shown that estrogens display renoprotective effects in AKI and reduce the risk for the development of kidney failure in females by promoting renal vasodilation and reducing inflammation, fibrosis, oxidative stress, and cell death. Additional contributing factors such as kidney transporter and receptor expression pattern, kidney structure and function, age, and pregnancy may also account for this. In contrast, testosterone is involved in driving kidney injury faster to CKD and kidney failure by mediating renal vasoconstriction and increasing inflammation, fibrosis, oxidative stress, and cell death. Additional contributing factors, such as transporter and receptor expression pattern, kidney structure and function, and age may also play a role in males. Ang II, angiotensin II; AQP1, aquaporin 1; GFR, glomerular filtration rate; OAT, organic anion transporter; ROS, reactive oxygen species; SGLT, sodium glucose transporter.

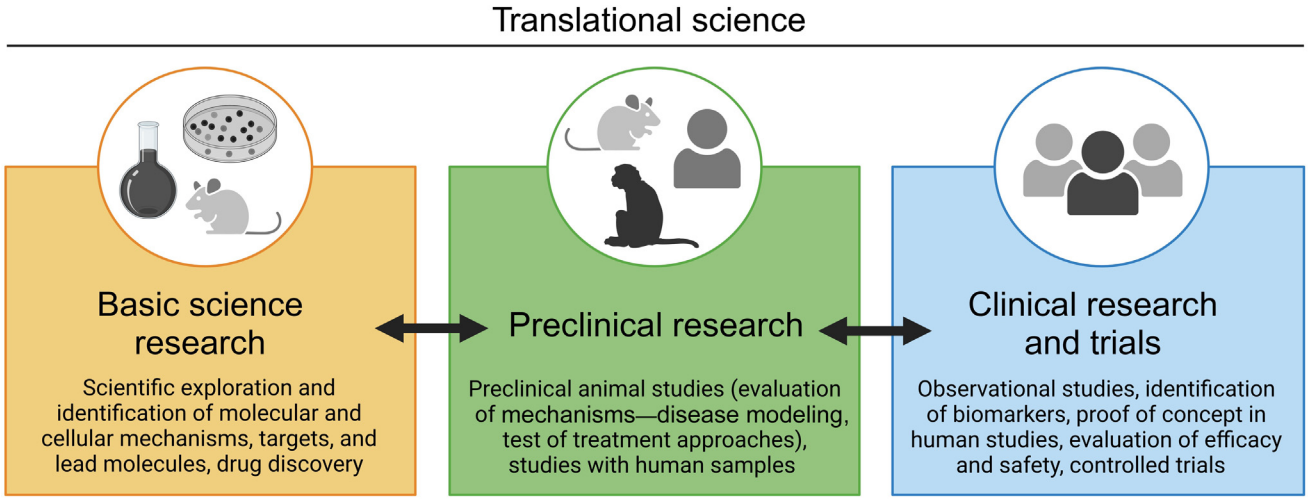

Figure 2 | Proposed guidance of using both sexes in preclinical research.

It is well recognized that the kidney function declines with advancing age in humans.[21] Possible reasons for this are reduced kidney plasma flow;[26,27] structural changes including thickening of the glomerular basement membrane and expansion of the glomerular mesangium and extracellular matrix, which contribute to glomerular sclerosis, podocyte loss, and fibrosis; low birth weight and dysfunction in nephrogenesis (reviewed in the paper by Perez-Coria *et al.*[21]); and structural changes due to kidney injury, all of which lead to loss of functioning nephrons.[105,106] Of note, in most individuals, this age-dependent loss of kidney function is sufficiently slow that it has no obvious impact in the absence of an underlying kidney disease.[107] There is a marked sex dimorphism in the aging kidney with a faster age-related decline in kidney function in men and postmenopausal women than in age-matched premenopausal women. Clinical studies show that an age-related GFR decline is delayed in women and proceeds relatively slowly when it occurs,[22,23] which contribute to the antigrowth effects on glomerular mesangial cells (Table 1, Figure 1). Indeed, CKD progression in premenopausal women is slower than in men. This protection is lost with the onset of menopause but can be restored with estradiol replacement.[14,108] Less information on the impact of progesterone exists, but it is reported that progesterone enhances some and opposes other estrogen-mediated effects.[109] Multiple pregnancies in women and female rats with normal kidney function have no adverse impact on age-related changes in kidney function,[107,110] suggesting no harmful effect of periodic elevations in progesterone levels on the kidney. However, this changes when maternal kidney function is already impaired before conception and may accelerate the underlying kidney damage.[107,110] Thus, abnormalities in kidney function that lead to or protect from kidney disease, as well as an age-dependent decline in kidney function, are mediated by sex hormones with both the protective estrogens and the damaging androgens, rather than genetically determined differences in kidney structure.[107]

Pathomechanisms associated with sex differences

Regardless of the underlying cause of AKI and CKD, sex differences in the immune response to injury, including kidney vascular tone regulation, renin-angiotensin system, inflammation, fibrosis, oxidative stress, and cell death, are caused by genetic, hormonal, and environmental factors or a combination thereof. Mechanisms that have been identified are briefly described below, depicted in Figure 1 and listed in Table 1.[25,111]

Cellular and molecular mechanisms of kidney injury in animals. To date, several mechanisms that are linked to cellular structural differences have been documented between sexes in animals.[112,113] For example, healthy male rats have a higher lithium clearance and less bicarbonate reabsorption than female rats, and proximal tubular cells in females express less aquaporin 1 and Na^+/Pi cotransporter 2 but increased phosphorylation of the Na^+/H^+ exchanger 3.[112] To account for sex differences between transporter patterns in proximal tubular cells, Li *et al.*[113] revealed sex differences in the single-nephron GFR, tubular dimensions and expression levels of apical and basolateral transporters in the rat kidney. Moreover, Na^+-Cl^- cotransporter activity is important for morphologic remodeling of the distal convoluted tubule structure and more abundant in healthy female mice.[114–116] Sex-specific effects on other kidney transporters have been demonstrated,[117] including organic anion transporters,[51,52] sodium glucose cotransporters,[53] and angiotensin type 2 receptor.[54,55,112]

Sex hormones have long been associated with kidney function. Androgens enhance salt reabsorption[118] and water handling[119] in the proximal tubules, promote kidney autophagy,[32] and stimulate total kidney volume in males.[118] Testosterone has also been shown to modulate urinary calcium and magnesium clearance[32,46] as well as ammonia metabolism and excretion.[47–50] Hormone injection studies and genetic removal of androgen receptors demonstrated androgen receptor–mediated regulation of gene activity in proximal tubular cells.[58] Besides androgen and estrogen

Box 1 | Proposed guidance of using both sexes in preclinical research

Guidance for preclinical animal studies

Literature search	Is there evidence of sex differences in humans in the incidence or prevalence, pathophysiology, treatment response, or morbidity or mortality in AKI and CKD?	Unclear/ not reported	Assume different pathophysiology between sexes and conduct **pilot experiment**.
		NO	Use both females and males in preclinical studies without need for powered testing of sex differences (pooled data) and report sex-based findings in publication.
		YES	Perform a well-designed **experimental study** using both sexes.
Pilot experiment	Perform pilot experiment with both sexes to generate preliminary data on potential sex differences. If sex differences occur, perform experimental study.	Use a small group size (n = 3–4) [a]*In vitro*: e.g., add sex hormones to cells or culture cells of different sexes *In vivo*: e.g., use female and male rodents in models of AKI or CKD	
Experimental study	**Practical strategies of using both sexes in preclinical animal studies** (1) Select animal model that mimics human disease more closely (2) Use appropriate genetic background and mouse strain because susceptibility, severity, and outcomes can vary between the sexes (3) Design the study appropriately to detect potential sex differences by considering (a) Equal group size, include control group (b) Larger group size that allows powered statistics (n = 6–8) (c) Decide on effect size (small or big) (d) Outcome measures (e.g., kidney function and inflammation) (e) Adjust severity of rodent model and use different rodent models of AKI or CKD (4) Investigations of disease progression should include both sexes (5) The phase of life of animals should be considered (e.g., young vs. old and use of a premenopausal animal model) (6) Consider effects of sex chromosomes in understanding the pathophysiology of disease (e.g., use the 4-core genotype mouse model, XY[a] mouse model, and sex-hormone receptor knockout mice)		
Experimental study	(7) Account for sex hormones (e.g., pregnancy versus nonpregnancy, androgens versus estrogens treatment, removal of gonads, and young versus old) (8) Studies testing new therapies should include both sexes (a) Consider safety measures of the drug as female and male rodents may respond differently (e.g., side effects) (b) Adjust dosage of the drug as female and male rodents may respond differently (c) Control groups must be included (d) Intervention should be started after disease and injury have been established		
Data analysis and reporting	(1) Perform sex-disaggregated data analysis on outcome measures in female and male rodents separately (a) To enhance understanding of underlying mechanisms in males and females (b) Compare effectiveness of drugs (e.g., on safety, survival, kidney function, injury, and inflammation) in each sex directly (c) Use appropriate statistical analysis for comparison of sex differences, do not pool data (d) Visualize data by sex (2) For reporting of experiments and their results, follow the ARRIVE guidelines, report all data acquired and discuss study limitations		

AKI, acute kidney injury; CKD, chronic kidney disease.
[a]Note: In *in vitro* studies, it should be first established whether cultured cells maintain their phenotype. If not, different culture conditions could be used. Cultured cells may include primary kidney cells isolated from mice of both sexes or murine and human kidney cell lines treated with sex hormones or human-induced pluripotent stem cells cultured with sex hormones or organoids.

receptors,[56,57] recent evidence indicates a role for the kidney epidermal growth factor receptor in sex disparities in kidney injury.[24] The authors found greater kidney epidermal growth factor receptor expression levels and increased glomerular and tubulointerstitial injury in adult male than female mice, while castration decreased kidney epidermal growth factor receptor expression in male mice.[24]

In the mouse kidney, sex dimorphic gene activity/expression maps predominantly to the proximal tubule segments.[58,120] Multiomic analyses of mouse kidneys identified several transcription factors whose interplay with proximal tubular cells may contribute to the sex bias in healthy mice[121] but also in response to injury.[122] Proximal tubular but also glomerular cells are central in kidney physiology and after kidney injury,[58,120,123] including the regenerative process after AKI.[124–127] However, a defective or abnormal regenerative response of renal progenitor cells has been shown to contribute to pathologic conditions, such as kidney cancer.[128] Whether sex dimorphism plays a role in this context is currently unknown. Moreover, evidence suggests that *Xist* ribonucleoprotein complexes act as immunogenic triggers underlying the greater prevalence of autoimmune diseases in females.[129]

It is known that sex-related differences in mitochondrial function and homeostasis exist and likely contribute to sex dimorphism in kidney injury, for example, via Sirtuin-3, which is more highly expressed in the kidneys of male mice versus females,[130,131] with males having a greater risk for developing ischemic AKI. Intact mitochondrial substrate efflux is essential for preventing tubular injury. McCrimmon *et al.*[37] showed that

male mice (12–15 months of age) shut down fatty acid oxidation and several other metabolism-related pathways in proximal tubular cells, whereas female mice of the same age were still able to oxidize fatty acid–based substrates in a CKD mouse model of tubular-specific mitochondrial overload. Inflammatory cytokine levels and oxidative stress are more increased in male mice and rats than in female mice and rats after AKI,[35,36] while nitric oxide production and expression of endothelial nitric oxide synthase and angiogenic factors are reduced (Table 1).[25]

Moreover, sex differences in kidney glucocorticoid and mineralocorticoid signaling during nephrogenesis have been reported and may account for the predisposition to kidney disease in male rodents.[43] Sex dimorphism of corticosteroid signaling is effective as early as the perinatal period with higher mineralocorticoid receptor expression and 11βHSD2 activity in female mice and higher cortisol metabolism in males,[44,45] thus, favoring mineralocorticoid signaling in the female fetus and neonates, and preferential activation of the glucocorticoid pathway in males.[43]

Cellular and molecular mechanisms of kidney injury in humans. Several pathomechanisms in AKI and CKD that have been identified in rodents were also shown to be prevalent in humans (Figure 1, Table 1).[25,41] For example, in middle-aged and old men, endothelin mediates greater vasoconstriction through endothelin receptor type A receptor,[28] whereas vasodilation mediated by the endothelin receptor type B receptor was recently shown to be present in premenopausal women but absent in postmenopausal women.[29] Interestingly, the proportion of endothelin receptor type B/A receptors is higher in women (1:1) than in men (1:3), leading to worsening vasoconstriction and glomerular damage in men.[28] Women tend to have higher circulating levels of angiotensinogen but lower aldosterone than men, whereas the expression of angiotensin-converting enzyme and angiotensin II receptor type 1 receptors is downregulated by estrogens.[30] Moreover, men have a higher blood pressure as well as increased angiotensin II and renin-angiotensin system levels.[31] Sex dimorphism in humans on the expression levels of androgen and estrogen receptors as well as the epidermal growth factor receptor have also been noticed.[24,32] In human proximal tubular epithelial cell lines and primary tubular cells, exposure to testosterone promotes apoptosis and autophagy.[33,34] A decrease in endothelial nitric oxide synthase and nitric oxide levels was observed in aging women, an effect that is associated with the onset of menopause.[38]

CKD is characterized by persistent inflammation and immune paralysis associated with increased production of proinflammatory cytokines, oxidative stress, and higher numbers of circulating immune cells.[39] Differences in $CD4^+$ T cells have been observed in humans as women have a higher proportion of these circulating cells that produce more interferon γ than men.[40] Among kidney transplant recipients, men exhibit higher oxidative and nitrosative stress.[12] In SLE, for example, estrogen and estrogen receptors have been shown to mediate the functions of monocytes, B cells, T cells, and dendritic cells, and promote toll-like receptor 4 responsiveness and cytokine release, processes that may contribute to the development of lupus nephritis.[41,42]

Differential sex-related effects on the development of AKI and CKD in animals

Preclinical animal studies represent the first step in the development of drugs or in the comprehension of pathogenetic mechanisms of diseases (Figure 1) and in turn a necessary step for the development of new or more appropriate therapeutic strategies.[132] However, sex differences are still scantily considered, and the great majority of preclinical animal studies do not take into account the relevance of such disparities. This also applies to sex differences in preclinical aging research.[133] Several preclinical animal studies that did however investigate sex differences in the pathogenesis of AKI and CKD in animals are briefly discussed below and listed in Table 2.[25,111]

Sex dimorphism in AKI. Sex-related differences have been extensively studied in several animal models of AKI and consistently show a protective effect of female sex in the course of injury and development of AKI (Table 2).[17,35,66,134] For example, in ischemia-reperfusion injury (IRI)-induced AKI, castration or estrogen administration to male mice before ischemia reduced kidney damage, whereas testosterone administration to female mice worsened IRI-induced kidney injury.[17] Similar results were found in Wistar rats.[15] Likewise, young female C57BL/6 or BALB/c mice demonstrated less kidney injury induced by nephrotoxins,[61–63] while in older female mice or younger/old male mice, there was no benefit of protection and efficient recovery from AKI.[62] Sex hormone concentrations were not measured. In contrast, male BALB/c mice seem to be more susceptible to AKI and did not survive after exposure to prolonged periods of kidney ischemia, while female BALB/c mice exhibited greater resistance and survival.[67] Male mice are also more vulnerable to endoplasmatic reticulum stress and tubular cell death induced by tunicamycin administration than female mice.[18]

AKI commonly causes systemic sequelae and predisposes patients to cardiovascular disease. To date, studies of the effects of AKI on cardiorenal outcomes have only been performed in male mice because females require an increased kidney ischemia duration compared with male mice to elicit similar functional injury (34 vs. 25 minutes).[59] Soranno *et al.*[59] showed that the GFR was similar between aged female and male mice 1 year after AKI. One year after AKI, female mice had preserved diastolic function, normal blood pressure and preserved levels of cardiac adenosine triphosphate, possibly due to an enriched arginine metabolism and amino acid energy production, and increased mitochondrial function compared with males.[59] Consistent with this finding, recent reports found that hemeoxygenase-2 deficiency contributes to the development of renovascular hypertension in male mice[77] and that infusion of angiotensin II results in a greater pressor response in male than in female mice.[68] Thus, sex-related differences play an

important role in cardiovascular outcomes after AKI and merit further investigation.

In addition, substantial IRI to the transplanted kidney occurs in 30%-50% of transplanted patients who receive an organ from a deceased donor. IRI usually manifests as delayed graft function and in severe cases results in primary nonfunction.[135] A recent experimental study found that IRI tolerance is profoundly increased in female compared with male mice and discovered an intermediate phenotype after neutering of either sex.[65] Transplantation of adult kidneys from either sex into a recipient of the opposite sex followed by ischemia at a remote time resulted in ischemia recovery that reflected the sex of the recipient, not the donor, revealing that the host sex determines recovery.[65] Likewise, kidney injury on IRI was exacerbated in female estrogen receptor α knockout mice, whereas female mice receiving estrogen administration before ischemia were protected,[65] implying sex differences in kidney IRI tolerance and cross-sex kidney transplantation outcomes.[64] Ikeda *et al.*[60] found that estrogen administration shortly after resuscitation from cardiac arrest ameliorates AKI in young males, whereas young females were not protected by estrogen. In aged females, the protective effect of exogenous estrogen may be recovered with loss of endogenous estrogen, indicating that postarrest estrogen administration is renoprotective in a sex- and age-dependent manner.[60]

Sex dimorphism in CKD. Sex differences have also been observed in preclinical animal models of CKD (Table 2). For example, in a rat model of adenine crystal–induced CKD, kidney function in female rats decreased to a lesser extent than in male rats, and pathologic features of CKD including oxidative stress, inflammation, and interstitial fibrosis were more pronounced in male than female rats.[80] In 5/6 nephrectomy models, male rats developed marked kidney damage, accompanied by anemia and malnutrition, which was associated with inflammation and albuminuria.[78] All these alterations were less severe in female rats, and moreover, inflammation was not detected.[78] Chronic inhibition of nitric oxide induced CKD as evidenced by severe hypertension, albuminuria, ischemia, glomerulosclerosis, and inflammation in Wistar rats, while females exhibited less severe kidney damage.[79] Moreover, a male susceptibility to kidney cystogenesis has been noted in rodents with polycystic kidney disease.[75] Hu *et al.*[75] found that nephron cilia disruption in male but not female mice reduced blood pressure before cyst formation, increased nitric oxide production, and induced polycystic kidneys. Similarly, female sex is protective and reduces the risk of the progression of polycystic kidney disease in rats.[76] Although male animals progress faster to CKD than female animals in most preclinical studies, there is evidence that estrogens may exacerbate CKD in stroke-prone mice. In contrast, female mice seem to be more vulnerable to calcium phosphate and oxalate stone formation than male mice due to an increased urinary pH and Ca^{2+} clearance, which was reversible after urine alkalization.[136]

In animal models of nondiabetic kidney diseases, females generally show a better kidney outcome than males. However, the available data on sex differences in type 1 and type 2 diabetes and kidney disease are controversial. Although some studies in *db/db* mice observed sex differences in the course of diabetic kidney disease,[72] others did not, for example in *eNOS–/– db/db* mice[70,137] and in the CD1 uninephrectomized streptozotocin mouse model.[71] Moreover, in Alport syndrome, twice as many women are affected by the X-linked Alport syndrome but usually have less severe disease than men, whereas both sexes are equally affected with similar kidney outcomes by the autosomal recessive Alport syndrome in humans[138] and in *Col4a3* knockout mice.[69]

In addition, in a model of obesity-related hypertension, female mice were shown to gain more body weight and fat mass and have increased angiotensin-converting enzyme 2 activity compared with male mice. Unlike obese female mice, male mice with obesity had elevated systolic and diastolic blood pressure that was eliminated by losartan treatment.[82] Sex differences on therapeutic approaches have also been noticed in animal models of SLE and lupus nephritis. For example, treatment with lithium chloride of females but not males in the NZB/W model at an early age during the onset of disease can prevent the development of kidney failure in a significant number of animals.[83] While on lithium treatment, up to 80% of females in this animal model exhibit long-term survival with evidence of mild glomerulonephritis without progressing to kidney failure despite ongoing autoimmunity.[83] Stopping the treatment led to a reactivation of the disease and kidney failure. Lithium treatment in other murine models of SLE was less effective and decreased survivorship in male BxSB mice, exhibited little effect on male MRL-*lpr* mice, and only modestly improved survivorship in female MRL-*lpr* mice.[83]

Taken together, to our knowledge, the majority of preclinical animal studies suggest a greater AKI susceptibility and faster CKD progression in male than female rodents. Disparities in kidney disease outcomes that occurred are mainly attributed to the genetic background of mice and the cause of AKI. Of note, preclinical animal studies evaluating therapeutic approaches have mainly been performed in male animals. Possible explanations are that sex differences were not investigated (majority) or noticed and carried out based on the clinical observation, for example, increased risk of CKD observed in men[139] or sex-independent disease manifestation in autosomal recessive Alport syndrome, leading to the use of male *Col4a3* knockout mice.[69,140]

Sex differences in humans in AKI and CKD

In general, women show an increased susceptibility to autoimmune disease development, such as SLE, whereas men show increased susceptibility to malignant cancers[3] (Figure 3). Although at a less pronounced magnitude, sex differences are also seen in the susceptibility to numerous infections.[3] The female-biased infectious disease risk is in part due to the reproductive status and immune-mediated pathology, whereas pathogen-associated damage including

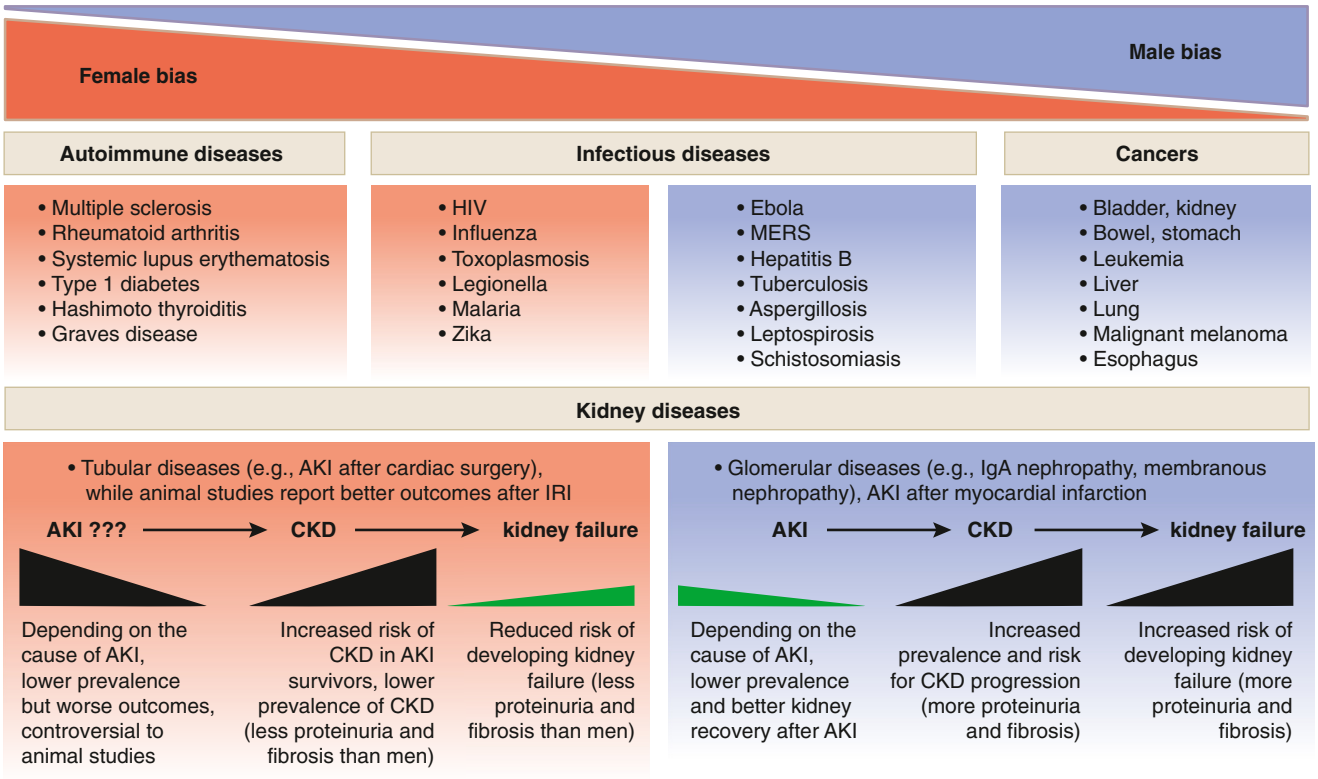

Figure 3 | Sex bias in autoimmune diseases, infectious diseases, cancers, and kidney diseases. At the extremes, males and females show robust differences in their susceptibility to autoimmunity and cancers. Women show increased susceptibility to autoimmune diseases, whereas men to malignant cancers.[3] Although at a less pronounced magnitude, sex differences are also seen in the susceptibility to various infectious diseases.[3] In kidney disease, preclinical animal studies report a protective effect of female sex in the course of injury and development of acute kidney injury (AKI) in models of ischemia-reperfusion injury and nephrotoxic-induced AKI, whereas male animals have a greater AKI susceptibility and faster chronic kidney disease (CKD) progression. In contrast, data on the incidence (increased risk) of AKI are controversial according to epidemiologic studies. Premenopausal women seem to have a lower prevalence of AKI and CKD progression, suggesting renoprotective effects of female sex. However, the kidney outcomes of severe AKI are worse in postmenopausal comorbid women as well as the acute rejection rate after kidney transplant with a higher risk of CKD in AKI survivors. Men show a faster decline in kidney function, progress more frequently to kidney failure, and have higher mortality and risk of cardiovascular disease than women. IgA, immunoglobulin A; MERS, Middle East respiratory syndrome.

delayed clearance is associated with male-biased infectious diseases.[3] Sex differences in the development of AKI[111] and CKD[25] have also been observed in humans (Table 3), although not as robustly or as consistently as in preclinical animal studies (Table 2).

Sex dimorphism in AKI. Evaluation of sex-related differences in human studies of AKI is more complex given the variations in sex hormone levels related to age, genetic predisposition, and structural and functional changes.[167] A study examining the effect of sex steroids on kidney injury found an unclear hormonal effect but did conclude that age-related proteinuria and glomerulosclerosis are worse in men than women; furthermore, women tend to tolerate nephron loss better.[168] Elevated serum estradiol and progesterone levels are associated with increased 28-day mortality in patients with septic shock and AKI.[169] A similar study[170] did not find sex differences in the incidence of AKI associated with moderately severe and severe pancreatitis but did observe that higher estradiol levels were associated with increased risk of AKI.

Although the 2012 Kidney Disease Improving Global Outcomes Clinical Practice Guideline for AKI reported that female sex is associated with increased rates of hospital acquired AKI,[171] several large epidemiologic meta-analyses did not show an increased risk of AKI in women (Table 3).[143,145,146,148,172,173] However, other observational studies reported worse outcomes and higher rates of severe AKI in women after cardiac surgery.[141,142] Of note, these women were older and had more comorbidities and a higher prevalence of CKD. In fact, after correction for confounders and variables, the risk of AKI was found to be lower in women, which is consistent with a recent meta-analysis.[143] In contrast, a study of aminoglycoside-induced nephrotoxicity found that women were at a higher risk of developing AKI.[144] However, subsequent studies suggested the opposite and found that men were at increased risk of aminoglycoside-associated AKI[145] as well as AKI-acquired after acute myocardial infarction.[174] Further studies exploring the effect of sex hormones in AKI are needed, but based on the current studies, there seems to be a detrimental sex-biased effect on

Table 3 | Epidemiologic and prospective human studies exploring sex differences in AKI and CKD

Study size	Etiology	Effect of female sex	Study limitation	Ref
AKI				
Single-center (n = 24,660)	Cardiovascular surgery–related	Harmful	• AKI definition not standardized	141
			• Single-center	
			• Limited adjustment for comorbidities	
Single-center (n = 13,734)	Cardiovascular surgery–related	Harmful or lower risk for AKI (?)	• Only 31.3% of patients were women	142
			• Once data were corrected for comorbidities and age, lower risk of AKI in women	
64 studies (meta-analysis) (n = 1,057,412)	Cardiovascular surgery–related	No sex difference	• Did not look at covariates that may influence AKI	143
Single-center (n = 214)	Aminoglycoside-related	Harmful	• Small study	144
			• Limited adjustment for covariates	
Single-center (n = 1489)	Aminoglycoside-related	Protective	• Small study	145
			• Limited multivariate assessment	
24 studies (meta-analysis) (n = 5980)	Aminoglycoside related	No sex difference	NA	146
Multicenter (n = 1 million)	All cause of AKI requiring dialysis	Protective	• Use of diagnostic codes to identify AKI	147
CKD				
MDRD study, multicenter (n = 840)	All cause of CKD, GFR of 25–55 ml/min per 1.73 m^2	Protective (slower GFR decline)	• Once data were adjusted for differences in blood pressure, proteinuria and HDL cholesterol, no association between sex and GFR decline could be documented	148
Ramipril Efficacy in Nephropathy study (n = 352)	All cause of CKD, ACE inhibitor therapy			149
Single-center (n = 1215)	ADPKD	• Better renal survival in women		139
		• Rapid decline of kidney function and earlier onset of kidney failure in men		
	ANCA-associated vasculitis	No sex difference in clinical outcomes		150,151
	LN	• SLE more prevalent in females but a higher prevalence of LN in males with SLE		152
		• More aggressive histopathologic features in men		153,154
		• Women more likely to achieve complete remission		155,156
		• No sex difference in long-term renal outcomes or mortality		157
	MCD	No sex differences in clinical phenotype or remission rates		158,159
	Anti-GBM disease	No sex differences in long-term renal outcomes		160
Meta-analysis (n = 11,345)	DKD	Slower progression to CKD and to kidney failure		14,161
	FSGS	• Lower level of proteinuria		162
		• Lower risk of relapse		159,163,164

(*Continued on following page*)

Table 3 | (Continued) **Epidemiologic and prospective human studies exploring sex differences in AKI and CKD**

Study size	Etiology	Effect of female sex	Study limitation	Ref
		• Increased risk of death in men		
	IgAN	• Higher antibody activity against aberrantly glycosylated IgA		165
		• Slower eGFR decline and disease progression		166
		• Sex-related gene polymorphism associated with reduced risk		162
		• No sex differences in proteinuria, disease activity, or outcomes		163,166

ACE, angiotensin-converting enzyme; ADPKD, autosomal dominant polycystic kidney disease; AKI, acute kidney injury; ANCA, antineutrophil cytoplasmic autoantibody; CKD, chronic kidney disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; -FSGS, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; GFR, glomerular filtration rate; HDL, high-density lipoprotein; IgA, immunoglobulin A; IgAN, IgA nephropathy; LN, lupus nephritis; MCD, minimal change disease; MDRD, modification of diet in renal disease; NA, not applicable; Ref, reference; SLE, systemic lupus erythematosus.

AKI incidence in humans,[175] which contradicts experimental studies investigating IRI- and nephrotoxic-induced AKI.[111] Thus, the incidence of AKI seems to be more favorable for women than men but is dependent on age, etiology, and levels of estrogen.[176,177]

Although the epidemiology of AKI incidence remains controversial, kidney outcomes after AKI are consistently worse in women. A large population-based study of AKI survivors in Canada showed that men are more likely to recover from AKI.[178] This is supported by a recently published risk prediction model for advanced CKD after AKI, which identifies female sex as a strong risk factor for grade 4 CKD in AKI survivors.[179] However, this is different from studies investigating sex-related differences in CKD and CKD progression. Evidence suggests that although CKD is more prevalent in women, men had a 1.5 times increased risk of developing kidney failure, suggesting a sex bias in health behaviors or processes of care after an AKI event.[180] Whether comorbidities including diabetes mellitus and hypertension contribute to worse outcomes in women after AKI is currently unclear. Although women exhibit stronger cellular- and humoral-mediated immune responses than men, this state of heightened immune responsiveness may contribute to their increased susceptibility to inflammatory and autoimmune diseases,[42] and promote necroinflammation in certain etiologies of AKI. Moreover, preclinical animal studies also demonstrated nuances of sex chromosomes, sex hormones, and epigenetic factors on AKI development and outcomes; however, these have not been well studied in humans.[111] Further clinical research is needed to address this.

Sex dimorphism in CKD. Women have a higher prevalence of CKD stages 3-5 than men, whereas men have a higher prevalence of albuminuria and hence CKD stages 1 and 2.[181] Men show a faster decline in kidney function, progress more frequently to kidney failure (50% higher incidence), and have higher mortality rates and risk of cardiovascular disease than women (Figure 3).[122,182] Epidemiologic studies including a large meta-analysis (including 11,345 patients from 68 studies) indicate that male patients with autosomal dominant polycystic kidney disease, IgA nephropathy, membranous nephropathy and focal segmental glomerulosclerosis, or CKD of unspecified etiology progress more quickly than do women even when adjusting for multiple covariates (Table 3).[14,139,163,182–184] Consistent with this, 2 population-based studies showed exacerbated CKD progression in men,[185,186] and the community-based PREVEND (Prevention of Renal and Vascular Endstage Disease) cohort study revealed that age, albuminuria, body mass index, and blood glucose levels are factors that promote the progression to kidney failure to a greater extent in men than in women.[187] Possible explanations for this are a lower incidence of hypertension, less microvascular disease in metabolic diseases, and a slower decline in GFR in premenopausal women.[188–190] In contrast, one meta-analysis evaluating the effect of angiotensin-converting enzyme inhibitors in 11 randomized studies observed a faster CKD progression in women than in men after correcting for blood pressure and proteinuria. However, most female participants were postmenopausal and women are less likely to undergo kidney biopsy than men, which might partially explain this discrepancy.[191]

Sex-related differences in the clinical outcomes were not observed in patients with antineutrophil cytoplasmic autoantibody–associated vasculitis,[150] antiglomerular basement membrane disease,[160] and minimal change disease[158] (Table 3). However, studies reported that SLE affects more commonly women, while male sex in patients with SLE is associated with worse outcomes and a higher probability of active lupus nephritis (Table 3).[154,157,192,193] Whether and to what extent sex hormones also play a role in diabetic kidney disease is still a matter of debate. Some studies revealed that men have a faster progression than women, while others suggest progression to be faster in women.[194] Furthermore, onset and duration of diabetes mellitus, quality of glycemic control, puberty, and menopause may also play a role in this context.[161,194]

Controlled data are scant and inconsistent because most clinical trials in CKD included disproportionately smaller fractions of female subjects, especially in the treatment arm, for example, in the DAPA-CKD and EMPA-KIDNEY trials,[195] as one would expect based on the epidemiology of some

Box 2 | Open questions and potential clinical implications

- Women have a higher risk of adverse drug reaction: is that because drug dosing is not adjusted to sex and/or body weight? Assessment of side effects of different therapeutic approaches in different preclinical models could be addressed first (e.g., the impact of different complement inhibitors on the risk of infection with encapsulated bacteria). Performing pharmacokinetic preclinical studies might help the translation process into clinical practice.
- The ongoing under-representation of women in clinical trials: is that because of inequity in access to care and thus to trials; or because they are not enabled to participate, not eligible (a separate issue); or because of competing interests on their time; or is it difficult to include age-matched males and females with similar features of CKD (e.g., lower risk of females in developing CKD)?
- Sex-stratified analyses are generally not performed in preclinical animal studies and clinical trials: is this because sex differences have not been observed or because of the low sample size of women or the effectiveness of a drug?
- Is estrogen therapy an option in postmenopausal women with kidney disease?
- Women (as well as other groups) do not have equitable access to proven therapies—for example, ACE and SGLT2 inhibitors. For women of childbearing age, this is often because of contraindication in theoretical pregnancy. Should these drugs only be withheld if actively trying for pregnancy?
- True incidence and prevalence of kidney diseases are largely unclear between women and men: is this compounded by undertaking fewer biopsies in women for reasons that are not clear?

ACE, angiotensin-converting enzyme; CKD, chronic kidney disease; SGLT2, sodium glucose cotransporter-2.

diseases. Potential explanations for the under-representation of women might be fertile, pregnant, or lactating women, which are standard exclusion criteria for clinical trials, and/or poor adhesion due to family or cultural reasons. A drawback of this imbalance is that the results of these studies may not be valid for women, in particular for relatively young women who might benefit the most from early intervention with renoprotective drugs.

Notwithstanding that much of this depends on detecting the disease in the first instance and women are less likely to undergo kidney biopsy than men[196] and are also under-represented in CKD cohorts.[197] Whether this is because of differences in identification of kidney impairment, inequity in access to care, or true differences in disease severity and prevalence remains unclear.

Conclusion and future directions

We provide evidence that sex is a biological variable that influences the immune response to injury, resulting in sex-specific outcomes in AKI and CKD in animals and humans. The International Society of Nephrology has recently released a consensus guidance for preclinical animal studies in translational nephrology.[198] Although international funding organizations indicate the importance of studying male and female animals, a clear consensus could not be reached with regard to whether sex should be a biological variable.[198] It is agreed, however, that both sexes should be included in the investigation of disease progression and that both sexes should be considered until there is clear evidence that there is a difference or not. If there are no differences, then sex as a biological variable may not be an obligatory analysis.[198] We now propose guidance and strategies on how preclinical animal studies should be conducted in future research to comprehend the pathophysiological differences in kidney diseases linked to sex chromosomes, reproductive organs, and sex hormones, and how to implement animal models that exhibit higher scientific quality and allow testing drug effectiveness (Figure 2, Box 1).[199] This is designed to better understand the mechanism of sex differences in kidney diseases, accelerate the development of new drugs for efficacious treatment, and improve the prognosis and quality of life of patients with a variety of kidney diseases.

If the long-term goal of personalized medicine is effective treatment for all based on individual characteristics, then will we ultimately treat men and women differently in an effort to protect them equally?[3,200] Future translational science studies must identify the precise mechanisms mediating sex differences in the immune responses to kidney injury, and the development of CKD, knowing that this will probably reflect complex interactions among hormones, genes, and the environment. One such example could be the use of the menopause and perimenopause mouse model to study sex differences in kidney disease.[201] Sex-based differences in the activity of the immune response are likely to have evolved through a process of convergent evolution, in which the fundamental mechanisms that underlie increased survival and reproductive success have sex-specific effects on the immune system including kidney disease.[3] Several important questions remain to be answered in clinical research and trials (Box 2) to improve the design of clinical trials and patient outcomes for translation into public health.

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