

# Chronic kidney disease

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**Abstract** | Chronic kidney disease (CKD) is defined by persistent urine abnormalities, structural abnormalities or impaired excretory renal function suggestive of a loss of functional nephrons. The majority of patients with CKD are at risk of accelerated cardiovascular disease and death. For those who progress to end-stage renal disease, the limited accessibility to renal replacement therapy is a problem in many parts of the world. Risk factors for the development and progression of CKD include low nephron number at birth, nephron loss due to increasing age and acute or chronic kidney injuries caused by toxic exposures or diseases (for example, obesity and type 2 diabetes mellitus). The management of patients with CKD is focused on early detection or prevention, treatment of the underlying cause (if possible) to curb progression and attention to secondary processes that contribute to ongoing nephron loss. Blood pressure control, inhibition of the renin–angiotensin system and disease-specific interventions are the cornerstones of therapy. CKD complications such as anaemia, metabolic acidosis and secondary hyperparathyroidism affect cardiovascular health and quality of life, and require diagnosis and treatment.

Chronic kidney disease (CKD) is a syndrome defined as persistent alterations in kidney structure, function or both with implications for the health of the individual<sup>1,2</sup>. Examples of structural abnormalities include cysts, tumours, malformations and atrophy, which are evident on imaging. By contrast, kidney dysfunction can manifest as hypertension, oedema, changes in output or quality of urine and growth delay in children; these changes are most often recognized by increased serum levels of creatinine, cystatin C or blood urea nitrogen. The most common pathological manifestation of CKD, regardless of the initiating insult or disease, is some form of renal fibrosis.

The Kidney Disease Improving Global Outcomes (KDIGO) initiative classifies an individual as having CKD if abnormalities of kidney structure or function persist for >3 months. KDIGO describes a classification of severity, defining numerous stages of CKD on the basis of glomerular filtration rate (GFR; either estimated (eGFR) or measured (mGFR)) and the extent of albuminuria<sup>1</sup> (FIG. 1). GFR and albuminuria are used to classify CKD because GFR is a well-established marker of renal excretory function and albuminuria is an indicator of renal barrier dysfunction (glomerular injury). Both have been found to be reliable predictors of long-term CKD outcomes.

As the kidney comprises many independent functional and anatomical ‘units’ (nephrons), GFR can be expressed by the equation:  $GFR_{(total)} = GFR_{(single-nephron)} \times \text{number of}$

nephrons, whereby  $GFR_{(single-nephron)}$  is the filtration capacity of single nephrons. This equation implies that when the number of nephrons declines, total GFR will not change as long as the remaining nephrons can increase their contribution. By contrast, a decline in total GFR implies a considerable loss of nephrons with remnant nephrons possibly operating at their maximum possible  $GFR_{(single-nephron)}$ . As such, CKD usually represents a loss in nephron number. Furthermore, the KDIGO categories (FIG. 1) describe the risk of progression to kidney failure — that is, end-stage renal disease (ESRD), which would require renal replacement therapy (peritoneal dialysis, haemodialysis or kidney transplantation) — and a number of other adverse outcomes that include risk of cardiovascular disease (CVD), death, acute kidney injury (AKI), infection and hospitalization. The KDIGO staging has proven to be instrumental in decision making on patient management but is not without controversy (BOX 1).

Although classifying the severity of CKD by GFR and albuminuria is useful, identifying the risk factors or underlying causes of CKD (BOX 2) is essential for optimal management and is recommended by current guidelines<sup>1</sup>. CKD is associated with numerous complications such as anaemia, metabolic acidosis (reduced acid excretion by the kidneys) and CVD, which increase the complexity of patient management. In this Primer, we discuss the global prevalence of CKD; the different

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diseases that can contribute to poor nephron endowment or nephron loss; the pathophysiology of CKD progression; the diagnosis, screening and prevention of CKD; and CKD management to improve outcomes and quality of life. Finally, we describe several research domains potentially offering improvements for CKD management in the near future.

## Epidemiology

### Prevalence

The prevalence of all stages of CKD varies between 7–12% in the different regions of the world<sup>3</sup>. CKD G3–G5 prevalence in adults varies worldwide, with values reported as 1.7% in China<sup>4</sup>, 3.1% in Canada<sup>5</sup>, 5.8% in Australia<sup>6</sup> and 6.7% in the United States<sup>7</sup>. In Europe, the prevalence ranges from 2.3% in Germany<sup>8</sup>, 2.4% in Finland<sup>9</sup>, 4.0% in Spain<sup>9</sup> to 5.2% in England<sup>10</sup>. The variability in these numbers is a point worthy of further study and might be attributable to different reasons (for example, some studies might use a single time point (therefore not fulfilling the definition of CKD)); accordingly, whether prevalence has been overestimated or underestimated is unclear<sup>11</sup>. The epidemiology of CKD in low- and middle-income countries (LMICs) is poorly characterized owing to the lack of community-based studies, inconsistent assessment of kidney function and non-standardized or non-calibrated approaches<sup>12</sup>. Nevertheless, in southeast Asia, some Latin American countries (such as Mexico) and in sub-Saharan Africa, when assessed, the prevalence of CKD seems to be consistent with the estimates of 10–16%<sup>12–14</sup>. Notably, most prevalence data are based on GFR only, without consideration of albuminuria, in line with the first CKD classification system reported in 2002.

Little is known about CKD in children because of the absence of registries and because children are not included in many clinical studies. In Europe, the 2014 incidence of paediatric ESRD was 5.7 per million age-related population (pmarp) in children aged 0–14 years; the prevalence was 32.2 pmarp<sup>15</sup>. Earlier estimates suggested the incidence and prevalence were 8.3 pmarp and 58.0 pmarp, respectively, in children aged 0–19 years<sup>16</sup>, which is lower than 14.7 pmarp and 103.9 pmarp for the age group 0–21 years in the United States<sup>17</sup>. In high-income countries, congenital disorders of the urinary tract (CAKUT) are responsible for the majority of cases of paediatric CKD; by contrast, acquired causes, such as infection and glomerular diseases, predominate in LMICs<sup>18</sup>.

### Risk factors

CKD (all stages) is most common in people >65 years of age, but the probability of progression to ESRD is higher in younger people ( $\leq 65$  years of age) with CKD<sup>3</sup>. Interestingly, although the prevalence of CKD is higher in women than in men, men are more likely to progress to ESRD<sup>3</sup>. The most common underlying diseases associated with CKD are diabetes mellitus and hypertension, particularly in high-income and middle-income countries. In those with diabetes, CKD prevalence is estimated at 30–40%; whether CKD in these individuals is caused by their diabetes per se or by microvascular disease as a consequence of diabetes is not known. However, in LMICs, CKD is associated with infectious diseases, glomerulonephritis (a group of diseases that lead to inflammation of the glomerulus) and inappropriate use of medications (such as traditional remedies with potential nephrotoxins, NSAIDs and nephrotoxic antibiotics)<sup>19,20</sup>. In LMICs, current trends in socio-economic status and an ageing population will increase the absolute number of people with CKD and the diabetes and obesity epidemic might eventually take over as the main aetiological cause for CKD. Furthermore, low birthweight (typically defined as  $<2,500$  g) due to preterm birth or intrauterine growth restriction is associated with CKD later in life; the global risks of preterm birth and low birthweight are ~10% and ~15%, respectively. Thus, millions of children are born at risk of CKD later in life and are found at the lower percentile of age-matched GFR (that is, they are typically among the youngest patients with CKD)<sup>21,22</sup>.

Populations who are at increased risk of CKD include Aboriginal Australians, African Americans, people of Spanish decent in central and South America, indigenous populations in Canada, south Asians, east Asians and Pacific Islanders; these populations are at risk owing to genetic factors or to the interaction of genetic and environmental factors<sup>23</sup>.

Endemic forms of CKD suggest regional triggers, which are often difficult to define but might include specific infections, toxins, behaviours or climate-related factors<sup>24</sup>. Reports of chronic interstitial nephritis or CKD of undetermined origin in sugar cane and other agricultural workers in Latin America, Sri Lanka, India, Cameroon, Mexico and Australia are examples of this phenomenon<sup>24–26</sup>.

### Kidney replacement therapy

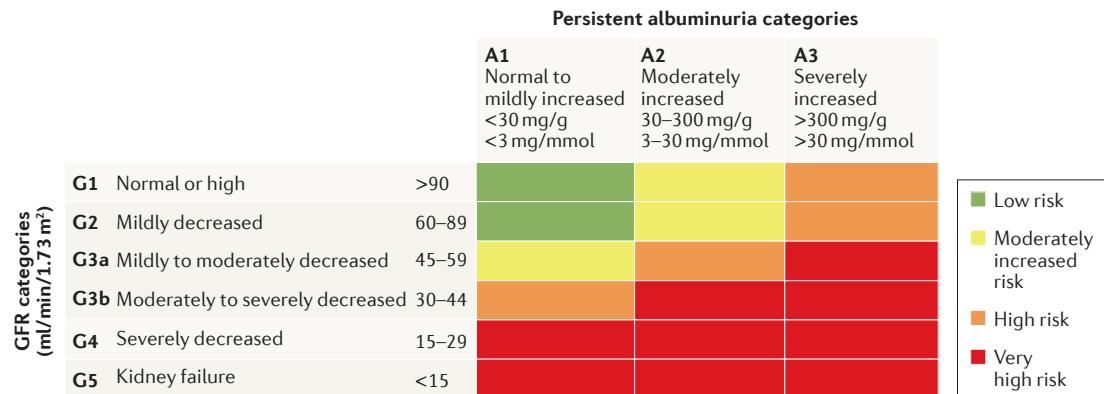
Often, countries do not know the number of patients with CKD but do have information on the use of renal replacement therapies (see Management)<sup>27</sup>, which can be used to estimate the number of patients with CKD. However, appropriate data on ESRD can only be obtained from countries with dialysis registries; such data are missing from LMICs in particular, where registries do not exist. In 2014, the incidence of kidney replacement therapy varied from 49 per million population (pmp) in Bangladesh to as high as 455 pmp in Taiwan<sup>17</sup>. Considerable variation has also been reported in the prevalence of kidney replacement therapy, from 113 pmp in Bangladesh to 3,219 pmp in Taiwan<sup>17</sup> (FIG. 2).

Dialysis is the first type of kidney replacement therapy for the majority of patients, because pre-emptive transplantation as an initial modality is not freely available. Globally, haemodialysis is most commonly used<sup>17,28</sup> — the exception being Hong Kong, where peritoneal dialysis is the preferred choice of dialysis treatment<sup>29</sup>. Kidney transplantation rates differ substantially between countries, from 1 pmp in Bangladesh to 60 pmp in Jalisco, Mexico<sup>30</sup>. In many European countries, >50% of patients on renal replacement receive transplants<sup>17,28</sup>, which contrasts with parts of Asia (such as Taiwan, Japan and the Philippines) where kidney transplantation is rarely performed<sup>17</sup>. The reasons why transplantation is not available include cultural preferences, socio-economic factors and health care infrastructure deficiencies (for example, lack of biopsy services, surgeons or immunology laboratories).

The availability of dialysis and transplantation services has not been systematically documented. However, the Global Kidney Health Atlas gives an overview of the availability of kidney replacement therapy worldwide<sup>30</sup> (full report available at [www.theisn.org](http://www.theisn.org)), although these data do not reflect the actual need for kidney replacement therapy. Estimates of unmet need are in the range 2–7 million people per year<sup>31</sup>. Furthermore, availability and accessibility are not the same — even when services are available, not all individuals have access to them for reasons that include cost reimbursement, demand and specific policies. Accordingly, many individuals do not receive renal replacement therapy despite having reached ESRD. Estimates of dialysis incidence and prevalence based on current data worldwide are, therefore, imprecise owing to inequities in access. Future studies should strive to determine numbers of dialysis-eligible individuals, not just those who receive the treatment.

### Mortality

Reports from the Global Burden of Disease study indicate an increasing burden of CKD over the past 20 years (with substantial worldwide variation) to which diabetes is the most important contributor<sup>32,33</sup>. CKD as a cause of mortality has also increased over the past 25 years (from being ranked 25th in 1990 to 17th in 2015) and now contributes 1.35% of the global burden of disability life years lost, growing at a rate of 1% per year<sup>32,34,35</sup>. Again, these data are largely based on the first CKD classification system that excluded albuminuria from the CKD definition.



**Figure 1 | The KDIGO classification of CKD.** This Kidney Disease Improving Global Outcomes (KDIGO) 2D matrix incorporates the level of albuminuria (given as a ratio to creatinine (in mg per g) and divided into three categories) and the glomerular filtration rate (GFR) — that is, the level of kidney function — to describe the risk of patients with chronic kidney disease (CKD) progressing to adverse outcomes (such as progression to end-stage renal disease (ESRD), cardiovascular disease, hospitalization, acute kidney injury or death). Notably, in primary care settings, proteinuria is generally measured rather than measuring albuminuria specifically; however, the proteinuria dipstick results can be used to approximate the albuminuria stages. Additionally, GFR can either be estimated using various clinical equations or directly measured using dyes. The KDIGO matrix defines different stages of CKD referred as, for example, CKD G2A2 whereby the GFR is 60–89 ml/min/1.73 m<sup>2</sup> and albuminuria is moderately increased; such a patient would have a moderately increased risk of progressing to ESRD. However, the staging for CKD G2–G4 might underestimate the extent of irreversible nephron loss<sup>25</sup>. For example, if total GFR relies on the filtration capacity of single nephrons (GFR<sub>(single-nephron)</sub>) and the number of nephrons, GFR<sub>(single-nephron)</sub> has to increase to compensate for nephron loss to maintain total GFR. However, full compensation is no longer possible with ongoing nephron loss as occurs with physiological ageing<sup>76</sup> and total GFR declines owing to further reductions in nephron number. Additionally, serum creatinine underestimates nephron loss because it increases late in the disease process, when more nephrons are lost than would be implied by GFR alone. Finally, the prognostic value of the matrix suffers from being based on studies potentially having a false-positive rate of ~30–35% owing to a lack of repeat analysis after 3 months (that is, true CKD diagnoses were not consistently obtained)<sup>41</sup>. Reproduced with permission from REF. 1, Elsevier.

Mortality increases with decreasing eGFR and increasing albuminuria<sup>36</sup> and is highest in patients on kidney replacement therapy; 5-year survival of those on dialysis is 40–50%<sup>17,28</sup> with similar survival between haemodialysis and peritoneal dialysis<sup>37</sup>. Patients receiving a kidney transplant have better prospects, with a 5-year survival of 86% in those receiving a deceased donor kidney and 93% in those receiving a kidney from a living donor. Life expectancy for those on dialysis (either modality) is one-third of that of the age-matched and sex-matched general population; life expectancy is 45–85% of that of the general population for those who receive a kidney transplant<sup>17,28</sup>.

### Mechanisms/pathophysiology

#### Nephron loss

Nephrons are generated in weeks 12–36 of gestation in humans, with a mean of 950,000 nephrons per kidney (with a range of ~200,000 to >2.5 million)<sup>38</sup>. No new nephrons can be generated after this period. During growth, the available nephrons increase in size to accommodate increased renal demands. Furthermore, GFR decreases with age (FIG. 3a). Although nephrons can contend with transient increases in filtration load (as with food and fluid intake) by transiently increasing GFR<sub>(single-nephron)</sub> without structural changes (a display of ‘renal reserve’)<sup>39,40</sup>, longer or persistent increases in body mass (for example, during pregnancy or obesity) promote nephron hypertrophy (mostly comprising increased dimensions of the glomerular tuft, Bowman’s capsule and the proximal tubule) as the compensatory mechanism. Nephron loss, for example owing to injury or donation of one of the kidneys, can have the same hypertrophic effect on the remaining nephrons. Indeed, either severe kidney injury or combinations of injury with ageing-related nephron losses — especially in individuals with poor nephron endowment and/or obesity — accelerates persistent increased GFR<sub>(single-nephron)</sub> and loss of remnant nephrons<sup>41</sup>.

**Nephron hypertrophy.** Remnant nephron hypertrophy is triggered by persistent elevations of GFR<sub>(single-nephron)</sub> and filtration pressure (that is, glomerular hypertension)

across the glomerular filtration barrier, which implies glomerular hyperfiltration. Glomerular hyperfiltration and glomerular hypertension together induce the expression of transforming growth factor- $\alpha$  and epithelial growth factor receptor<sup>42,43</sup>, which promote nephron hypertrophy that, in turn, reduces glomerular hypertension by increasing the filtration surface<sup>44</sup>. Indeed, increased GFR<sub>(single-nephron)</sub> and remnant nephron hypertrophy enable kidney donors to maintain an apparently ‘normal’ renal function, despite lacking 50% of their nephrons. Obviously, kidney donation does not necessarily cause CKD when donors are carefully selected for good nephron endowment, the absence of obesity, diabetes and other sources of nephron injury<sup>45,46</sup>. However, in other circumstances, hyperfiltration-driven increases in glomerular size can potentially be harmful<sup>44,47,48</sup>. Beyond a certain threshold of hypertrophy, increasing shear stress on podocytes (which are key octopus-shaped cells that maintain the glomerular filtration barrier of the nephron) promotes podocyte detachment, focal segmental glomerulosclerosis (FSGS, a pathological entity in which renal injury results in sclerotic lesions in segments of glomeruli), global glomerulosclerosis and subsequent nephron atrophy, a vicious cycle that further reduces nephron number and increases the GFR<sub>(single-nephron)</sub> of remnant nephrons<sup>42,44,49–52</sup> (FIG. 4).

**Impaired glomerular filtration.** Angiotensin II production and mechanistic target of rapamycin (mTOR) signalling maintain persistent podocyte hypertrophy and glomerular hyperfiltration and ultimately aggravates podocyte loss and proteinuria. Angiotensin II is a peptide hormone that is part of the renin–angiotensin system (RAS) that drives vasoconstriction and aldosterone secretion (and, therefore, sodium retention and an increase of blood pressure). Aldosterone, in turn, directly impairs the glomerular barrier sieving function, possibly by inhibiting expression of the podocyte protein nephrin, which is a structural component of the slit diaphragm necessary for maintaining the glomerular filtration barrier<sup>53</sup>. Angiotensin II possibly also contributes to the dysregulated response of progenitor parietal epithelial cells along Bowman’s capsule, generating FSGS lesions instead of replacing lost podocytes<sup>54</sup>. This structural remodelling of the glomerulus presents clinically as proteinuria, which is a marker of nephron damage and is predictive of CKD progression (defined as a GFR decline of >5 ml/min/1.73 m<sup>2</sup> per year or sevenfold the normal rate of loss with ageing<sup>42,55,56</sup>.

**Fibrosis.** Nephron loss involves nonspecific wound-healing responses that include interstitial fibrosis (FIG. 5). Infiltrating immune cells, albuminuria and, in diabetes, glucosuria, activate proximal tubular epithelial cells, resulting in the secretion of proinflammatory and profibrotic mediators that promote interstitial inflammation and fibrosis<sup>57</sup>. Interstitial fibrosis seems to drive further nephron injury through the promotion of renal ischaemia<sup>57</sup>, but — as in other organs — scar formation might also mechanically stabilize the remaining nephrons<sup>58</sup>. The increased tubular transport workload of remnant

#### Box 1 | Thresholds, age and CKD

Whether chronic kidney disease (CKD) should be diagnosed and staged using absolute thresholds irrespective of age remains controversial<sup>248,249</sup>. The glomerular filtration rate (GFR) in healthy adults 20–40 years of age is ~107 ml/min/1.73 m<sup>2</sup> and declines at a rate of ~0.7 ml/min/1.73 m<sup>2</sup> per year<sup>250,251</sup>. Accordingly, by 75 years of age, many otherwise healthy individuals (without major comorbidities) will have lost 50% of their nephrons and their GFR will be half that of when they were 25 years of age<sup>252</sup>. Indeed, a substantial number of older healthy individuals have ‘low’ GFR (that is, <60 ml/min/1.73 m<sup>2</sup>) but normal albuminuria (that is, a Kidney Disease Improving Global Outcomes (KDIGO) CKD classification of G3aA1 (FIG. 1)), which is associated with having only a small increase in relative risk of all-cause mortality<sup>253,254</sup>. The threshold of GFR that should be used to detect CKD in younger people is similarly controversial<sup>116</sup>. The range of GFR in a healthy person 25 years of age being considered as a living kidney donor is ~78–136 ml/min/1.73 m<sup>2</sup> (REF. 251); some have suggested that a cut-off value of GFR <75 ml/min/1.73 m<sup>2</sup> is more appropriate for young adults to confirm a diagnosis of CKD, and values below this threshold are associated with a significantly increased relative risk of all-cause mortality and end-stage renal disease<sup>255</sup>.

**Box 2 | Risk factors for chronic kidney disease onset**

- Monogenic kidney disease (for example, autosomal dominant polycystic kidney disease, podocytopathies causing steroid-resistant nephrotic syndrome, Fabry disease, Alport syndrome and complementopathies such as atypical haemolytic-uraemic syndrome)
- Congenital abnormalities (for example, congenital anomalies of the kidney and the urinary tract and vesico-ureteric reflux)
- Type 1 or type 2\* diabetes mellitus
- Poorly controlled arterial hypertension
- Obesity\*
- Prolonged exposure to nephrotoxins\* (for example, chemotherapy for cancer treatment, proton pump inhibitors, NSAIDs, antimicrobial agents, contaminated herbs and plant-based food, agricultural chemicals, heavy metals and irradiation)
- Climate (excessive heat exposure and dehydration)
- Infections and chronic inflammation\* (for example, HIV, hepatitis virus, malaria, bacterial infections and autoimmune diseases)
- Malignancy\* (for example, multiple myeloma)
- Episodes of acute kidney injury\*
- Low nephron endowment at birth (due to low birthweight or fetal dysmaturity)
- Obstructive uropathy

\*Denotes risk factors that also influence chronic kidney disease progression, which also include arterial hypertension, proteinuria, obstructive uropathy, smoking, hyperhomocysteinaemia and hyperuricaemia.

nephrons also involves anaerobic metabolism, intracellular acidosis and endoplasmic reticulum stress, which promote secondary tubular cell injury<sup>42,59</sup>.

#### Contributing factors

Several factors can contribute to the pathogenesis of CKD, including low birthweight, pregnancy, obesity, diabetes and ageing. These scenarios contribute different factors that lead to and/or exacerbate nephron loss, promoting the cycles of injury and ultimately resulting in ESRD.

**Prematurity and low birthweight.** Newborn babies with low birthweight frequently display incomplete kidney development<sup>60,61</sup>; poor nephron endowment can cause CKD at any age<sup>60–63</sup>. Indeed, one study documented that for every 13 individuals born at low birthweight in the United States, one had reduced GFR and one had raised systolic blood pressure, the risks for which increased with age<sup>22</sup>. The infants who are born <2,500 g in weight face a fourfold higher risk of being diagnosed with CKD by the time they are 17 years of age than those born weighing ≥2,500 g (REF. 62). CKD at puberty is common in these individuals when rapid body growth exceeds the capacity of nephron number to accommodate the increasing filtration load<sup>64</sup>. In milder cases, poor nephron endowment at birth promotes the development of arterial hypertension, diagnosis of CKD later in adults or a more-rapid progression of glomerulonephritis to ESRD<sup>22,61,65</sup> (FIG. 3b). All of these factors increase the risk of CVD.

**Genetic factors.** Genetic abnormalities can cause CKD by fostering nephrocalcinosis<sup>66</sup> or cystic degeneration, by weakening epithelial integrity or by abnormal processing or storage of metabolites or glycoproteins<sup>67,68</sup>. CAKUT are the most common congenital abnormalities, resulting

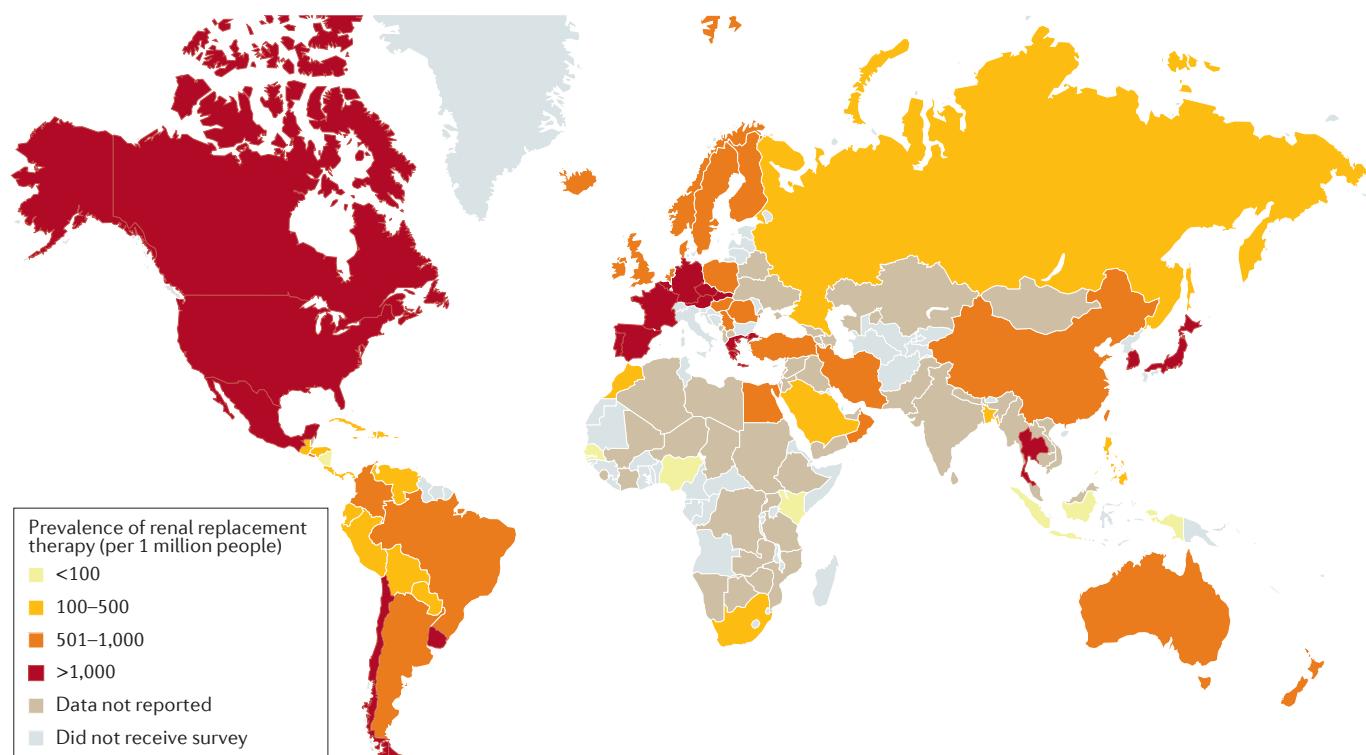
in kidney hypodysplasia, low nephron count and risk of CKD<sup>69–71</sup>. Aside from CAKUT, ciliopathies, cystic kidney diseases, tubulopathies and podocytopathies can cause CKD<sup>68,70–72</sup>. Genetic testing has revealed that ~20% of early-onset CKD (defined as CKD manifesting before 25 years of age) can be attributed to a monogenic cause<sup>72</sup>.

Until recently, monogenic causes of CKD were mostly reported in children or adolescents, but genetic variants also contribute as cofactors to CKD progression in adults (FIG. 6). For example, a uromodulin (*UMOD*) gene variant, present in 17% of the alleles in the general population, is associated with developing CKD<sup>73</sup>. Another example is gene variants of apolipoprotein L1 (*APOL1*) in African Americans, which confer resistance to *Trypanosoma brucei* infections in sub-Saharan Africa<sup>74</sup> but affect endosomal trafficking and autophagic flux. In the presence of additional inducers of kidney injury (the nature of which remains unclear), these *APOL1* variants promote podocyte loss, glomerulosclerosis, nephron loss and CKD progression<sup>75</sup>.

**Obesity.** A larger glomerular size in moderately obese (body mass index (BMI) of 30–35 kg per m<sup>2</sup>) but otherwise healthy individuals suggests an increased GFR<sub>(single-nephron)</sub> (REF. 76). In general, the association between obesity and poor renal outcomes persists even after adjustments for higher blood pressure and diabetes, suggesting that obesity-driven glomerular hyperfiltration directly contributes to nephron loss<sup>77,78</sup>. Various fat tissue-derived hormones as well as obesity-related systemic inflammation might also contribute. Morbid obesity (BMI >35 kg per m<sup>2</sup>) or moderate obesity in combination with other factors (such as genetic variants, low nephron number or advanced age) can lead to development of proteinuria, secondary FSGS and progressive CKD<sup>77,79–81</sup> (FIG. 6).

**Pregnancy.** The last trimester of pregnancy involves volume expansion (that is, an increase in blood volume) that increases total GFR by 50%<sup>82</sup>, implying a respective increase of GFR<sub>(single-nephron)</sub>. These physiological adaptations are transient and without consequences in women with normal nephron number. However, in women with low nephron endowment or previous injury-related CKD (such as in women with lupus nephritis), pregnancy-related glomerular hyperfiltration exacerbates remnant nephron glomerular hyperfiltration and glomerular hypertrophy. In some patients, pregnancy-related glomerular hyperfiltration in the final trimester passes the threshold of compensation and triggers rapid CKD progression, presenting with proteinuria and arterial hypertension — a condition known as pre-eclampsia. Pre-existing CKD during pregnancy is a well-known risk factor for pre-eclampsia, eclampsia (in which seizures occur), premature birth, intrauterine growth restriction and neonatal mortality<sup>83</sup>.

**Diabetes.** Diabetes is a well-known condition associated with massive glomerular hyperfiltration, as evident from increased total GFR and renomegaly<sup>48</sup>. Hyperglycaemia promotes the sodium/glucose cotransporter 2 (SGLT2)-driven reabsorption of sodium in the proximal



**Figure 2 | Global prevalence of renal replacement therapy.** As countries do not consistently track patients with chronic kidney disease (CKD), the use of renal replacement therapies, which are typically registered, can provide useful proxies for the prevalence of CKD. The map depicts the prevalence of renal replacement therapy (haemodialysis, peritoneal dialysis and kidney transplantation) per 1 million individuals by country. 'Data not reported' indicates that data were either not known or not provided on the questionnaire for countries that received the survey. Figure reproduced with permission from *JAMA* 2017. **317** (18): 1864–1881. Copyright © (2017) American Medical Association. All rights reserved. (REF. 30).

tubule, a process that subsequently inactivates tubuloglomerular feedback and activates the RAS at the macula densa in the renal tubule<sup>84,85</sup>. The result is induction of a permanent dilatation of the afferent arteriole and vasoconstriction of the efferent arteriole — increasing GFR<sub>(single-nephron)</sub> and total GFR<sup>86</sup>.

Although diabetes-driven glomerular hyperfiltration can be counteracted for many years in younger patients with normal nephron number, it serves as a drastic accelerator of single-nephron hyperfiltration in those with low nephron endowment, injury-related or ageing-related nephron loss or obesity or in those who are pregnant<sup>87</sup>. Unfortunately, this is a highly prevalent combination of risk factors in older patients with type 2 diabetes, for which dual SGLT2 and RAS inhibition can elicit potent nephroprotective effects by reducing glomerular hyperfiltration as well as proximal tubular work load as well as other potentially protective mechanisms<sup>88</sup>.

**AKI.** AKI is a clinical syndrome defined by an acute deterioration of renal function either due to pre-renal (for example, hypovolaemic shock), intra-renal (direct renal parenchymal injury) or post-renal (obstruction of urinary tract) disturbances. AKI results in the accumulation of metabolic waste and toxins, subsequent uraemic complications and possible failure of other organs<sup>89</sup>.

AKI is highly prevalent in hospitalized patients and can imply irreversible losses in nephron number<sup>90</sup>. In western countries, AKI occurs mostly in outpatient and inpatient settings; the inpatient setting (which includes patients in intensive care) has been the focus of multiple studies showing a strong association between AKI and CKD. The causes of outpatient AKI are infections, dehydration and medications. In hospitals, AKI can be attributed to these same factors as well as to exposures to nephrotoxins and is mostly observed in patients with multiple comorbidities<sup>91</sup>. By contrast, in LMICs and tropical countries, pre-renal AKI occurs frequently outside the hospital setting following episodes of diarrhoea, infection and obstetric complications<sup>92</sup>. Nephrotoxins can also cause AKI-related nephron loss regardless of setting, for example, in neonates treated with aminoglycosides and in patients with cancer receiving chemotherapy.

**Ageing.** The decline of GFR with age (FIG. 3a) might relate to physiological ageing, genetic factors, arterial hypertension, diseases implying kidney injury, increase in body weight or a combination of these factors. Histologically, kidney ageing presents as global glomerulosclerosis, the respective atrophy of entire nephrons and subsequent interstitial fibrosis<sup>50,76</sup>. Whether ageing-related nephron loss is associated with hypertrophy (and glomerular

hyperfiltration) of remnant nephrons is not consistently reported in the literature<sup>50,76</sup>, but the analytical difficulties in precisely assessing nephron number and glomerular volume and how the different functions of juxtamedullary versus cortical nephrons are acknowledged can affect the interpretation of such data<sup>50,76</sup>. Ageing is also associated with decreasing podocyte density and total numbers<sup>50</sup>.

### Systemic complications of CKD

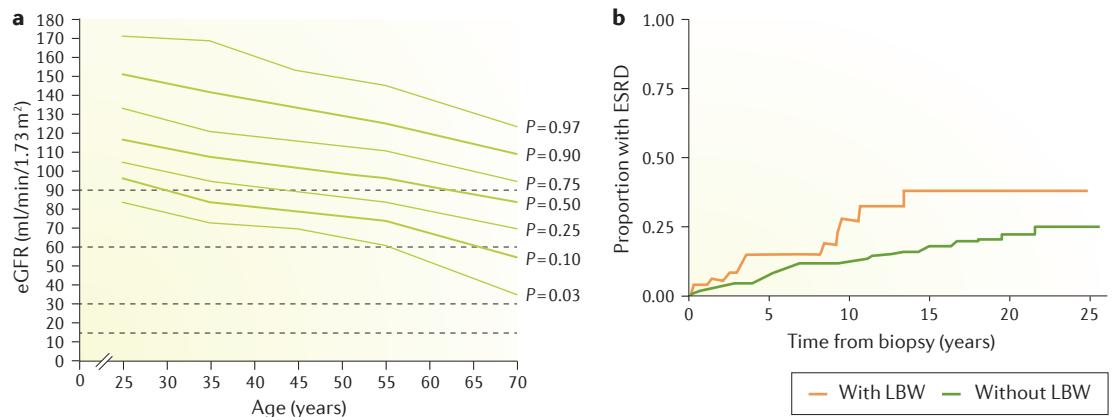
The kidney is involved in several complex processes important in homeostasis of blood, bone integrity, acid-base balance, electrolyte levels and blood pressure. As nephron number declines, patients experience complications associated with dysregulation of many of these systems such as metabolic acidosis, anaemia, mineral bone disorder (MBD, which is associated with vitamin D deficiency, hyperparathyroidism, hyperkalaemia and hyperphosphataemia), arterial hypertension, hyperuricaemia and expansion of effective circulating fluid volume. Dyslipidaemia, endocrine abnormalities and growth impairment in children can also occur. Of these complications, CVD is the leading cause of death in patients with CKD worldwide<sup>34</sup> and is associated with dyslipidaemia, hyperuricaemia and hypertension. Nonspecific symptoms of these effects include fatigue, anorexia, weight loss, pruritis (itch), nausea, vomiting, muscle cramping, oedema and shortness of breath.

Interestingly, not all individuals experience these issues at the same point in the progressive loss of kidney function; some individuals maintain excellent tubular and excretory function. Additionally, not all of the derangements are symptomatic, and the severity of the symptoms varies between individuals.

**Fluid and electrolyte abnormalities.** Derangement of sodium and water handling can become evident at all stages of CKD, with a tendency to become more severe at lower levels of kidney function. Increased accumulation of fluid (hypervolaemia) can be overt or occult, and manifests as arterial hypertension, oedema and/or shortness of breath (alone or in combination). Some patients, including those with nephronophthisis (an autosomal recessive disease characterized by chronic tubulointerstitial nephritis) or obstructive uropathy, have an impaired ability to concentrate urine and have symptoms of polyuria (large volume of urine, and consequent frequent urination). Defects in urine concentration increase the risk of hypovolaemia.

Potassium excretion is dependent upon an exchange with sodium at the distal tubule. Accordingly, low GFR decreases the delivery of sodium to the distal tubule, decreasing the potassium exchange into the urine and leading to hyperkalaemia. Other contributory factors for hyperkalaemia include high dietary potassium intake, catabolic conditions with increased tissue breakdown, metabolic acidosis with or without secondary type IV renal tubular acidosis, decreased renin production by the juxtaglomerular apparatus and hypoaldosteronism related to RAS inhibitor-related impaired cellular uptake of potassium.

**Anaemia.** The causes for anaemia in CKD are multifactorial and include reduced renal erythropoietin production, reduced lifespan of red blood cells, impaired intestinal iron absorption mediated by hepcidin (a key regulator of iron circulation) and repetitive blood losses in patients on haemodialysis. Hence, the anaemia of CKD is usually normocytic (with normally sized red



**Figure 3 | CFR with ageing and effect of LBW on progression of CKD.** **a** | Cross-sectional population studies assessing estimated glomerular filtration rate (eGFR) have shown that eGFR declines with age; here, the data were obtained from men in Morocco<sup>41</sup>. P values from 0.03 to 0.97 represent the percentiles of the eGFR distribution across the age range of the entire population at a given time point, with P=0.50 representing the mean. Horizontal lines correspond to the GFR values for the chronic kidney disease (CKD) G1–G5 stages as in FIG. 1. At 70 years of age, the nephron number is ~50% of that at 25 years of age, but whether this reduction implies increased filtration capacity of single nephrons ( $GFR_{\text{single-nephron}}$ ), that is, single-nephron hyperfiltration) among remnant nephrons or reflects a reduced demand for filtering metabolic waste is debated. Regardless of which process is in play, the nephron loss and total GFR also depends on comorbidities, such as obesity and history of acute kidney injury episodes. **b** | Low birthweight (LBW) increases the risk of developing CKD; here, LBW is associated with a shorter time to end-stage renal disease (ESRD) in patients with IgA nephropathy (HR 2.0; 95% CI 1.0–3.7; P=0.03)<sup>63</sup>. Part a is adapted with permission from REF. 41, Elsevier. Part b is adapted from REF. 63.

blood cells) and normochromic (with normal haemoglobin levels inside red blood cells). By comparison, the finding of microcytosis might reflect iron deficiency or aluminium excess whereas macrocytosis can be associated with vitamin B<sub>12</sub> or folate deficiency. Anaemia in CKD is associated with fatigue, weakness, reduced attentiveness, drowsiness and low exercise tolerance.

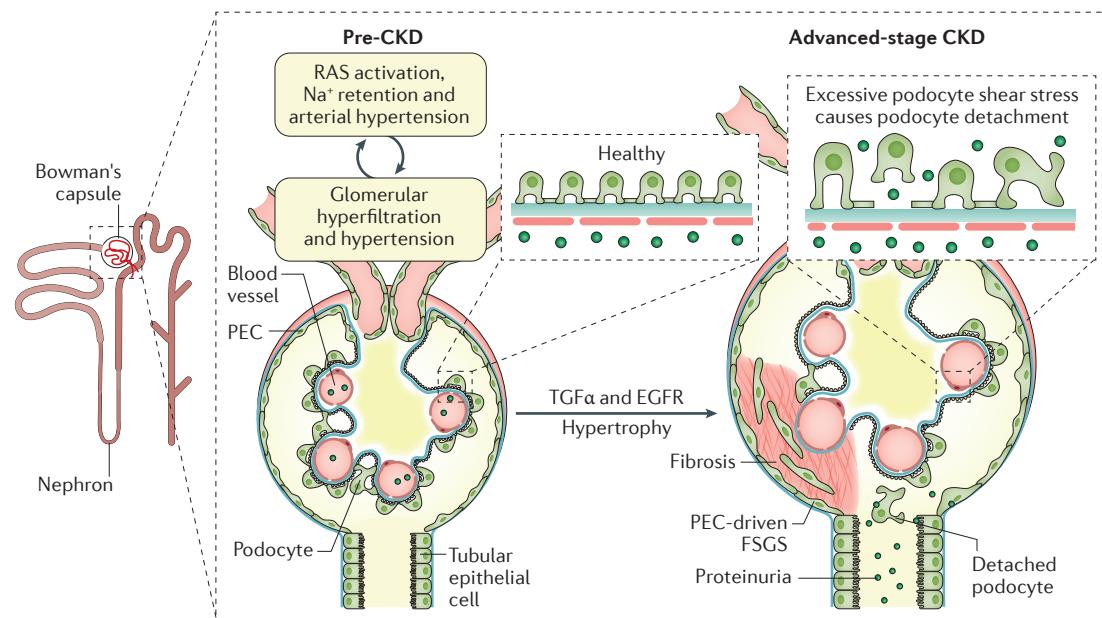
**MBD.** Chronic kidney disease–mineral bone disorder (CKD-MBD) encompasses abnormalities in mineral metabolism, bone structure and extraskeletal calcifications that occur with progressive CKD. Patients with mild CKD (CKD G2) can have reduced serum 25-hydroxyvitamin D and/or 1,25-dihydroxyvitamin D<sub>3</sub> levels, and an elevated serum parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23) level<sup>93</sup> — the key hormones that regulate bone integrity and mineral (calcium and phosphate) homeostasis. Patients with advanced CKD-MBD might have bone pain, difficulty walking and/or skeletal deformities as well as a higher risk of fracture<sup>94</sup>. In children, growth retardation is a common manifestation of MBD as well as CKD-related changes on the hormonal system.

**Metabolic acidosis.** Metabolic acidosis is related to the fall in total renal ammonium excretion that occurs when the GFR decreases to <40–50 ml/min per 1.73 m<sup>2</sup> (CKD G3). In addition, both titratable acid excretion (primarily as phosphate) and bicarbonate reabsorption

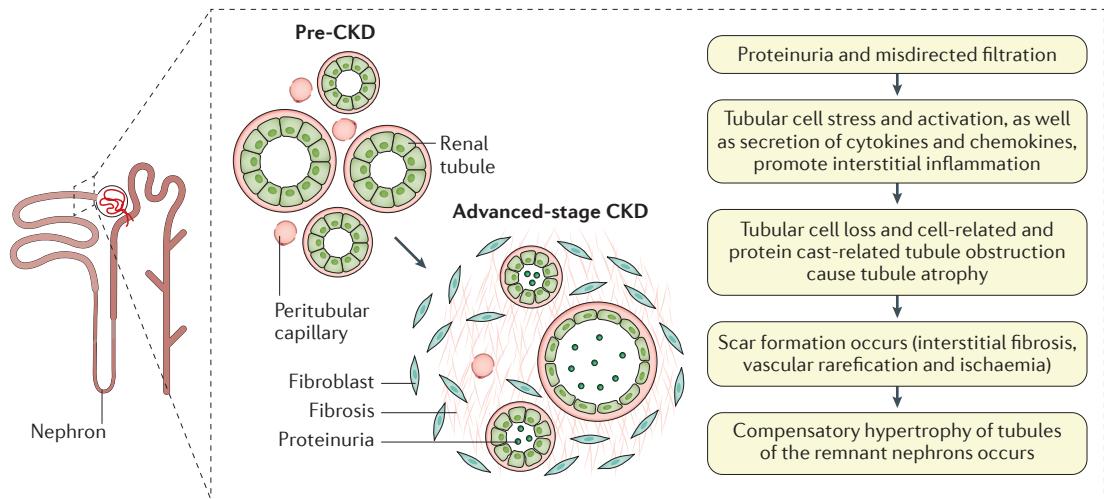
are reduced. As the patient approaches ESRD, the serum bicarbonate concentration stabilizes (to 12–20 mEq/l), which is thought to contribute to bone demineralization, muscle wasting and the progression of CKD. In children, metabolic acidosis has a negative impact on growth.

**Hyperuricaemia.** Elevated uric acid levels can develop in patients with CKD due to decreased urinary excretion. Serum uric acid >7.5 mg per dl is an independent risk factor for accelerated progression of CKD. Whether treating hyperuricaemia can improve renal outcomes remains to be assessed in an adequately powered randomized, placebo-controlled, double-blind trial.

**Arterial hypertension.** In the majority of patients, arterial hypertension is not a cause but a consequence of CKD<sup>95,96</sup>. Hypertension can be present in the earliest stages of CKD and is well documented to contribute to cardiovascular morbidity and mortality. The prevalence of hypertension is high in children with CKD (54–70% of patients)<sup>97</sup>. Hypertension is a consequence of activation of the neurohumoral axis (namely, catecholamine and aldosterone activity), RAS activation and hypervolaemia. In some cases, arterial hypertension arises from corticosteroids or calcineurin inhibitors used to treat the underlying kidney disease. Controlling arterial hypertension is a central element of CKD management to prevent CVD.



**Figure 4 | Injury, hyperfiltration and hypertrophy of the nephron.** In response to nephron loss, glomerular hypertension induces an increase in nephron size (through the activation of the renin–angiotensin system (RAS) and activities of transforming growth factor- $\alpha$  (TGF $\alpha$ ) and epidermal growth factor receptor (EGFR)) as a compensatory mechanism to maintain total glomerular filtration rate and to reduce intraglomerular pressure. Accordingly, podocytes need to undergo hypertrophy to maintain the filtration barrier along the enlarged filtration surface. However, podocyte hypertrophy is limited; beyond a certain threshold, barrier dysfunction first manifests as mild proteinuria. At later stages of chronic kidney disease (CKD), the increasing podocyte shear stress promotes podocyte detachment. Parietal epithelial cells (PECs) are putative podocyte progenitors but proteinuria and potentially other factors inhibit their potential to replace lost podocytes; instead, scar formation is promoted in the form of focal segmental glomerulosclerosis (FSGS).



**Figure 5 | Interstitial fibrosis.** Glomerular hyperfiltration and proteinuria both imply an increased reabsorption workload for proximal tubules. Albuminuria, complement and infiltrating immune cells cause (not shown) tubular cells to secrete proinflammatory mediators that promote interstitial inflammation, which, alongside progression of focal segmental glomerulosclerosis to global glomerulosclerosis, promotes tubular atrophy and interstitial fibrosis. Scar formation is associated with vascular rarefaction and ischaemia. Accordingly, the remnant nephrons have to further increase in size to meet the filtration demands, which accelerates the mechanisms of chronic kidney disease (CKD) progression in a vicious cycle.

**Dyslipidaemia.** Abnormal lipid metabolism and uraemic toxin-related modifications in lipid particles that promote atherogenesis are common in patients with CKD<sup>98</sup>. CKD-related post-translational modifications of lipid particles (the nature of which are not well characterized) imply proinflammatory effects and endothelial dysfunction<sup>99</sup>. The relative contribution of individual abnormalities to the accelerated development of CVD in patients with CKD remains to be defined in detail.

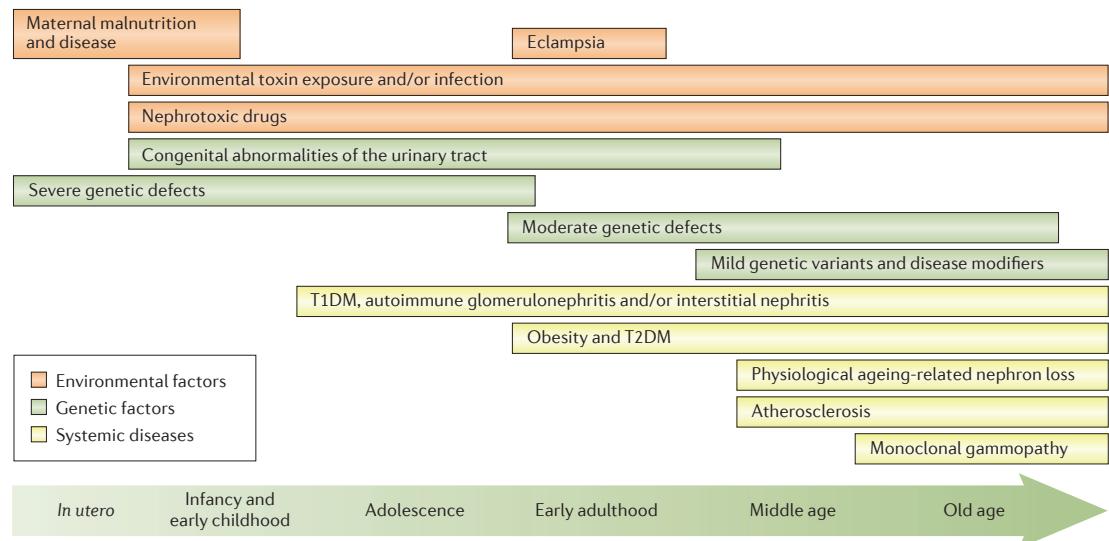
**CVD.** The high incidence of CVD in CKD can be attributed to the high prevalence of hypertension, dyslipidaemia, hyperuricaemia, abnormal glucose metabolism, obesity, systemic inflammation and oxidative stress. Young adults (25–34 years of age) with CKD have at least a 100-fold higher risk of CVD-related mortality compared with the general population<sup>100</sup>.

The CKD-related cardiovascular alterations resemble an accelerated ageing process that is associated with a shortening of telomere length<sup>101</sup>. The mechanisms underlying the accelerated vascular and cardiac calcification found in CKD and ESRD are only partially understood. In early CKD (CKD G1–G2), atherosclerotic processes (such as macrophage invasion, plaque formation and arterial wall thickening) dominate; as CKD progresses, inflammatory factors and media calcification contribute to vascular wall degeneration. The different factors involved cause distinct changes in the risk factor profile and contribute differently to outcomes during the course of CKD. Additionally, left ventricular hypertrophy (either concentric (in the presence of arterial hypertension) or eccentric (in the presence of hypervolaemia and anaemia)) and dilatation can occur, leading to systolic and diastolic dysfunction. Early and sustained induction of FGF23 has been shown to be a driver of left ventricular hypertrophy in CKD<sup>102</sup>.

In individuals with CKD who have not commenced renal replacement therapy, the risk of cardiovascular events is as high as that of people with established coronary artery disease<sup>103</sup>. Risk increases with insulin resistance<sup>104</sup>, increased blood pressure, vascular calcification<sup>105,106</sup>, inflammation and protein–energy wasting<sup>107</sup>. Haemodialysis can have a direct negative effect on the heart, a phenomenon referred to as myocardial stunning in which transient episodes of ischaemia are experienced<sup>108</sup>. As a consequence, cardiovascular mortality is several times higher in patients with low GFR or in patients who are on haemodialysis than in the general population. Accordingly, risk factors for CVD should be managed intensively in the pre-dialysis period, during transition and at dialysis initiation.

**Endocrine dysfunction.** In patients with CKD, several endocrine systems become dysfunctional as kidney function progressively deteriorates. Abnormalities in gonadal hormones can result in reduced fertility and sexual problems in men and women. These abnormalities result in delayed puberty in two-thirds of adolescents with ESRD<sup>109</sup>. End-organ resistance to growth hormone due to decreased renal breakdown of insulin growth factor-binding proteins seems to play a major part in growth impairment in children with CKD<sup>110</sup>. Abnormalities in thyroid function are common in CKD at all ages, but their functional importance remains under debate<sup>111</sup>.

**Uraemia.** At the onset of ESRD, untreated patients can experience anorexia, vomiting, weakness and fatigue, which are collectively referred to as symptoms of uraemia. Uraemia is a systemic inflammatory state that is thought to contribute to ESRD-related CVD, malnutrition, sarcopenia, osteoporosis and frailty<sup>2,107</sup>. CKD-related intestinal barrier dysfunction causing bacterial



**Figure 6 | Contributing factors to nephron loss.** In addition to ageing-related, acute and chronic forms of kidney injuries, environmental factors and genetic causes can contribute to low nephron endowment, nephron loss and nephron injury over the course of one's life. These factors are commonly (but not exclusively) encountered at different phases of life and the combination of factors determines the individual's lifetime risk of chronic kidney disease. For example, congenital abnormalities of the urinary tract can lead to end-stage renal disease (ESRD) early in life, or to secondary focal segmental glomerulosclerosis (FSGS)-related ESRD later in life. Nephrotoxic agents such as antibiotics, NSAIDs, contrast media for imaging or chemotherapy can also influence risk, as can bacterial, parasitic and viral infections. Severe genetic defects that lead to FSGS, Alport syndrome, cysts and atypical haemolytic uraemic syndrome typically become evident early in life, whereas moderate genetic defects (such as mutation in uromodulin (*UMOD*)) can become evident in adulthood. Genetic variants in genes such as apolipoprotein L1 (*APOL1*) can modify the course of diseases such as lupus nephritis. T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

endotoxin leakage into the circulation, but also dialysis-related or infection-related immune activation, can contribute to this problem<sup>112,113</sup>. Neurological changes encompass peripheral neuropathy and central nervous system abnormalities, including loss of concentration, lethargy, seizures, coma and death<sup>2</sup>. In adults, cognitive alterations predominate, whereas in children, development of all neurocognitive domains is affected<sup>114</sup>, which can lead to severe intellectual disability or subtle deficits. Daytime sleepiness and fatigue are common and increase with decreasing kidney function. Restless leg syndrome can disturb sleep, but sleep-disordered breathing, excessive daytime sleepiness and insomnia disorder are also common<sup>115</sup>.

### Diagnosis, screening and prevention

The clinical presentation of CKD depends on the underlying disorder and the severity of renal impairment. Patients with early stages of CKD (G1–G2) are usually asymptomatic, but from CKD G3 onwards, patients may experience weakness related to anaemia and polyuria.

### Detection and diagnosis

CKD can be detected during a routine periodic health assessment, during evaluation of individuals at risk of CKD (BOX 2), as a consequence of the incidental finding of abnormal laboratory values in connection with another acute or chronic illness, during an investigation of symptoms and/or signs relating to the kidneys or urinary tract (such as haematuria) or after discovery of abnormal

laboratory values in a population-based screening programme. Importantly, the two biochemical parameters — GFR and albuminuria — used in the KDIGO matrix<sup>1</sup> define and classify a ‘generic’ form of CKD; adding an aetiological diagnosis is both highly desirable and recommended by KDIGO (the so-called cause/GFR/albuminuria (CGA) classification system) whenever possible, such that the underlying conditions can be treated first to halt progression of CKD. Several tests can be performed to confirm a CKD diagnosis and identify its cause, but — importantly — a diagnosis requires persistence or progression of the defining abnormality for ≥3 months. A single GFR value or albuminuria result is insufficient and, if used for diagnosis of CKD, may lead to a high false-positive rate for diagnosis<sup>116</sup> (FIG. 1). Progression is defined according to changes in eGFR by KDIGO<sup>1</sup>.

**Estimating and measuring GFR.** The assessment first begins with measurement of serum creatinine concentration under steady-state conditions and using formulae for estimating GFR (several of which are available, such as the CKD-EPI creatinine equation). The results of these creatinine-based tests can be influenced by changes in muscle bulk (atrophy or hypertrophy), dietary intake of cooked red meat and alterations in tubular secretion of creatinine owing to exposure to drugs (such as trimethoprim/sulfamethoxazole)<sup>117,118</sup>. Alternative approaches using serum cystatin C concentrations have also been proposed; although these are not influenced by muscle bulk and diet, the cystatin C-based

formulae for eGFR can be affected by inflammation, obesity, thyroid disease, diabetes and steroid administration<sup>119</sup>. Importantly, some eGFR formulae have not been extensively validated in older people and might not apply to people of Asian or African descent<sup>120,121</sup>. Demographic variables of age and sex, which might be used to correct for differences in creatinine generation, might also create unwanted complications in determining prognostic implications of an eGFR. Newer eGFR formulae, such as the full age spectrum (FAS) equation, use serum creatinine, cystatin C or a combination of both and have improved accuracy<sup>122,123</sup>. In certain circumstances, such as when stratifying long-term risks of unilateral nephrectomy for potential living kidney donors, measuring rather than estimating GFR can be useful<sup>124,125</sup>. Although cumbersome and expensive, mGFR assessments using urinary clearance methodology can sometimes be needed. However, methods of plasma clearance of the contrast agent iohexol or of radiolabelled iothalamate could avoid some of these issues.

**Measuring proteinuria.** Abnormal urinary excretion of albumin or total protein is essential to detect CKD when GFR is normal and contributes to the assessment of prognosis<sup>126</sup>. Proteinuria (or albuminuria) can be determined in several ways, including simple dipstick qualitative methods, point-of-care urinary albumin concentration tests, random urine samples to calculate the urine protein to creatinine ratio (UPCR) or the urine albumin to creatinine ratio (UACR) or timed 24-hour urine collections to measure absolute protein or albumin excretion<sup>127,128</sup> — each have advantages and disadvantages. Despite some limitations, UACR and UPCR are widely used to assess proteinuria in spot urine samples, although qualitative dipstick values can be approximated to corresponding protein concentrations and predominate in primary care settings and LMICs. Urinary protein or albumin excretion are more variable than serum creatinine levels, and can be influenced by posture, activity, fever or drug use; accordingly, multiple specimens must be collected to enhance reliability. UPCR and UACR methods can be influenced by the prevailing urinary creatinine excretion rate; that is, low creatinine excretion (for example, in patients with sarcopenia) can increase UPCR or UACR values even at normal absolute protein or albumin excretion rates. Hence, adjusting for the effect of urinary creatinine excretion can enhance the accuracy of UPCR and UACR measurements<sup>127,128</sup>. In the KDIGO schema (FIG. 1), UACR values are divided into three categories, namely, normal or moderately increased, moderately increased and severely increased<sup>1</sup>. Even with a normal eGFR, CKD can be diagnosed with a persistent, moderately increased UACR of >30 mg per g. Each incremental increase in UACR is associated with an increased risk of mortality and ESRD, so sustained albuminuria (or proteinuria) is a powerful prognostic marker. Given that persistent proteinuria is a good predictor of the risk of CKD progression, albuminuria or proteinuria can enable detection of CKD (see Screening, below). However, several forms of progressive CKD can present with normal or only slightly increased

albuminuria or proteinuria, such as autosomal dominant polycystic kidney disease<sup>129</sup>. Marked proteinuria (>3.5 g per day in adults), especially when accompanied by a reduction in serum albumin concentration (<3.5 g per dl) — the so-called nephrotic syndrome — nearly always implies a diagnosis of a primary or secondary glomerulopathy underlying CKD<sup>130</sup>.

**Biopsy and pathology.** Percutaneous kidney biopsy is a valuable tool in assessing the underlying cause of CKD. The indications for renal biopsy in a patient with CKD depend on the potential benefits (precise diagnosis, prognostication or determination of appropriate therapy) and the risk of biopsy-related complications. The risks of renal biopsy are minimal in experienced hands, with complications being mostly related to bleeding after the procedure. Fatal complications are rare (about 1 in every 10,000–20,000 biopsies) and major complications, such as need for nephrectomy or blood transfusion, occur in about 0.7–1.8% of biopsies<sup>131–133</sup>.

Kidney biopsies are commonly recommended for adults with nephrotic syndrome but can also be indicated in those with unexplained, rapidly progressive loss of kidney function, persistent haematuria and low-grade proteinuria (0.5–3.0 g per day) or isolated proteinuria (1.0–3.0 g per day)<sup>134</sup>. Depending on the circumstances leading to the procedure, the pathological findings can vary widely; in those with marked proteinuria, glomerular diseases are most likely to be evident. The degree of tubulointerstitial scarring can provide useful prognostic information.

**Other tests.** Detection and determination of the cause of CKD also rely on renal imaging (ultrasonography, CT and MRI), careful examination of the urinary sediment and specialized biochemical and serological tests suitable to detect specific disorders that cause CKD (TABLE 1). Imaging tests are particularly valuable as they provide information on kidney size, contours, location and density as well as information on the anatomy of the urinary drainage system (renal pelvis, ureters and bladder). Specific lesions, such as cysts, dilatation of ureters or pelvis, calcification, masses and scars can provide valuable clues to the cause of CKD or confirm a specific diagnosis (such as autosomal dominant polycystic kidney disease or obstructive uropathy)<sup>135</sup>. Urine sediment examination is important to detect and quantify haematuria, leukocyturia and casts (which form in the distal tubules by aggregating components present in the tubule lumen — such as tubular cells and debris, white blood cells, red blood cells, proteins and/or lipids — into a glycoprotein matrix that is excreted into the urine).

Genetic testing is also emerging as an important tool for determining the cause of CKD, particularly in children and young adults. Autosomal dominant polycystic kidney disease, podocytopathies causing steroid-resistant nephrotic syndrome, Fabry disease and Alport syndrome are well-known entities that can be diagnosed using genetic tests. Next-generation sequencing studies have revealed unexpected genetic heterogeneity as well as alterations in numerous different genes in a

Table 1 | Diagnostic tests and therapeutic interventions for selected conditions associated with CKD risk

Disease entity	Diagnostic test	Therapeutic interventions
<b>Genetic cause of CKD</b>		
Polycystic kidney disease	<ul style="list-style-type: none"> <li>• Perform echography or MRI to detect cysts</li> <li>• Genetic testing using next generation and Sanger sequencing</li> </ul>	<ul style="list-style-type: none"> <li>• Tolvaptan (vasopressin V2 receptor antagonist that benefits selected patients)</li> </ul>
Alport syndrome	<ul style="list-style-type: none"> <li>• Genetic testing for collagen mutations</li> </ul>	<ul style="list-style-type: none"> <li>• ACEi to reduce filtration pressure in remnant nephrons</li> </ul>
Fabry disease	<ul style="list-style-type: none"> <li>• Measure serum α-galactosidase activity</li> </ul>	<ul style="list-style-type: none"> <li>• α-Galactosidase A replacement therapy</li> </ul>
Primary hyperoxaluria	<ul style="list-style-type: none"> <li>• Perform echography to detect nephrocalcinosis</li> <li>• Measure urinary oxalate levels</li> <li>• Genetic testing for mutations in genes encoding serine–pyruvate aminotransferase, glyoxylate reductase/hydroxyypyruvate reductase and dihydrodipicolinate synthase-like protein</li> </ul>	<ul style="list-style-type: none"> <li>• Increase fluid intake</li> <li>• Supplementation with potassium citrate, magnesium oxide pyridoxine and orthophosphate</li> <li>• Oxalate-reduced diet</li> <li>• Liver transplantation</li> </ul>
Cystinosis	<ul style="list-style-type: none"> <li>• Measure leukocyte cystine levels</li> <li>• Slit lamp exam of the eyes</li> <li>• Genetic testing for mutations in cystinosin (CTNS)</li> </ul>	<ul style="list-style-type: none"> <li>• Cysteamine substitution</li> </ul>
Coenzyme Q <sub>10</sub> -related gene mutations causing FSGS	<ul style="list-style-type: none"> <li>• Genetic testing for mutations in genes encoding AarF domain containing kinase 4, coenzyme Q<sub>2</sub>, coenzyme Q<sub>6</sub> and decaprenyl diphosphate synthase subunit 2</li> </ul>	<ul style="list-style-type: none"> <li>• Coenzyme Q<sub>10</sub> replacement therapy</li> </ul>
C3 glomerulonephritis	<ul style="list-style-type: none"> <li>• Perform kidney biopsy</li> <li>• Specific complement tests</li> <li>• Genetic testing for complement-related genes alterations</li> </ul>	<ul style="list-style-type: none"> <li>• Plasma exchange or blood transfusion</li> <li>• Rituximab or eculizumab (depending on specific cause)</li> </ul>
<b>Immune-related cause of CKD</b>		
Acute or subacute immune complex glomerulonephritis	<ul style="list-style-type: none"> <li>• Measure antibodies against nuclear autoantigens or ANCAs, such as those against proteinase 3 or myeloperoxidase</li> <li>• Measure C3 and C4 serum levels</li> <li>• Assess urinary sediment</li> <li>• Perform kidney biopsy</li> </ul>	<ul style="list-style-type: none"> <li>• Immunosuppressive drugs and plasma exchange (in certain settings)</li> </ul>
Renal vasculitis	<ul style="list-style-type: none"> <li>• Measure ANCAs</li> <li>• Assess urinary sediment</li> <li>• Perform kidney biopsy</li> </ul>	<ul style="list-style-type: none"> <li>• Immunosuppressive drugs and plasma exchange (in certain settings)</li> </ul>
Systemic lupus erythematosus	<ul style="list-style-type: none"> <li>• Measure anti-nuclear antibodies and anti-dsDNA antibodies</li> <li>• Measure C3 and C4 serum levels</li> </ul>	<ul style="list-style-type: none"> <li>• Steroids</li> <li>• Chloroquine</li> <li>• Immunosuppressive and immunomodulatory drugs</li> </ul>
<b>Vascular cause of CKD</b>		
Recent-onset renal artery stenosis (fibromuscular or vasculitic)	<ul style="list-style-type: none"> <li>• Angiography of the renal arteries</li> </ul>	<ul style="list-style-type: none"> <li>• Surgical revascularization or catheter-based angioplasty</li> </ul>
<b>Metabolic cause of CKD</b>		
Diabetic kidney disease	<ul style="list-style-type: none"> <li>• Measure blood glucose and albuminuria levels</li> <li>• Perform kidney biopsy</li> </ul>	<ul style="list-style-type: none"> <li>• Antidiabetic drugs</li> <li>• SGLT2 blockade and RAS inhibitors</li> </ul>
Chronic urate nephropathy	<ul style="list-style-type: none"> <li>• Confirm clinical diagnosis of tophaceous gout</li> <li>• Measure serum uric acid levels</li> <li>• Perform kidney biopsy</li> </ul>	<ul style="list-style-type: none"> <li>• Purine-reduced diet</li> <li>• Uricosuric drugs, xanthine oxidase inhibitors or rasburicase</li> </ul>
<b>Toxic cause of CKD</b>		
Toxic nephropathies (caused by, for example, lead, aristolochic acid or phenacetin)	<ul style="list-style-type: none"> <li>• Take medical history</li> <li>• Measure specific toxin levels</li> <li>• Perform kidney biopsy</li> </ul>	<ul style="list-style-type: none"> <li>• Abandon toxin exposure</li> </ul>
<b>Infectious cause of CKD</b>		
Bacterial pyelonephritis	<ul style="list-style-type: none"> <li>• Assess urine culture</li> </ul>	<ul style="list-style-type: none"> <li>• Increased fluid intake</li> <li>• Antibiotics</li> </ul>
Viral nephropathies	<ul style="list-style-type: none"> <li>• Serological test for virus</li> <li>• Measurement of CD4+ T cell counts and viral RNA/DNA copies (in those with HIV)</li> <li>• Perform kidney biopsy</li> </ul>	<ul style="list-style-type: none"> <li>• Antiviral therapy</li> </ul>

Table 1 (cont.) | Diagnostic tests and therapeutic interventions for selected conditions associated with CKD risk

Disease entity	Diagnostic test	Therapeutic interventions
<b>Malignant cause of CKD</b>		
Multiple myeloma*	<ul style="list-style-type: none"> <li>Measure serum or urinary free light chains</li> <li>Serum or urinary immunofixation assessment</li> <li>Measure serum albumin levels, serum phosphorous levels, total protein serum levels and serum albumin-to-globulin ratio</li> <li>Perform bone marrow aspirate</li> <li>Perform kidney biopsy</li> </ul>	<ul style="list-style-type: none"> <li>Myeloma-directed chemotherapy</li> <li>Myelosuppressive therapy</li> <li>Stem cell transplantation</li> </ul>
<b>Mechanical cause of CKD</b>		
Obstructive nephropathy	<ul style="list-style-type: none"> <li>Perform kidney imaging (echography)</li> </ul>	<ul style="list-style-type: none"> <li>Relieve obstruction</li> </ul>

\*Treatment for multiple myeloma can also be a toxic cause of CKD. ACE, angiotensin converting enzyme inhibitors; ANCA, anti-neutrophil cytoplasmic antibody; C3, complement 3; CKD, chronic kidney disease; FSGS, focal segmental glomerulosclerosis; RAS, renin–angiotensin system; SGLT2, sodium/glucose cotransporter 2.

substantial proportion of patients with these diseases (familial, syndromic and sporadic), suggesting the need to update the current diagnostic algorithms and therapeutic choices<sup>72,136</sup>.

Continuing advances in the field of serum and urine proteomics, microRNA biology and serology are providing new powerful and non-invasive tools to identify specific diseases or groups of diseases<sup>137</sup>. These new tools might also expand prognostication beyond GFR and proteinuria estimation — giving rise to exciting new possibilities for precision medicine tailored to the exact diagnostic and prognostic characteristics of each patient.

### Screening

In the context of CKD, screening can take two forms: opportunistic screening, whereby physician encounters for other medical reasons can be used to screen for CKD; or population screening, for example, using dipstick urinary testing of particular populations such as schoolchildren or military personnel. Population-based screening can be further divided into general population screening or targeted screening of high-risk population groups (BOX 2). Unfortunately, the benefits and harms of either screening form for CKD have not been rigorously tested in long-term prospective studies and the overall benefits and harms are poorly understood<sup>138,139</sup>. Accordingly, population-based screening for CKD is not recommended by the US Preventive Task Force largely because of insufficient evidence of benefit (or harm)<sup>140</sup>.

However, opportunistic testing and targeted screening have merit, especially if other risk factors such as diabetes, hypertension or a family history of CKD are used to define the screened population. In these individuals, eGFR and albuminuria (or total protein excretion by dipstick), UACR or UPCR should be measured. In older people with CKD G3 that has been detected by screening (population or opportunistic), prognosis over 5 years is typically very good. For example, a very low rate of ESRD (0.2%) and stable CKD or remission of CKD was found in 53% of such people (mean age of 73 years at study entry) after 5 years of follow up<sup>141</sup>. This low rate of ESRD raises questions regarding the efficiency and cost-effectiveness of population-based screening for CKD in the elderly as a means of reducing the overall societal burden of treated ESRD.

Evidence in favour of targeted screening is stronger, but still incomplete. Given that early treatment might impart substantial effects on delaying CKD progression and progression to ESRD<sup>142</sup>, targeted screening strategies using albuminuria in those with diabetes or hypertension might be of benefit; indeed, Monte Carlo simulations of probabilities support such an approach<sup>143</sup>. Some studies have also suggested that testing for abnormal albuminuria is an efficient way to identify and stratify individuals who are at risk of progressive CKD and cardiovascular events<sup>144</sup>. Indeed, abnormal proteinuria (even only slightly above the upper limit of normal) identifies people at increased risk of ESRD and/or cardiovascular morbidity and mortality<sup>145</sup>. Other at-risk individuals might include first-degree relatives of a patient with autosomal dominant polycystic kidney disease, who are eligible for screening with renal ultrasonography or MRI regardless of their eGFR or proteinuria results. Siblings of patients with Fabry disease, Alport syndrome or thin basement membrane nephropathy might benefit from genetic analysis as well. African Americans with hypertension or HIV infection could gain more-detailed prognoses through assessment of *APOL1* risk alleles, but population-based screening for *APOL1* risk alleles is not yet justifiable<sup>146</sup>.

Both general population screening and targeted screening for CKD are logistically hampered by the need for re-evaluation at a defined interval to fulfil the KDIGO duration requirement (3 months) for diagnosis and staging of CKD. Thus, one-off testing using eGFR or proteinuria have high false-positive detection and diagnosis rates that can be further confounded with the use of non-age-sensitive eGFR thresholds (BOX 1). The potential harms of general population screening include excessive follow-up diagnostic procedures (including renal biopsy, with its associated risks), unnecessary referral of individuals erroneously diagnosed as having CKD, the anxiety induced by being labelled as having CKD and potential impact on insurability. Accordingly, the American College of Physicians determined that current evidence was insufficient to evaluate the benefits (or harms) of population-based or targeted screening for CKD<sup>147</sup>. However, several other countries have long-established programmes (for example, Japan<sup>148</sup>) or have introduced them as part of universal health care systems (for example, the United Kingdom<sup>149,150</sup>)<sup>151,152</sup>.

Going forward, general population screening needs to take into account the age-specific likelihood of finding CKD, the effectiveness of treatment of limiting CKD progression to ESRD once found (or the occurrence of premature death) and the overall cost-effectiveness per quality-adjusted life years (QALY) gained. In using a Markov decision analysis model, Boulware *et al.*<sup>153</sup> showed that annual screening for CKD by dipstick proteinuria in persons without hypertension or diabetes was not cost-effective (\$282,818 per QALY gained), although the cost-effectiveness improved in people >60 years of age. By contrast, screening in those with hypertension or diabetes was cost-effective, particularly for a death benefit<sup>153</sup>. Furthermore, the overall cost-effectiveness of periodic screening for reduced eGFR alone, independent of proteinuria, is largely unknown as studies are lacking, but would be expected to be cost-ineffective; similar conclusions were reached in a systematic review by Komenda *et al.*<sup>154</sup> in 2014. Accordingly, less-frequent screening, inclusion of older people only and/or screening of populations with increased incidence of proteinuria could form the basis of a cost-effective screening strategy.

### Prevention

Primary prevention before CKD is established and secondary prevention to slow the rate of CKD progression (or to affect the associated comorbidities or complications; see below, Management) can be considered. Both are more preferable than after-the-fact treatment with renal replacement.

Primary prevention targets the root causes of CKD and includes mitigating exposures to nephrotoxic agents and events (BOX 2). Reducing the burden of infectious diseases (such as HIV, malaria and *Streptococcus* infections) can reduce rates of CKD, but many challenges remain in the quest to reduce the prevalence of CKD by interventions directed at noncommunicable diseases. For example, preventing obesity and the associated type 2 diabetes mellitus is a global challenge<sup>155</sup>, but the discovery of the central role of sugar and fructose intake and metabolism in obesity can be cited as an example of progress with implications for primary prevention. Indeed, better glycaemic control might also eventually prevent CKD and its progression<sup>142,156</sup>.

Other dietary factors could be modifiable risk factors to be targeted for primary prevention. For example, excessive sodium intake in patients with hypertension can influence blood pressure control and perhaps aggravate glomerular hyperfiltration. Excessive protein intake in diabetes can promote hyperfiltration and predispose to CKD. In this regard, strict vegetarian diets with low dietary acid load have been associated with lower CKD burden in observational retrospective studies<sup>157</sup> and might be useful as preventive strategies. However, observational studies of the impact of diet quality and composition on CKD incidence have been inconsistent<sup>158–161</sup>. Large prospective cohort studies have suggested that ‘healthy’ dietary patterns are associated with fewer renal deaths and lowered incidence of ESRD, but causality remains unproven<sup>162</sup>. Increased vegetable

and fruit intake with restricted red meat consumption has been associated with a lower incidence of CKD in case-control cohort studies, but these studies are subject to confounding by unmeasured variables so they cannot prove causality<sup>163</sup>.

A major focus of interest has been on the influence of acid-base homeostasis on the development and progression of CKD<sup>164</sup>. So far, these studies have primarily examined the deleterious influence of metabolic acidosis on the progression of established CKD (secondary prevention of ESRD) rather than prevention of incident CKD<sup>165</sup>. Indeed, low serum bicarbonate and high dietary acid load (as assessed by net urinary acid excretion) has been shown to be associated with ESRD risk among patients with established CKD<sup>164,165</sup>. Furthermore, in those with diabetes, a low capacity for acid excretion might influence CKD progression independent of dietary acid load<sup>166</sup>, which implicates metabolic acidosis in the progression of established CKD. This finding led to a randomized controlled trial of the safety of oral bicarbonate supplementation in those with moderate to severe CKD, which is recruiting at the time of writing (the BASE study, NCT02521181). To our knowledge, no studies are currently examining whether oral bicarbonate supplementation can prevent the occurrence of CKD in otherwise healthy people of any age.

Improved recognition and reduction of the prevalence of AKI should also prevent CKD, especially in regions where AKI is common, under-recognized and under-treated (such as in equatorial Africa). Given the importance of low nephron endowment, fetal malnutrition and/or dysmaturity manifested by low birth-weight, global efforts to reduce fetal malnutrition and dysmaturity should have enormous preventive effects in later years; focused effects are beginning to address this important topic<sup>61</sup>.

### Management

Several aspects need to be considered when managing patients with CKD, including controlling further nephron injury, normalizing single-nephron hyperfiltration, controlling CKD-related complications and preparing the patient for kidney replacement therapy (TABLE 1). At the core of these is the principle of ‘the earlier, the better’, which is the effort to reduce the progression to ESRD and optimize renal outcomes. To achieve this, a systems-level approach to patient and physician education has been undertaken by numerous organizations (BOX 3).

The benefits of early therapy are well documented for Alport syndrome<sup>167</sup>. Initiating RAS blockade after a genetic diagnosis but before any signs of kidney disease can have dramatic effects on renal outcomes, whereas initiating RAS blockade once CKD G3 is evident only somewhat delays progression to ESRD<sup>167</sup> (FIG. 7). Further support comes from a post hoc analysis of clinical trial data of RAS blockade in diabetic kidney disease; the gain of ESRD-free years was highest when RAS blockade was initiated at the time of microalbuminuria identification and lowest when initiated once a diagnosis of CKD G3 or G4 was made<sup>168</sup>. Thus, early diagnosis and treatment are essential to prevent nephron loss as early as possible.

**Box 3 | System-level approaches to CKD**

Several health care systems have population-based programmes to assure awareness of the public to chronic kidney disease (CKD) or to ascertain certain standards of care for patients with CKD among health care providers. For example, the US CKD Surveillance Project of the US Centers for Disease Control and Prevention provides focused information about all aspects of CKD prevalence, populations at risk, health consequences, quality of care and health care system capacities ([nccd.cdc.gov/ckd/](http://nccd.cdc.gov/ckd/)). In Canada, the Alberta Health Services host a strategic clinical network to achieve excellence in sustainable quality kidney care and outcomes through innovation and evidence-based practice that focuses on prevention, early identification and appropriate management across all ages and stages of CKD ([www.albertahealthservices.ca/scns/kidneyhealthscn.aspx](http://www.albertahealthservices.ca/scns/kidneyhealthscn.aspx)). Many health care providers offer information with the opportunity of support via online forums, such as the UK National Health Care System Choices platform ([www.nhs.uk/conditions/kidney-disease-chronic/pages/introduction.aspx](http://www.nhs.uk/conditions/kidney-disease-chronic/pages/introduction.aspx)) or the National Kidney Disease Education Program by the US National Institute of Diabetes and Digestive and Kidney Diseases ([www.niddk.nih.gov/health-information/health-communication-programs/nkdep/Pages/default.aspx](http://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/Pages/default.aspx)). Private organizations, often endorsed by patient groups, exist in many countries and flank governmental services with patient-oriented support. For example, Kidney Health Australia is a not-for-profit organization devoted to promoting good kidney health through education, advocacy, research and support programmes such as camps for children with kidney disease and housing programmes for those undergoing kidney transplant and their families ([www.kidney.org.au](http://www.kidney.org.au)). The Kidney Education Foundation supports patient education around the world and has published a book on kidney health that is freely available ([www.kidneyeducation.com](http://www.kidneyeducation.com)). The book is available in 31 languages (including many spoken in low-resource settings) and endorses patient education, particularly in regions where disease management programmes might not exist or are inaccessible to many patients.

**Controlling ongoing nephron injury**

Nephron injury can be driven by numerous triggers, and abrogating these triggers will slow progression to CKD and ESRD (TABLE 1). Specific cures for genetic kidney diseases exist and are mostly limited to enzyme replacement therapy or substrate supplementation. The genetic basis of immune-mediated nephron injury is not yet fully explored, but progression of CKD associated with C3 glomerulonephritis or atypical haemolytic uraemic syndrome can be controlled with complement inhibitors<sup>169</sup>. Most acute forms of immune-mediated nephron injury present either as vasculitis, immune complex glomerulonephritis or interstitial nephritis (including allograft rejection). These disorders can often be targeted with immunomodulatory drugs (and sometimes with plasma exchange) to limit nephron loss from attack by the humoral and/or cellular elements of the immune system<sup>170</sup>.

By contrast, in smouldering immune injury, such as in chronic IgA nephropathy, it is difficult to dissect CKD progression driven by immune versus non-immune mechanisms and the effectiveness of immunosuppression versus RAS blockade and blood pressure control is less evident<sup>171</sup>. Kidney biopsy can establish the underlying diagnosis and guide management by assessing the ongoing activity of immune injury versus irreversible damage in, for example, lupus nephritis, IgA nephropathy or allograft dysfunction. Specific treatments are also available for CKD related to urinary tract obstruction, infections and some forms of toxic injury. However, even with complete abrogation of the injurious trigger, recovery of lost nephrons is impossible.

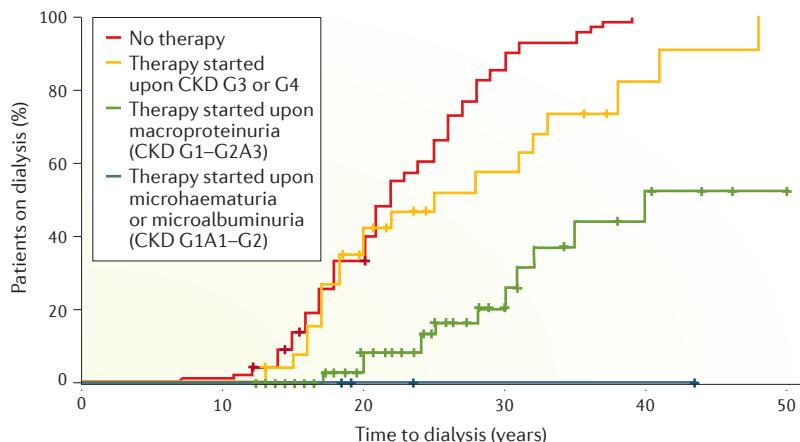
Avoiding further episodes of AKI is crucial to minimize stress on the remnant nephrons in CKD. This implies patient education on avoidable nephrotoxins (such as large volumes of radio contrast media, NSAIDs, certain antibiotics, possibly proton pump inhibitors or other endemic or occupational toxins). Hypovolaemic states as well as urinary outflow obstruction should be avoided. Additionally, asymptomatic leukocyturia alone might not imply bacterial infection, and antibiotic treatment should be limited to cases in which dysuria, bacteriuria and leukocyturia indicate infection. Smoking cessation is essential to minimize CVD<sup>172</sup>.

**Normalizing single-nephron hyperfiltration**

Rigorous RAS inhibition with angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) has the capacity to substantially reduce GFR<sub>(single-nephron)</sub> and glomerular filtration pressure, which leads to a decline in not only proteinuria but also total GFR — and, hence, moderately increases serum creatinine levels<sup>173</sup>. At first, this serum creatinine increase is worrisome to patients (and physicians) and requires clarification that reducing hyperfiltration in remnant nephrons is the central strategy to retard CKD progression in patients with proteinuria. By contrast, ACEi or ARBs do not retard the progression of non-proteinuric forms of CKD such as autosomal dominant polycystic kidney disease but might benefit on the associated cardiovascular complications<sup>174</sup>. ACEi or ARBs should be titrated to the maximal possible dose, whereas hyperkalaemia can be corrected using loop diuretics (which act at the ascending limb of the loop of Henle) or potassium-binding resins<sup>175</sup>. A moderate increase in serum creatinine levels indicates a decline in GFR<sub>(single-nephron)</sub>, which is a powerful predictor of the intended nephroprotective effect<sup>176</sup>. Numerous randomized clinical trials have documented that RAS inhibitors can retard or even halt CKD progression<sup>42</sup>. Reducing dietary salt and drugs that support the control of blood pressure and hyperlipidaemia, often referred to as the ‘remission clinic protocol’, can further reduce proteinuria and retard CKD progression<sup>177,178</sup>. Such interventions are affordable and are essential when kidney replacement therapy is not available or affordable.

Next, blood pressure targets remain an area of debate. A subgroup analysis of the Systolic Blood Pressure Intervention Trial documented reduced rates of major cardiovascular events and all-cause death when a systolic blood pressure <120 mmHg was reached (compared with <140 mmHg) in patients with CKD and hypertension without diabetes<sup>179</sup>. However, these effects might not apply to patients with CVD who are susceptible to compensatory neurohumoral stimulation and sudden cardiac death upon tight blood pressure control. Blood pressure target levels also depend on the method of blood pressure measurement.

Finally, lifestyle modifications such as avoiding or correcting obesity can also reduce filtration load and glomerular hypertension; hence, a normal BMI is a treatment target to retard CKD progression<sup>180</sup>. However, any immunosuppression-related benefit of using steroids in CKD can be counterbalanced by steroid-related obesity



**Figure 7 | The earlier, the better.** In those with Alport syndrome, the time to renal replacement therapy was longest for those who started renin–angiotensin system (RAS) inhibition early, at the onset of microhaematuria (usually at birth) or microalbuminuria (30–300 mg protein per day or per g creatinine). Delaying until macroproteinuria was evident (>0.3 g protein per day or per g creatinine) or until chronic kidney disease (CKD) G3 or G4 was evident considerably shortens the time to renal replacement. ‘No therapy’ here represents relatives of the treated patients who have the same genotype. Figure is reproduced with permission from REF. 167, Elsevier.

that drives glomerular hyperfiltration and secondary FSGS, which could explain why steroid treatment falls short in retarding progression of IgA nephropathy-related CKD<sup>171</sup>. Additionally, concomitant diabetes has important implications for CKD management<sup>181</sup>. Hyperglycaemia maximizes glomerular hyperfiltration via SGLT2-driven vasodilation of the afferent arteriole of the remnant nephrons, which cannot be controlled by RAS inhibitors<sup>84</sup>. Accordingly, SGLT2 inhibitors can reverse this process and elicit profound additive nephro-protective effects on CKD progression<sup>88,182</sup>; their capacity to also reduce CVD in patients with type 2 diabetes<sup>182,183</sup> provides a strong rationale for dual RAS and SGLT2 blockade in patients with diabetes and CKD.

#### Controlling CKD complications

CKD is associated with a number of secondary complications that require management (BOX 4), the most relevant of which in terms of overall mortality is CVD<sup>34</sup>. Cardiac and vascular alterations also arise from endocrine failure (for example, a lack of erythropoietin, vitamin D or PTH), which causes anaemia and secondary hyperparathyroidism<sup>184</sup>. Myocardial fibrosis is the final consequence of the multiple underlying causes.

Large randomized controlled trials in patients on haemodialysis have tested a number of different interventions intended to reduce cardiovascular events, including frequency and length of dialysis sessions and flux (filtration coefficient of the membrane in the dialyser), erythropoietin-stimulating agents, statins, RAS blockade, folic acid, cinacalcet (a calcium mimetic used to treat secondary hyperparathyroidism) or vitamin D derivatives but have largely been unsuccessful<sup>185–187</sup>. For example, reduction of low-density lipoprotein cholesterol with simvastatin (a statin) plus ezetimibe (which decreases cholesterol absorption) reduced the incidence of major atherosclerotic events more efficiently in patients with

CKD G2–G4 than in patients with CKD G5 or who were on dialysis<sup>187</sup>. Guideline-directed approaches on the basis of diabetic status aim to achieve target blood pressure through administration of RAS blockers, salt restriction and anaemia prevention<sup>188,189</sup>. Guidance is also available to correct acidosis, as well as to assess and manage CKD-MBD<sup>190</sup> (BOX 4).

#### Preparing for kidney replacement therapy

Once the stage of ESRD is reached, renal replacement therapy is usually required, although conservative treatment is a potential alternative option, especially in older adults with limited lifespan. Counselling on the options (kidney transplant, haemodialysis, peritoneal dialysis or no dialysis) should be coordinated by the nephrologist and involve a multidisciplinary team that includes the general practitioner. Early counselling is essential because informed patients are better prepared to face kidney failure. Indeed, late referral at the time of ESRD is associated with worse health status at the time of kidney replacement therapy initiation, higher mortality after starting dialysis and reduced access to transplant<sup>191</sup>.

Although practical equations are available to predict CKD progression<sup>192</sup>, one of the greatest challenges nephrologists face is to predict kidney disease progression, which does not follow a steady linear decline. This unpredictability often becomes a barrier to timely shared decision making between patients and physicians<sup>191</sup> and can offset the early pre-dialysis nephrology care for adults with late-stage CKD and compromise outcomes<sup>193</sup>. KDIGO recommends the initiation of dialysis when symptoms or signs of kidney failure are evident<sup>1</sup> (typically when GFR is 10–5 ml/min/1.73 m<sup>2</sup>). Pre-emptive (that is, before dialysis initiation) living donor renal transplantation should be considered in individuals with GFR <20 ml/min/1.73 m<sup>2</sup> and evidence of progressive CKD over the preceding 6–12 months<sup>1</sup>.

**Haemodialysis.** Preparing patients for haemodialysis, which uses pumps, membranes and dialysates to clear uraemic toxins from the blood, involves referral for vascular access placement. The types of access include arteriovenous fistulae, arteriovenous grafts and central venous catheters (which are for short-term use) (FIG. 8a–c); arteriovenous access is the preferred option for haemodialysis, although there is no consensus about the optimal timing for creation, especially for arteriovenous fistulae<sup>194</sup>. To protect the blood vessels for permanent vascular access, attention should be taken to avoid venous puncture or intravenous catheter placement proximal to the wrist, which preserves venous access at the back of the hand. Arteriovenous access (either fistulae or grafts) is associated with better outcomes than central venous catheters<sup>195,196</sup>, as is conversion from central venous catheter to arteriovenous access<sup>197</sup>. Thus, a functional arteriovenous access is preferable for all patients in whom this is possible.

**Peritoneal dialysis.** Peritoneal dialysis uses the peritoneal membrane as an exchange interface to clear uraemic toxins from the blood. For this, a transcutaneous

catheter is implanted into the peritoneal cavity that can be drained daily and used to refill dialysate fluid. After some hours of reaching equilibrium between uraemic blood and fresh dialysate, each dwell is expected to drain excess fluid and metabolic waste products including uraemic toxins (FIG. 8d). Although guidelines for dialysis catheter insertion are available, marked variability in techniques (open surgery, blind via trocar or via Seldinger technique) and perioperative management have been recorded<sup>198</sup>; whether these affect patient outcomes remains unclear. Patients starting on peritoneal dialysis show better initial outcomes and preservation of residual renal function in the first 2 years, compared with patients on haemodialysis but these differences normalize after 2 years<sup>199</sup>.

**Kidney transplantation.** When available, suitability for kidney transplantation should be evaluated according to age and comorbidities, but it can take months to complete<sup>200</sup>. Comorbidities such as cancer, chronic infections, cardiac or peripheral vascular disease and the risk of medical noncompliance are carefully evaluated in this process. Depending on the regional ratio of donors to recipients and on allocation rules, waiting time for a deceased donor kidney can vary from a few months (in Belgium and Austria) to many years (in Germany). Thus, the option of living kidney donation should be explored.

To test for eligibility, potential donors must undergo a comprehensive health assessment including tests for blood group and human leukocyte antigen compatibility with the potential recipient, GFR measures, imaging of the kidneys and the urinary tract, cardiac testing and other tests depending on the medical history. Such rigorous testing is recommended to ensure the short-term and long-term well-being of the donor after donation. Pre-emptive transplantation can offer several benefits to patients with ESRD, but its benefits remain under evaluation<sup>201</sup>. The half-life of a transplanted kidney is <20 years, making these patients also potential candidates for CKD treatments during their lifespan<sup>202</sup>. For example, recurrent glomerulonephritis is an unpredictable complication that can have a negative impact on graft outcome<sup>203</sup>.

#### Conservative treatment and palliative care

Kidney replacement therapy might not be available or affordable but it also might not be advisable for medical reasons. Particularly in very old patients with ESRD and comorbidities, dialysis might neither increase lifespan nor improve quality of life (QOL)<sup>204–206</sup>. In such patients, palliative care that aims to control the symptoms of uremia that negatively affect QOL<sup>207</sup> and education starting at CKD G4 that aims to explain comorbidity management might be appropriate. Withdrawal from dialysis is a related issue and is common in very old patients receiving haemodialysis<sup>208</sup>.

#### Box 4 | Key strategies to managing CKD complications

##### Renal anaemia

- Erythropoiesis stimulating agents (ESAs) are given only when all correctable causes of anaemia (such as iron deficiency and inflammatory states) have been addressed<sup>188</sup>
- Adults receive iron supplementation when transferrin saturation is <30% and ferritin <500 ng per ml; children (<18 years) receive iron supplementation when transferrin saturation is <20% and ferritin <100 ng per ml<sup>188</sup>
- ESAs can be used to avoid haemoglobin levels that are <9.0 g per dl, with a maximum target of 11.5 g per dl<sup>188</sup>
- Avoid blood transfusions, especially in potential transplant recipients to avoid sensitization and ESAs should be avoided in those at risk of stroke or who have malignancy<sup>188</sup>

##### Arterial hypertension

- Individual blood pressure targets are based on age and comorbidities, with special recommendations for people with diabetes mellitus<sup>189</sup>
- Normalize body weight (body mass index of 20–25 kg per m<sup>2</sup>) and NaCl intake (<5 g per day)<sup>189</sup>
- Take regular physical exercise and limit alcohol intake to two drinks per day in men and one drink per day in women<sup>189</sup>

##### Mineral bone disorder

- Monitor calcium, phosphorus, parathyroid hormone (PTH) and alkaline phosphatase activities in adults beginning at CKD G3a and in children beginning at chronic kidney disease (CKD) G2; 25-hydroxyvitamin D levels might also be measured and corrected in these populations using vitamin D supplementation as for the general population<sup>190</sup>
- In CKD G3a–G5 (including those on dialysis), lower elevated phosphate levels towards the normal range but avoid hypercalcaemia by restricting the dose of calcium-based phosphate binders<sup>190</sup>

- Avoid long-term exposure to aluminium in phosphate binders or dialysate<sup>190</sup>

- Measure bone mass density in patients with CKD G3a–G5 (including those on dialysis) who show evidence of bone disease to assess fracture risk<sup>190</sup>

- In adults, 25-hydroxyvitamin D and vitamin D analogues are no longer recommended for routine use unless secondary hyperparathyroidism in CKD G4–G5 is severe and progressive

- For patients on dialysis, PTH-lowering therapy, calcimimetics, 25-hydroxyvitamin D or vitamin D analogues are recommended<sup>190</sup>

- Consider patients with vascular calcifications at high risk of cardiovascular disease; avoid calcium-based phosphate binders in these patients and limit dietary phosphate intake<sup>190</sup>

##### Hyperlipidaemia

- Adults >50 years of age with CKD who are not on chronic dialysis should receive a statin; when estimated glomerular filtration rate is <60 ml/min/1.73 m<sup>2</sup>, a statin or statin plus ezetimibe combination should be given<sup>256</sup>
- Adults <50 years of age with CKD and other cardiovascular risk factors should receive a statin<sup>256</sup>

##### Metabolic acidosis

- Oral bicarbonate can be used to correct mild metabolic acidosis

##### Chronic hyperkalaemia

- Dietary potassium restriction should be implemented
- Loop diuretics and potassium-binding resins should be administered, or dose adjustments of renin–angiotensin system (RAS) inhibitors and aldosterone antagonists must be considered

### Quality of life

CKD-related symptoms increase as CKD progresses and are key drivers of poor QOL in patients with CKD and ESRD<sup>209–211</sup>. Although symptoms rapidly improve with kidney transplantation, these are most severe in patients on dialysis, who frequently report fatigue, nausea, dyspnoea, anorexia, pruritus, restless legs and cramps<sup>212</sup>. Pain is especially common: in a survey of 205 patients undergoing haemodialysis, ~25% had severe pain during the 24 hours preceding the interview and an additional 12% had moderate pain<sup>213</sup>. Mental illnesses, including depression and anxiety, are also common<sup>214</sup> but are understudied among people with CKD.

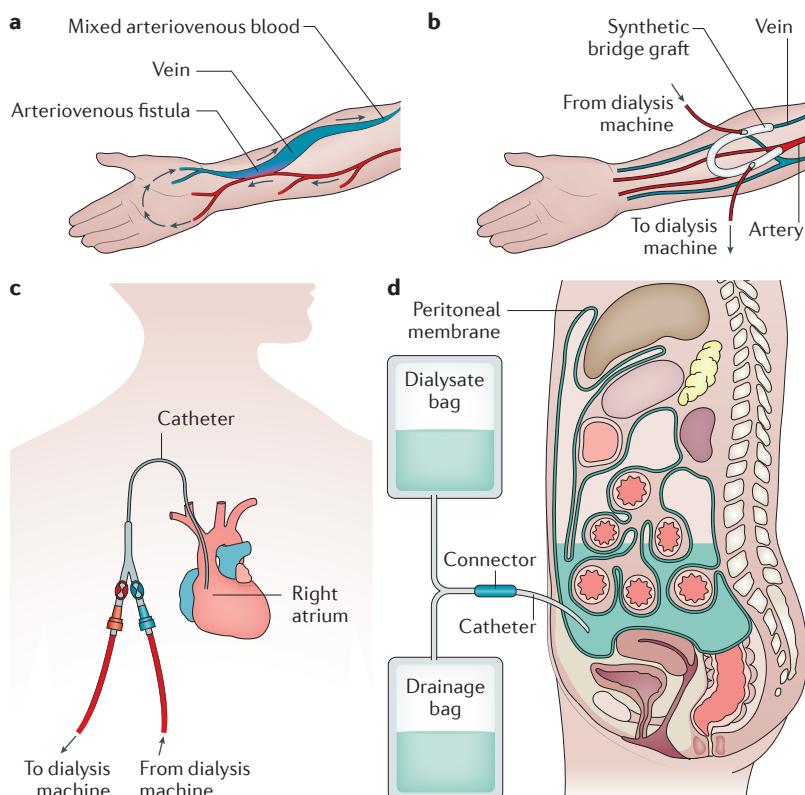
Unfortunately, clinical and epidemiological characteristics associated with the presence, severity, onset and remission of uraemic symptoms are incompletely

described, their pathophysiology is poorly understood and few drugs have been approved by regulatory authorities for their treatment<sup>215</sup>. A key barrier for better management of uraemic symptoms is lack of information about the link between body levels of uraemic toxins and the specific symptoms that patients experience; specific toxin patterns might correlate with symptoms and could be addressed with targeted blood purification strategies. Studies evaluating this paradigm should be a high priority for researchers and funders.

Comorbidities and complications of CKD also substantially contribute to the reduced QOL in CKD patients. For some, such as anaemia, effective treatments are available, but for others, treatment has major limitations or can cause additional symptoms and morbidity (for example, the dialytic management of hypervolaemia). Despite the best efforts of clinicians, interactions between complications and their treatments can further compromise QOL for patients (for example, hypervolaemia resulting from sodium bicarbonate treatment for acidosis). Management of multiple comorbid conditions is already complex in patients with normal kidney function<sup>216</sup>; the situation is even more challenging in people with CKD, in whom the pathophysiology and optimal treatment of common coexisting conditions can differ from the general population. Lack of knowledge of how to prioritize and manage comorbid conditions undoubtedly contributes to the lower QOL in CKD patients through multiple mechanisms — including drug–drug and drug–condition interactions, pill burden and decisional conflict for patients.

Key challenges for haemodialysis that specifically compromise QOL include poor functional status (driven in part by procedure-related immobilization, uraemia-related malnutrition and muscle wasting), the intrusive and time-consuming nature of the treatment and vascular access infection and dysfunction<sup>217</sup>. Instruction for some home-based, low intensity physical exercise can improve physical performance and QOL in patients on haemodialysis<sup>218</sup>. Peritoneal dialysis also poses major challenges for QOL, including gastrointestinal distension, hernia and chronic hypervolaemia. Both forms of dialysis make employment difficult and both are associated with high rates of infectious complications and undue pill burden. Some studies suggest that peritoneal dialysis is associated with slightly better QOL than haemodialysis<sup>219</sup>, but it is possible that this observation is confounded by patient selection<sup>220</sup>. Home dialysis strategies are constantly improving and are becoming possible tools to improve QOL<sup>221</sup>. Kidney transplantation is associated with substantially better QOL than either form of dialysis<sup>222</sup>, but even recipients with good graft function must face CKD-related symptoms as well as complications of immunosuppression and other treatments.

In addition, findings from contemporary patient-centred research should help to drive uptake of patient-centred care at the bedside, especially if supported by patient-reported outcomes<sup>223</sup>. Such paradigm shifts should help to prioritize the management of patient-important issues such as reduced QOL.



**Figure 8 | Haemodialysis and peritoneal dialysis.** **a** | Arteriovenous fistulae are created by surgical anastomosis of a peripheral artery with a larger subcutaneous vein, for example, in the forearm. The increased flow and perfusion pressure leads to structural modifications in the draining vein that enables repetitive venous puncture for haemodialysis. Occasionally declining blood flow to the hand and fingers (steal phenomenon), compensatory increases in cardiac output or aneurysm formation cause problems and require surgical correction. **b** | Arteriovenous grafts might be necessary when the patient's vascular status does not support a fistula. Polytetrafluoroethylene grafts are mostly used and can be repetitively punctured for haemodialysis. Common problems are sterile inflammatory postimplantation syndromes or prosthetic graft infections causing bacterial sepsis. **c** | Central venous catheters become necessary when immediate initiation of renal replacement therapy is needed until a fistula or graft implant becomes ready for use. Such catheters remain the only vascular access option for patients in whom fistula or graft placement is not possible. Catheter infections or thrombotic complications remain constant concerns. **d** | Peritoneal dialysis requires placement of a transcutaneous catheter into the peritoneal cavity, which enables the filling, draining and refilling of dialysate (usually four times a day). The peritoneum serves as an exchange membrane with the uraemic blood.

## Outlook

Key areas for development in the field are to improve the identification of CKD and to reduce the impact and/or prevalence of CKD risk factors, to improve the understanding of causes and consequences of CKD, to improve outcomes and to develop and test new therapeutic strategies<sup>27</sup>. Indeed, global initiatives on CKD launched by the International Society of Nephrology have defined knowledge gaps in CKD and propose how to address them in the future<sup>27</sup>; here, we expand on some of the most promising domains.

## Genetic kidney disease contributions to CKD

Next-generation sequencing studies have unveiled the extreme genetic heterogeneity of kidney disease, with, for example, >40 different genes identified as possible causes of steroid-resistant nephrotic syndrome<sup>136</sup>. These data should be integrated into diagnostic strategies that go beyond the renal biopsy to enable personalized diagnosis and treatments<sup>136</sup>.

With this in mind, study of the genetic predisposition to kidney diseases has made major progress over the past decade. Genome-wide screens and association studies have identified genetic susceptibility variants, mapped risk loci and provided the basis for the projection that the genetic forms of CKD will increase exponentially alongside our understanding of the genetic component of kidney function in health and disease<sup>224</sup>.

## Biomarkers for CKD management

Earlier identification CKD with biomarkers that can also predict CKD progression would help to initiate nephroprotective interventions<sup>27</sup>. Most attractive would be a marker of nephron number. Defining nephron number at birth would identify low nephron endowment and help to dissect endowment from injury-related or ageing-related nephron loss later in life. Such a marker could also detect CKD G2, and could serve as an end point parameter for clinical trials to quantify nephroprotective effects and drug toxicity. However, identifying a clinically applicable biomarker of nephron number in serum or urine has been unsuccessful so far. Biomarkers do not clearly discriminate nephron number from the compensatory remnant nephron hypertrophy. Imaging studies using tracers or the combination of imaging with kidney biopsy to indicate the number of glomeruli (or GFR<sub>(single-nephron)</sub>) are promising proof-of-concept strategies<sup>76,225</sup>.

## Triggers of nephron loss and CKD progression

Dissecting the relative contributions of low nephron endowment, nephron injury, wound healing (interstitial fibrosis) and compensatory hyperfiltration to CKD remains notoriously difficult. Furthermore, to what extent fibrosis itself contributes to nephron loss remains under debate, and several antifibrotic drugs are under study to test this concept<sup>226,227</sup>. Finding ways to define the contributions of these factors and selectively target them in a personalized manner will remain a research focus in the coming years.

## Modifying CKD progression

Aside from targeting fibrosis to slow CKD progression, urate-lowering therapies are also being explored. Such agents have already showed promising results in small trials and the results of an ongoing multicentre trial are eagerly awaited<sup>228</sup>. Additionally, the nuclear factor erythroid-related factor-2 agonist bardoxolone and folic acid supplementation have shown nephroprotective effects in randomized clinical trials in some patient populations in a dose-dependent manner, although the mechanisms of action are not yet fully understood<sup>186,229,230</sup>.

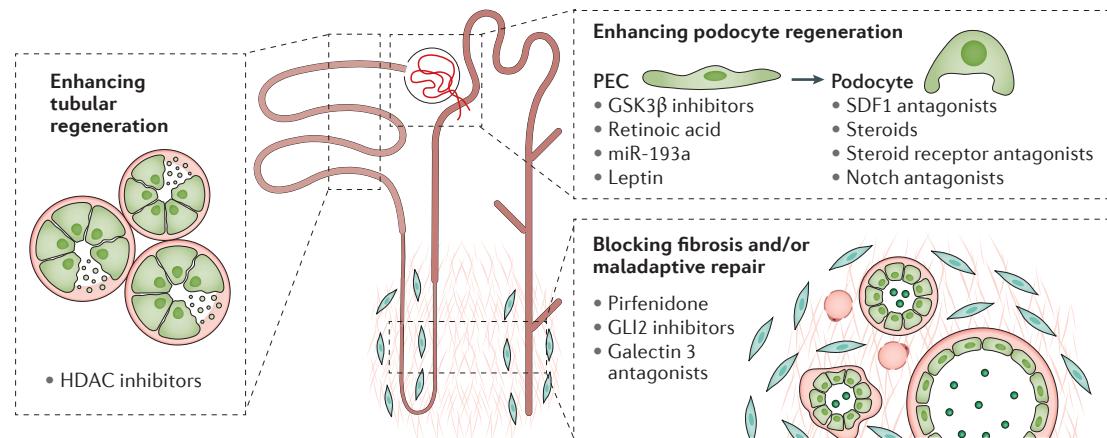
## Nephrogenesis and regeneration

Given the substantial hurdles in accessing renal transplantation, current work is exploring the regeneration of injured nephrons (FIG. 9). For this to be a viable option, a growing research field is trying to unravel the physiology and pathophysiology of the intrinsic capacity of the nephron to regenerate.

Several studies have identified possible druggable targets to prevent nephron loss in AKI and CKD<sup>231</sup>. For example, targeting parietal epithelial cells that act as progenitors to podocytes to promote their differentiation into fully functional podocytes and/or to block their excessive proliferation and matrix production might promote remission of glomerular disorders<sup>232–234</sup>. In addition, enhancing tubular regeneration by promoting tubular epithelial cell proliferation can reduce the occurrence of CKD after AKI<sup>233,235</sup>. Although *in vivo* experimental studies seem promising, no clinical trials are available yet<sup>232–234</sup>. Finally, several early (phase I–II) clinical trials are looking at inhibiting maladaptive repair mechanisms to ebb nephron loss in CKD<sup>236</sup>. Other antifibrotic drugs are also being tested in clinical trials<sup>233,236,237</sup>.

Regenerative medicine is also being explored to treat kidney disorders. For example, mesenchymal stroma cells (MSCs) — a population of well-characterized, easily obtainable cells — have improved kidney function and structure in experimental models of CKD<sup>238,239</sup>. MSCs impart immunomodulatory and paracrine effects, secreting microvesicles and/or exosomes that deliver genes, microRNAs and proteins to recipient cells; these are currently being tested in early (ongoing or recently closed) clinical trials (NCT02012153, NCT02166489 and NCT02585622). Similarly, numerous experimental studies have reported improvement of kidney function and/or structure by activating tissue-based renal progenitor cells injected into different mouse models of AKI as well as CKD<sup>231–235</sup>. However, the translation of preclinical studies into robust, effective and safe patient therapies remains limited<sup>232,233,236</sup>.

Finally, the generation of 3D organ buds termed ‘organoids’ from human induced pluripotent stem cells and embryonic stem cells has been achieved for the kidney; these organoids consist of a variety of renal cell types *in vitro* that mimic organs *in vivo*<sup>240,241</sup>. The organoids can be used to study human diseases and testing of drug toxicity *in vitro*, especially when combined with CRISPR–Cas9-based genome-editing



**Figure 9 | Targeting kidney regeneration.** In the future, it may be possible to target kidney regeneration and maladaptive repair to minimize the loss of injured nephrons and to protect the remnant nephrons. The most promising areas of research include enhancing podocyte regeneration (which could be achieved using drugs such as glycogen synthase kinase 3 $\beta$  (GSK3 $\beta$ ) inhibitors, steroids or steroid receptor antagonists that promote differentiation of parietal epithelial cell (PEC) progenitors into podocytes and/or block the excessive proliferation of PECs), blocking fibrosis and/or maladaptive repair by inhibiting fibroblast expansion (which could be achieved using the antifibrotic drug pirfenidone, inhibitors of the transcription factor zinc-finger protein GLI2 or antagonists of the fibrotic mediator galectin 3) and enhancing tubular regeneration (with IL-22 or histone deacetylase (HDAC) inhibitors, which enhance tubular cell proliferation)<sup>232–237</sup>. miR, microRNA; SDF1, stromal cell-derived factor 1.

techniques<sup>242,243</sup>. However, the complex kidney structure and function are far from being recapitulated for clinical use, and the question remains whether a 'laboratory-grown' kidney will ever be possible.

**Limiting cardiovascular morbidity and mortality**  
Targeting the association of CKD with cardiovascular morbidity and mortality will require additional, rigorous functional studies in animals and humans to identify molecular targets that are suitable for therapeutic intervention<sup>27</sup>. Controlling hyperlipidaemia by modulating lipid transport (for example, with proprotein convertase subtilisin/kexin type 9 inhibitors), suppressing systemic inflammation (with innovative anti-inflammatory drugs such as complement inhibitors), modulating the intestinal microbiota (with probiotics to limit microbiota-related systemic inflammation and dysfunctional metabolism) or interfering with vascular calcification and cardiac fibrosis (with vitamin K analogues) could offer new solutions for this imminent problem in the future.

#### Animal models

Innovative approaches to better link translational research to clinical trial findings will need to start with well-defined human genotypes and phenotypes to identify molecular targets, which could subsequently be validated in animal models. Selection of such animal models for validation should be based on models that recapitulate CKD progression in humans and should require identical end points in subsequent clinical trials. Such models might include mice with identical pathogenetic mutations as in human disease, mice with a humanized immune system or models in higher animals (such as pigs or nonhuman primates) that can be used to close the 'gaps' between preclinical and clinical trials<sup>244,245</sup>.

#### Clinical trial design

Patient heterogeneity is considered one of the main reasons why clinical trials in nephrology commonly fail<sup>246</sup>. Indeed, in adults, a CKD diagnosis might be the consequence of several contributing factors that have accumulated over time, such as *APOL1* or *UMOD* variants (which modify CKD progression), low nephron endowment or AKI episodes earlier in life. Such complexity has important implications for the design of CKD trials that necessitates the characterization of homogeneous patient subgroups. The ensuing targeted clinical trials will require fewer participants and increase the possibility of identifying appropriate drugs for different patients.

Trial design could be improved by reconsidering disease entities defined by descriptive histological features without causative clues such as FSGS, avoiding add-on designs that incorporate drugs with redundant mechanisms of action, preselecting patients on the basis of biomarker profile and studying end points that better predict CKD progression to ESRD. For example, to test the efficacy of the complement 5a receptor (C5AR) inhibitor avacopan in patients with anti-neutrophil cytoplasmic antibody (ANCA) vasculitis, the CLEAR trial at first avoided the usual add-on standard of care approach and instead compared avacopan plus low-dose steroids versus placebo plus high-dose steroids on top of either cyclophosphamide or rituximab<sup>247</sup>. This strategy enabled researchers to prove that avacopan was effective in replacing high-dose glucocorticoids in treating vasculitis.

#### Translation of advances into daily practice

The ever-growing complexity of interpreting kidney biopsy (pathology) findings, assessing laboratory diagnostics and integrating genetic testing will require

centres of excellence with sufficient resources to meet these demands. Similar degrees of expertise are needed to implement emerging, costly therapies as patient selection becomes of increasing importance to ensure benefit. Educational efforts are also needed to alert patients and general physicians to the increasing number of more-affordable therapeutic options, such as SGLT2 inhibitors, for patients with diabetes who have CKD. Finally, awareness of the public, health care providers and policy makers is needed to generate important support for implementation of standards of care<sup>27</sup>. Global guidelines created by the KDIGO initiative have become instrumental in this process, starting from a global definition of CKD stages up to defining standards for the management of CKD complications but these must be refined and improved as our knowledge increases.

## Note added in proof

On 13 November 2017, the American College of Cardiology and American Heart Association Task Force reported new guidelines on the prevention, detection, evaluation and management of hypertension in adults. The document has updated blood pressure thresholds for the initiation of treatment, which might affect the primary prevention of CKD in the general population as well as the management of hypertension in patients with CKD. Accordingly, information in this Primer might require cross-referencing against these new guidelines. See Whelton, P. K. *et al.* 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APHA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. *Hypertension* <https://doi.org/10.1161/HYP.0000000000000065> (2017).

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**Author contributions**

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**Competing interests statement**

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