

Maintaining kidney health in aging societies: a JSN and ERA call to action

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ABSTRACT

Chronic kidney disease (CKD) is the fastest growing cause of death, expected to become the fifth global cause of death and the third in some countries with long life expectancy, such as Japan and Spain, by 2050. This reflects societal aging, as advancing kidney age is the main risk factor for CKD. The forecasted 140% increase in the death rate from CKD by 2050 is reduced to 33% when adjusted for age. The increasing mortality burden is paralleled by higher personal, healthcare, socio-economic and environmental burdens and the need for kidney replacement therapy to treat kidney failure. To some extent, the higher CKD burden represents the price of success in prolonging longevity by decreasing other causes of death. Now is the time to act to minimize the negative impact of CKD on aging societies through primary prevention and early diagnosis and treatment of CKD. Action aimed at maintaining kidney health and delaying biological kidney aging will contribute to healthy aging, as the kidneys have gerosuppressor functions and CKD has the highest negative impact on body aging among chronic non-communicable diseases. This action should be part of a move towards novel holistic approaches to healthy longevity represented by concepts such as cardiovascular–kidney–metabolic health, geromedicine, gerosuppressors and organ rejuvenation. We discuss a conceptual framework for the present and future of kidney aging and kidney health in the elderly, emphasizing opportunities for intervention that underlie the Japanese Society of Nephrology and European Renal Association call to action on Achieving Kidney Health in Aging/Aged Societies.

Keywords: aging, chronic kidney disease, gerosuppression, kidney aging, kidney replacement therapy

KIDNEY DISEASE BURDEN IN AN AGING WORLD

The world population is aging because of decreasing birth rates and longer life expectancy. The global number of people >65 years of age will more than double by 2050, increasing to 1.6 billion from 761 million in 2021. Older people represent 29% and 37% of the population in Europe and Japan, respectively [1]. By 2100, this aged population will reach 2.37 billion people, compared with 1.7 billion people <20 years of age [2]. Population aging will burden societies and healthcare systems, especially if longer life expectancy is not aligned with longer healthy life expectancy. To address the impact of aging societies on health, the World Health Organization (WHO) is implementing the United Nations Decade of Healthy

Aging (2021–2030) [3], which is running in parallel with the US and European Decade of the Kidney [4]. This is no coincidence, as chronic kidney disease (CKD) has the highest global prevalence among age-associated chronic non-communicable diseases (NCDs)—nearly 850 million people—and represents the fastest growing global cause of death. Most of the growth depends on an aging population; the forecasted 140% increase in all-age death from CKD by 2050 is reduced to 33% when adjusted for age [5–7]. In contrast, age-standardized death rates from other common NCDs (ischaemic heart disease, stroke, chronic obstructive pulmonary disease, diabetes) are projected to decrease by 13.7–44.8%. As a result, CKD will become the fifth leading global cause of death by 2050 [7]. In some countries with long life expectancy

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in Europe and Japan, CKD is forecasted to become the third leading cause of death by 2050 and potentially the second by 2100 (Fig. 1A) [7, 8]. A longer forecasted life expectancy in 2050 is associated with a greater forecasted impact of CKD as a cause of death (Fig. 1B) [9]. Therefore, understanding and eventually correcting the drivers of CKD in the elderly is necessary. Strikingly, diabetes mellitus only ranks third as a cause of CKD among people ≥ 75 years of age and starting kidney replacement therapy (KRT) in Europe, after hypertension and unknown [10]. However, given the lack of gold standard diagnostic criteria, the role of hypertension as a cause rather than a consequence of CKD has been questioned, illustrating our poor understanding of CKD drivers in the elderly [11].

Here we review the role of kidney disease as a treatable contributor to biological aging and kidney care in an aging society. Kidney care implies primary prevention of kidney aging and CKD, which is maintaining kidney health. Maintaining kidney health or early identification of CKD with subsequent treatment can be termed primary prevention of cardiovascular disease (CVD). Treatment of progressive CKD with developing systemic CVD consequences fulfils secondary prevention criteria. Additional measures to minimize the negative impact of CKD in elderly and aging societies include a rational approach to treatment of kidney failure and research into kidney rejuvenation. These concepts provide the rationale for the Japanese Society of Nephrology (JSN) and European Renal Association (ERA) call to action on Achieving Kidney Health in Aging/Aged Societies.

BIOLOGICAL AGING AS A TREATABLE CONDITION: KIDNEYS AS GEROSUPPRESSORS

Aging leads to a gradual decrease in physical and mental capacity, a growing risk of systemic disease and ultimately death [12]. Although no consensus has been reached, most experts think that aging begins around birth or, at the latest, sexual maturity, based on evidence of molecular and cellular aging that predates clinical features of aging by decades [13]. Moreover, aging is exponential and non-synchronous for diverse organs and systems, meaning that once aging (overall body aging or single organ aging) is clinically evident, it progresses rapidly [14, 15]. Consequently, interventions to delay the impact of aging and associated conditions on kidney health should precede the clinical onset of kidney aging (i.e. should be targeted to younger individuals) (Fig. 2) [16]. The non-synchronous characteristics of aging may underlie the traditional piecemeal approach to managing aging-associated conditions, which consists of disaggregating them into specific organ diseases cared for by different medical specialties with different therapeutic approaches (Fig. 3A). As biological aging is characterized by common cellular and molecular hallmarks that likely represent shared cellular and molecular mechanisms [17], a burgeoning area of research explores ways to prevent, treat and even reverse aging itself, rather than specific age-associated conditions. The new fields of geroscience and geromedicine aim to develop biomarkers of aging for the identification and evaluation of longevity interventions that promote gerosuppression (i.e. suppress aging) in diverse organs simultaneously [18–20] (Fig. 3B). The hallmarks of aging represent potential targets for intervention [17] and are also observed in NCDs: NCDs of individual organs are associated with accelerated aging of both the involved organs and other organs [14]. CKD is associated with the greatest acceleration of biological body aging among the 16 NCDs studied to date. Specifically, the mean body age is 6.15 years older than the

chronological age in persons with CKD [14, 21]. In addition, CKD is associated with the largest increase in organ-specific biological age, as the kidneys of patients with CKD are 8.03 years older than their chronological age [14]. Other chronic conditions, such as diabetes, also accelerate kidney aging [14]. This novel paradigm suggests that tissue aging may be a final common pathway triggered by different causes of tissue injury that may also spill beyond the original target organ of the insult. Thus kidney aging may play a key role in body aging. A potential contributor is the albuminuria- or inflammation-driven loss of Klotho, a key gerosuppressor produced by kidney tubular cells, as its deficiency recapitulates the cardiovascular phenotype of CKD [22–24]. This may contribute to the increasing risk of CVD with increasing albuminuria categories in the Kidney Disease: Improving Global Outcomes (KDIGO) risk heat map [25]. Another potential contributor is the accumulation of inflammatory mediators and uraemic retention molecules, causing direct cytotoxicity or leading to post-translational protein modifications that may disrupt interorgan communication [26] (Fig. 4). This may contribute to the increasing risk of CVD in low glomerular filtration rate (GFR) categories in the KDIGO risk heat map [25].

The clinical implications are slowly dawning on clinicians, who are adopting more holistic approaches to NCDs, spurred on by the evidence that certain drugs, such as renin-angiotensin system (RAS) blockers, mineralocorticoid receptor antagonists (MRAs), sodium-glucose co-transporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, have multiple beneficial effects on diverse age-associated NCDs, including CKD, CVD and the overweight/obesity/type 2 diabetes mellitus spectrum [25, 27–31] (Fig. 3B). This change in approach is exemplified by the recent Cardiovascular-Kidney-Metabolic Health Presidential Advisory from the American Heart Association [32]. SGLT2 inhibitors have also been identified as gerosuppressors [33] that preserve Klotho production by tubular cells [34], and the aging process could be a therapeutic target shared by multiple NCDs. However, the clinical implementation of gerosuppressor therapeutic strategies is impeded currently because aging is not considered a disease and thus regulators cannot approve drugs to prevent or treat aging. Lifestyle is a key factor in longevity, as illustrated by the negative impact of the Okinawa shift towards an American lifestyle. Once touted as one of five world blue zones of exceptional longevity, it no longer ranks among the most long-lived prefectures in Japan [35].

Overall, the negative features of aging, such as progressiveness, acceleration and irreversibility, suggest that the concept of healthy aging is an oxymoron, in which apparently contradictory terms appear in conjunction. However, healthy aging represents a practical approach defined as ‘the process of developing and maintaining the functional ability that enables well-being in older age’ [3] (Fig. 2). If we cannot yet intervene in the aging process itself, we can try to keep it oligo-/asymptomatic. Key components of healthy aging include physical and mental health, social engagement, autonomy and independence. Given the large impact of CKD on biological aging, a focus on maintaining kidney health will likely contribute to the aim of healthy aging at the societal level.

KIDNEY CARE IN AN AGING SOCIETY

As the world population ages, an expected increase in the prevalence of CKD among older individuals will pose a considerable challenge for healthcare systems in terms of resource allocation for disease management. Health policy for an aging society

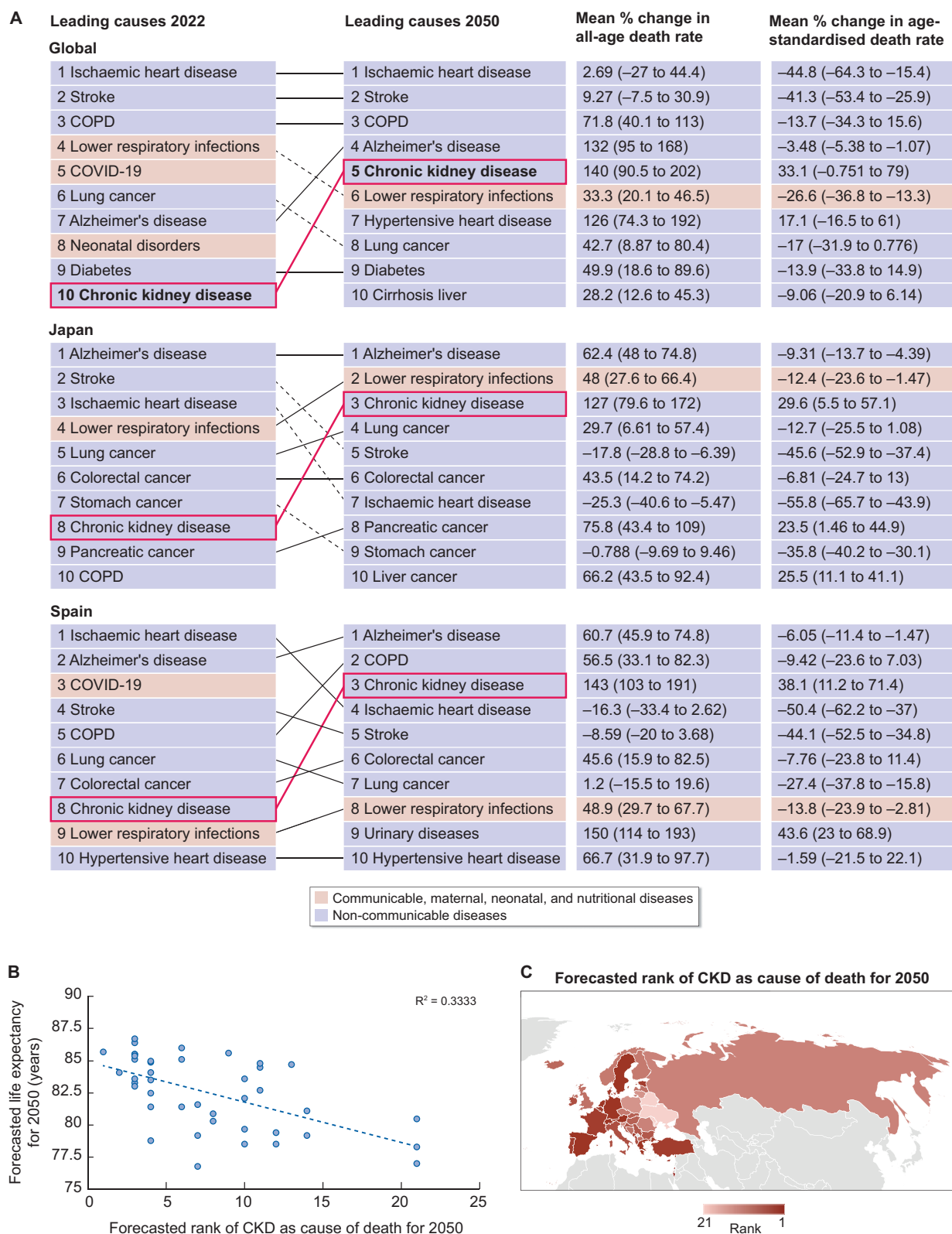


Figure 1: GBD forecasts for major causes of death by 2050. **(A)** Leading causes of death in 2022 and forecast for 2050. Global data and data for two representative countries with long life expectancy are shown. Note that most of the forecasted global increase in CKD deaths depends on population aging, as the age-adjusted increase (33.1%) is much lower than the all-age change (140%) in death rate. Values are given as mean (95% CI). NCDs are represented by blue cells and communicable diseases by red cells. **(B)** Relationship between forecasted 2050 life expectancy and forecasted 2050 rank of CKD as cause of death in European countries and Japan. Pearson correlation, $r = -0.5773$, $P = 0.000063$. **(C)** Forecasted 2050 rank of CKD among causes of death in European countries and Japan. Figure uses data from Vollset et al. [7] and Statista [9].

A 'Healthy' aging: so far, so good

Optimal time window
to act in high-risk
individuals to prevent
CKD in the elderly

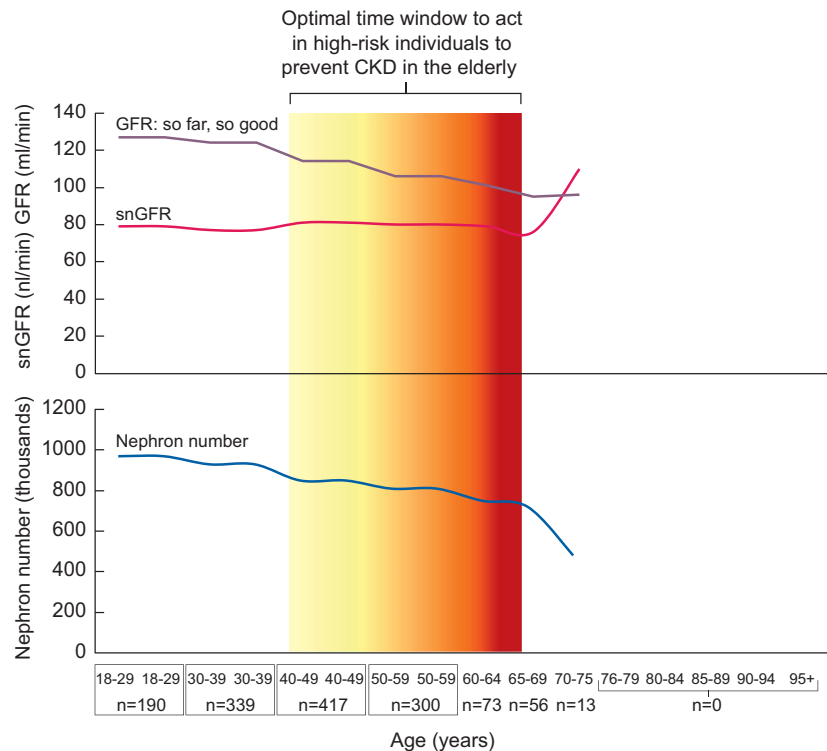
**B**

Figure 2: The 'so far, so good' phenomenon in kidney aging. **(A)** Conceptual representation of the 'so far, so good' phenomenon. Healthy aging refers to the subclinical stage of aging, as cell and molecular aging is thought to start at some point between birth and sexual maturity. **(B)** Kidney aging is characterized by progressive nephron loss and a slow age-related decrease in eGFR that frequently remains above the GFR threshold for long periods to diagnose CKD. However, the nephron loss and eGFR loss accelerate beyond 60 years of age in association with an increase in single-nephron hyperfiltration, a key driver of CKD progression. The timing of the acceleration process may vary from person to person. The challenge is identifying persons who are thought to be healthy from the kidney point of view ('so far, so good': normal eGFR, no CKD) but who are about to start the rapid downturn in kidney health so that preventive action can be taken. To prevent CKD in the elderly, preventive efforts should be targeted to high-risk younger people, identified as the optimal time window in the figure. Data obtained from healthy kidney donors with preserved eGFR [16], who represent a selected population that may convey an overoptimistic view of kidney aging, since lower eGFR is common at older age. The lines in the figure connect datapoints representing mean measured values for each age range. At age 65–69 years the mean single-nephron GFR (snGFR) was 76 nl/min and at age 70–75 years it was 110 nl/min. The message is that even in this selected population, there is evidence for an acceleration of nephron loss and an increase in snGFR during the 60–69 years decade, which coincides with the timeline for the acceleration of kidney aging as determined by measured GFR in men [44] and of aging in other organs [14, 15]. Note that the original data source provided data for 10-year categories for ages of <60 years and did not provide data for those >75 years.

should consider planning and investing in kidney prevention and care systems, designing kidney care services and delivering kidney care. This requires understanding of the priorities of younger and older people. Evidence of effectiveness needs to be assessed for new services and treatments, ensuring that older patients are included in research studies. Evidence should be generalizable to them and the decisions they need to make.

Kidney care should encompass prevention and treatment of CKD, treatment of kidney failure and research into gerosuppressors and kidney rejuvenating therapies targeting the aging process itself [18].

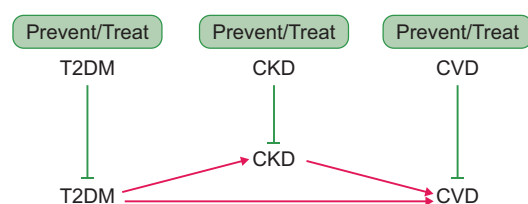
Maintaining kidney health: biological kidney aging as a preventable condition

The extent to which the CKD epidemic can be mitigated depends largely on the education of at-risk individuals and the uptake of prevention efforts. Modifiable risk factors (e.g. overweight/obesity, diabetes, hypertension) should be addressed. The implementation

of cost-effective screening programs in high-risk individuals for early detection of a very high risk of CKD and of CKD is mandatory. Widespread access to new-generation kidney-protective drugs to prevent the development of CKD and delay its progression [36] should be affordable.

Given the long natural history of CKD, understanding the causes of CKD in the elderly is key to developing strategies that can be deployed from a younger age with the aim of preventing CKD later in life. The burden of some treatable CKD risk factors is projected to increase in parallel with the rapidly aging global population [36]. Over the past 25 years, obesity prevalence has almost doubled to $\approx 25\%$ in Europe and increased by 12% in Japan [37, 38]. At the same time in both regions, diabetes prevalence increased by 30–50%, more in males than females [36, 39]. The global prevalence of hypertension continues to increase while blood pressure is better controlled in high-income countries. However, advancing kidney age is the main risk factor for CKD and the need for KRT (Fig. 5A). Strikingly, the 2024 KDIGO CKD guideline does not list age as a risk factor for CKD, unlike other

A Traditional approach: treat individual age-associated NCDs



B Future: treat aging

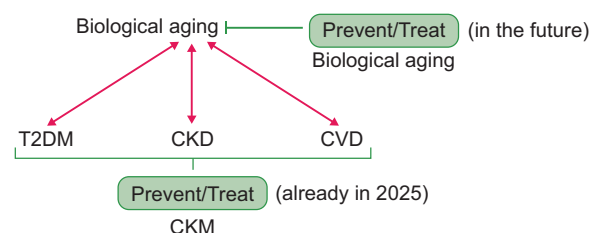


Figure 3: Evolving conceptual framework for the prevention and treatment of CKD. **(A)** The traditional approach involves silos, i.e. different medical specialties diagnose and treat different NCDs that are clearly interrelated, sometimes generating friction between specialists that confuses patients. **(B)** As recently as 2023, a new paradigm was defined that considered cardiovascular, kidney and metabolic conditions, such as overweight/obesity and diabetes mellitus, as part of the same disease spectrum for which there are therapeutic approaches that address all components. As all of the conditions are associated with features of accelerated biological aging that are thought to contribute to disease pathogenesis and progression, the aging framework will likely be a common thread to address multiple NCDs simultaneously.

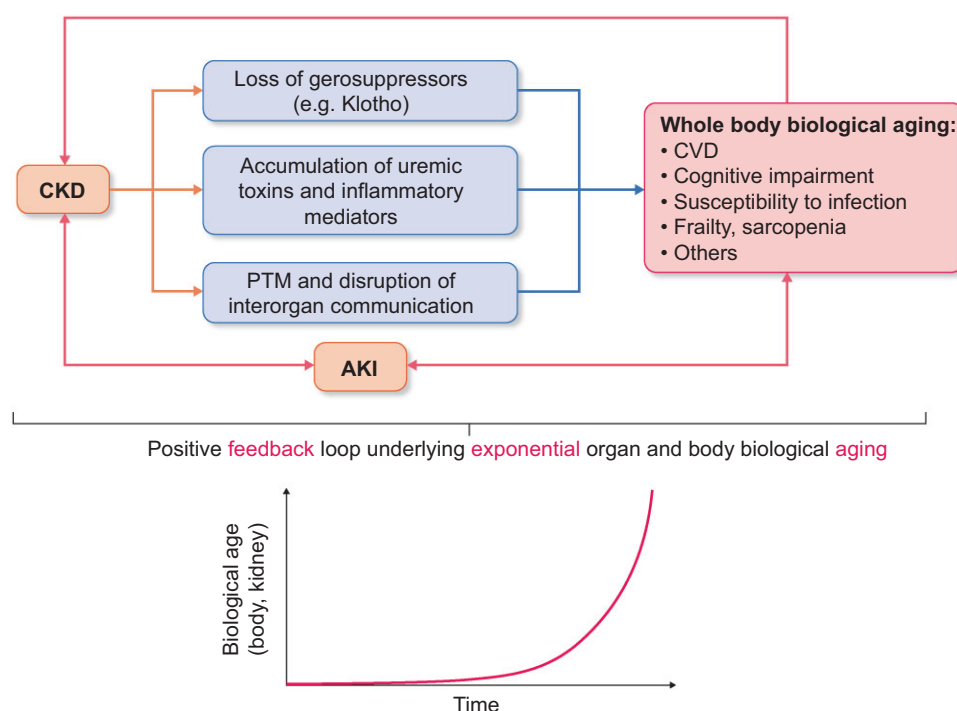


Figure 4: AKI, CKD and whole-body biological aging are part of a positive feedback loop (vicious circle) that results in accelerated CKD progression and whole-body aging. This feedback loop may underlie the exponential rate of biological aging at both the local kidney level and whole-body level. The figure emphasizes some well-characterized, key pro-aging mechanisms activated during CKD and well-characterized consequences outside the kidneys.

guidance documents for NCDs [40] that have developed screening programs aimed at people over a certain age. Kidney care should incorporate this approach, as already recommended by some guidelines [41].

The distribution of causes of CKD appears to differ in the elderly and the young [42]. Overall, the cause of kidney failure was unknown in 14% of patients in the ERA Registry who started KRT in 2022 [42]. However, in patients ≥ 75 years of age with incident KRT in 2010–2013, unknown cause (22.2%) was 17% more common than diabetes as a cause of kidney failure [10]. The persistent high frequency of unknown causes in the elderly in 2022 is remarkable (Fig. 5B, C) [42], as the ERA Registry has listed ‘aging kidney’ as a primary renal diagnosis since 2012 [43]. Aging kid-

ney seems to be a perfect match for the clinical situation in the elderly in which there is no other obvious cause of CKD. It is similar to the diagnosis of hypertension, which is used clinically as a cause of CKD when there is no other obvious cause in individuals with high blood pressure [11]. However, since most elderly people never need KRT (even for a very high incidence of KRT in the elderly ≥ 75 years of age, such as 2000 per million age-related population, means that only 0.2% of such elderly start KRT in that year), accelerated or premature kidney aging (Fig. 6) may be more appropriate than kidney aging as a primary renal diagnosis. Aging also predisposes to repeated episodes of acute kidney injury (AKI), a frequently overlooked cause of CKD progression. In this regard, some consider kidney aging a physiological process

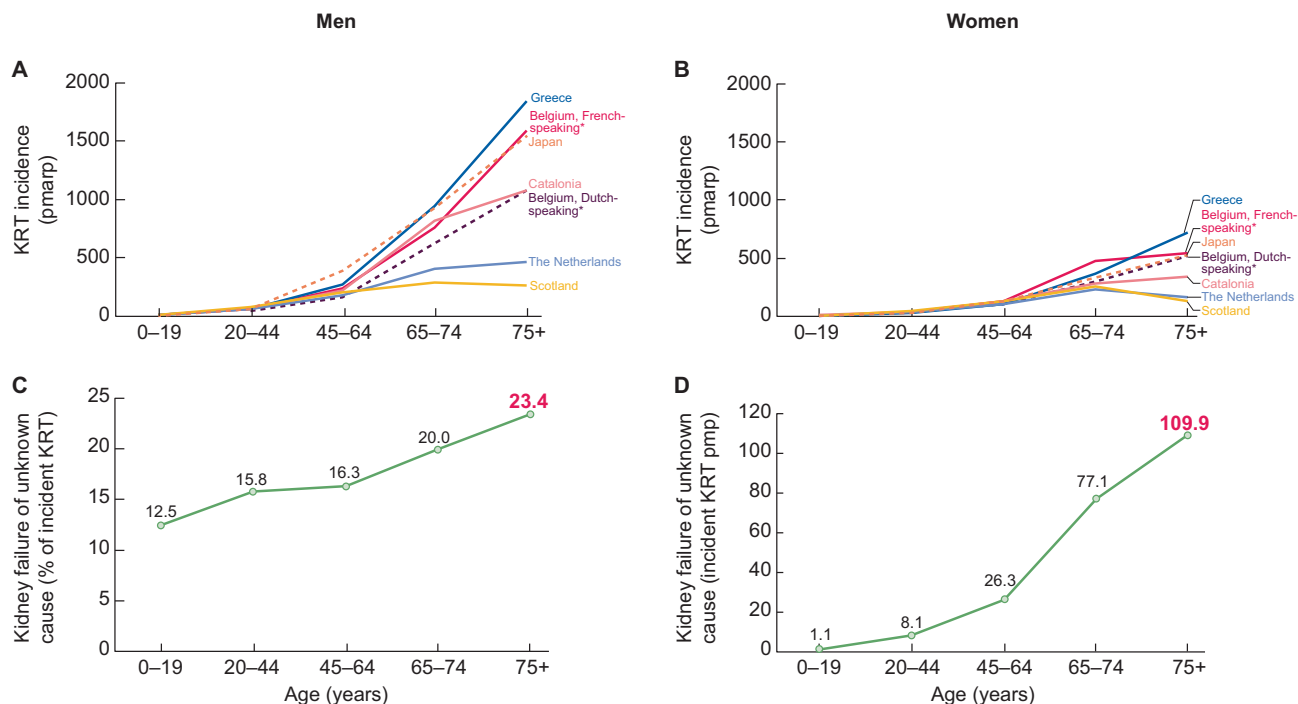


Figure 5: Incidence of kidney failure treated with KRT according to age. **(A, B)** Incidence of kidney failure treated by KRT in Japan and selected European countries and territories that have a high uptake of KRT in the elderly as well as examples of European countries with a lower uptake of KRT in the elderly. Data are presented separately for **(A)** men and **(B)** women in different age ranges and expressed as incidence per million (age-related) population (pmarp) by age and sex, unadjusted at day 1 in 2022. Japan KRT data obtained from the Japanese Society for Dialysis Therapy [70] and Japan population on 1 December 2020 from eStat [82]. European KRT data obtained from Boenink et al. [42]. **(C)** Incidence of kidney failure treated with KRT due to unknown causes in the ERA Registry, expressed as a percentage of incident KRT in 2022. **(D)** Incidence of kidney failure treated with KRT due to unknown cause in the ERA Registry, expressed as per million population.

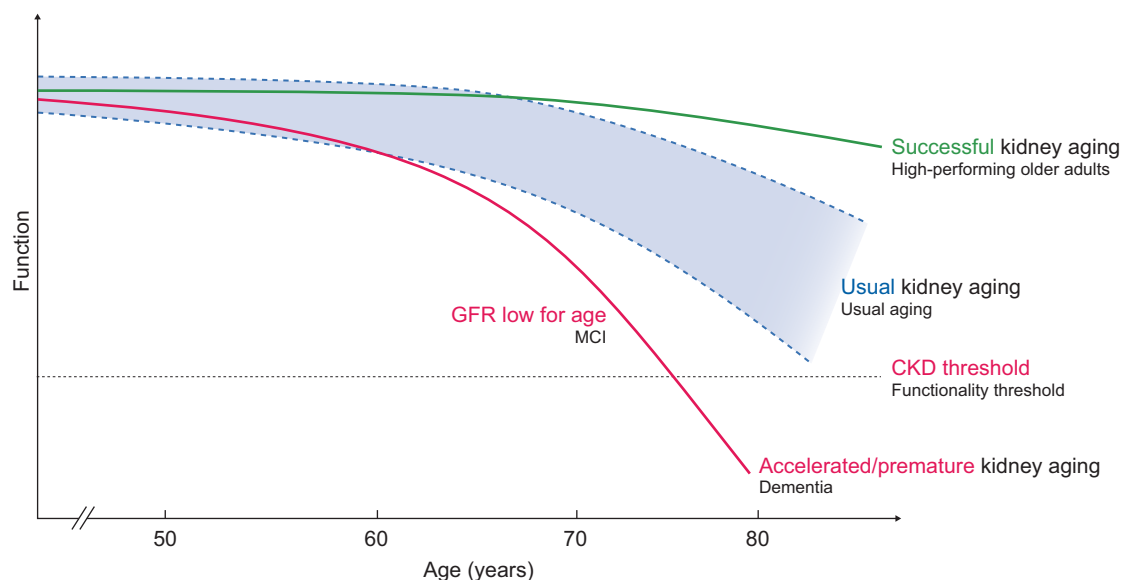


Figure 6: Conceptual representation of successful and accelerated/premature kidney aging following paradigms proposed for brain aging. Adapted to kidney health from Borelli et al. [83]. Smaller font represents brain health concepts that have been adapted to kidney health (larger, colour-coded font). MCI: mild cognitive impairment.

associated with nephron loss. From the age of 40 years onwards, a mean progressive decline in GFR of 0.75–1.0 ml/min/1.73 m²/year, which can accelerate up to 3-fold in apparently healthy men >60 years of age, coincides with an acceleration in nephron loss [16, 44, 45] (Fig. 2B). These two time points (40 and 60 years of

age) coincide with peaks of accelerated body aging [15]. However, the underlying histological changes (i.e. atrophy of parenchymal structures and fibrosis) of aging kidneys are difficult to reconcile with the definition of physiological (i.e. a characteristic of healthy or normal functioning) aging. These are known features of CKD

that, by themselves, allow diagnosis of CKD according to the current KDIGO definition [25, 46].

Some have suggested that reaching the GFR diagnostic thresholds for CKD because of kidney aging is not concerning and does not require treatment and have proposed an age-adapted CKD definition [45]. This is not feasible now. In one framework, the eGFR threshold to diagnose CKD would decrease from 60 to 45 ml/min/1.73 m² after age 65 years. This approach has serious shortcomings. An eGFR of 50 ml/min/1.73 m² at age 64 years would be termed CKD, but it would no longer be termed CKD (in the absence of other findings) after the 65-year birthday. As a consequence, from that day onwards, therapy for CKD would no longer be necessary, as it may be considered inappropriate care [45, 47]. Alternatives have been proposed based on continuous age-adapted thresholds for CKD diagnoses related to the distribution of eGFR values by age in the general population. In this proposal, multiple eGFR thresholds to diagnose CKD would coexist, a different one for each age or age range. While it is worth considering this proposal, there are multiple practical and theoretical arguments against it. From a practical point of view, it would lead to chaos. It is unlikely that physicians outside nephrology and across the world would be able to implement multiple eGFR CKD definitions into clinical practice when the albuminuria arm of the CKD definition remains widely unimplemented after >20 years. Second, it would be unusual for a cardiovascular risk factor to be defined based on the most frequent values for each age range. This would be equivalent to defining diabetes, hypercholesterolaemia and hypertension by using the most common values of serum glucose, cholesterol and blood pressure found in each age group, i.e. using higher thresholds as people get older, as these are age-associated conditions whose prevalence increases with age, as is the case for CKD. There is wide consensus that for cardiovascular risk factors, the actionable diagnostic thresholds are based on the association with adverse outcomes and on clinical trials implementing these thresholds, not on prevalence measures. In this regard, we lack precise information on which eGFR thresholds, different from 60 ml/min/1.73 m², are associated with adverse outcomes at, for example, age 72 versus age 71 or 67 or 63 years. Even if that information were available, the coexistence of multiple definitions of CKD that change whenever the patient becomes older will lead to a persistent risk of the Birthday Paradox: if muscle mass loss is faster than expected for age, eGFR may remain stable for several years and the diagnosis of CKD may need to be backtracked and CKD-associated kidney (and cardiovascular) protective medication stopped. Finally, the rationale for proposing age-adjusted eGFR thresholds may be flawed [47]. Denic *et al.* [47] hypothesized that the values for a putative optimal eGFR range associated with lower all-cause mortality progressively decrease with older age from ≥ 105 ml/min/1.73 m² at age <55 years to 60–74 ml/min/1.73 m² at age ≥ 75 years. They further proposed that any risks associated with low eGFR values should be assessed for each age group in comparison with these age-associated optimal eGFR values. However, the lowest all-cause mortality in people ≥ 75 years of age with a urine albumin:creatinine ratio (UACR) <10 mg/g was observed for eGFR values between 90 and 105 ml/min/1.73 m², voiding the argument. The view of Denic *et al.* [47] is in clear contrast with recent evidence that in people >65 years of age with eGFR creatinine of 45–59 ml/min/1.73 m², the current KDIGO GFR and albuminuria thresholds used for CKD diagnosis are associated with adverse outcomes, such as kidney failure with replacement therapy, all-cause mortality and CVD mortality [hazard ratio (HR) 5.81

[95% confidence interval (CI) 4.70–7.19], HR 1.13 [95% CI 1.09–1.17] and HR 1.20 [95% CI 1.14–1.26] for UACR <10 mg/g and HR 7.48 [95% CI 5.69–9.84], HR 1.37 [95% CI 1.31–1.44] and HR 1.48 [95% CI 1.36–1.61] for UACR 10–29 mg/g, respectively, for these three outcomes] [48]. Adverse cardiovascular outcomes associated with CKD include coronary heart disease, stroke, heart failure, atrial fibrillation and peripheral vascular disease. Furthermore, the absolute risk of adverse outcomes is higher in the elderly than in the young [48]. Increased risks of adverse outcomes have also been noted in elderly (>65 years) people with preserved GFR (>60 ml/min/1.73 m²) and albuminuria in the 10–29 mg/g range [48]. However, it is worth noting that this information does not refer to people without any other health condition (i.e. non-smokers not taking any chronic medication and not diagnosed with overweight, obesity, hypertension, diabetes, cardiovascular disease or any other condition).

Others consider kidney aging a central contributor to CKD and its adverse consequences for health. In this framework, differences in the baseline number of nephrons and interactions between genetics and the environment will determine the extent to which kidney aging contributes to the current CKD pandemic. Genetic factors may vary according to ancestry. For example, in West Africans and their descendants, high-risk variants of APOL1 predispose to CKD. However, the impact of these risk variants on the risk of CKD in older age appears to be lower than in younger people [49]. Thus a physiological rate of kidney aging may result in kidney failure in persons born with fewer nephrons or who live long enough. In addition, the ‘magic’ number of age-associated GFR slopes (0.75–1 ml/min/1.73 m²/year) represents mean values, but kidney function may be lost faster or slower with aging, depending on genetics, comorbidities and environmental factors [44] (Fig. 6).

Research into the molecular mechanisms of kidney aging will help design novel interventions aimed at shifting the age-associated GFR loss towards levels found in the slowest progressors (Fig. 6). Preclinical and clinical data suggest that CKD shares molecular and cellular mechanisms with kidney aging and aging of other organs and systems, termed hallmarks of aging. Hallmarks of aging are genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, disabled macroautophagy, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation and dysbiosis [17, 50, 51]. Most, if not all, of these hallmarks are also involved in AKI and/or CKD. However, the potentially different kidney-aging patterns need to be defined, as recently done for brain aging. Five different brain aging patterns are associated with diverse combinations of biomedical, lifestyle and genetic factors that may become targets for intervention [52]. One of these patterns was associated with NCDs, including CKD. From kidney transcriptomics data, artificial intelligence identified four molecular categories of disease spanning CKD stages and histopathological diagnoses that represent transcriptional activation of distinct biological pathways associated with disease progression rates [53]. A 25-protein urine proteomics signature captured this information. Whether it could inform on kidney aging should be explored.

There is preclinical and clinical evidence that slowing biological kidney aging may be possible. In mice, early RAS inhibition, from weaning, increased the number of nephrons in old age 3 to 4-fold [54]. RAS inhibitors are the mainstay of treatment for Alport syndrome, a condition in which persistence of foetal type IV collagen leads to accelerated aging of the glomerular

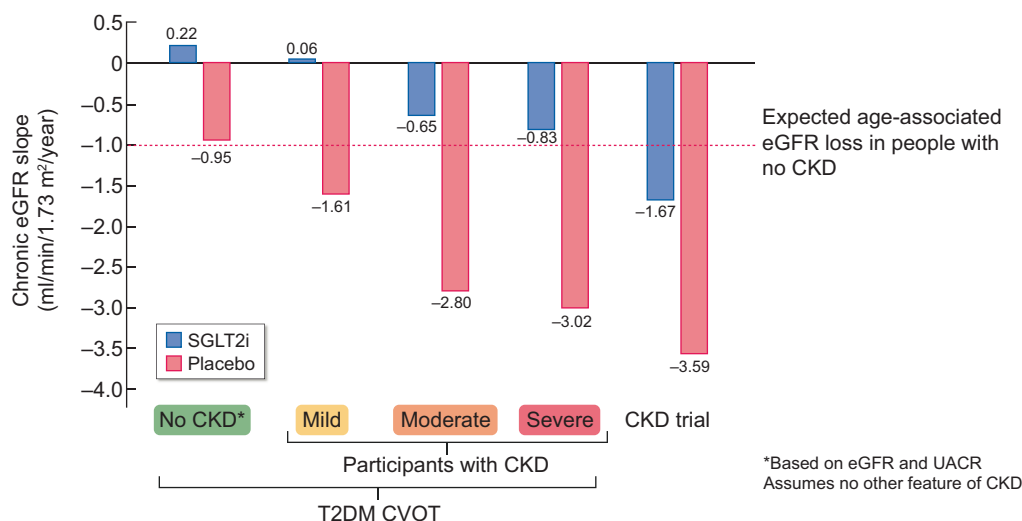


Figure 7: Median chronic eGFR slopes in SGLT2 inhibitor cardiovascular outcomes trials (CVOTs) and CKD phase 3 trials. The figure summarizes data from CVOTs (which enrolled participants with type 2 diabetes mellitus plus high CVD risk: CANVAS, DECLARE-TIMI 58, EMPA-REG Outcome) and CKD trials (CREDENCE, DAPA-CKD, EMPA-KIDNEY) testing canagliflozin, dapagliflozin and empagliflozin. Mild, moderate and severe CKD categorization is based on European Society of Cardiology terminology for KDIGO risk categories of moderate, high and very high risk. The reason for using this simplified nomenclature is that it may facilitate implementation by non-nephrologists. CANVAS enrolled 5876 (57.9%) participants with no CKD, DECLARE-TIMI 58 enrolled 10 958 (63.8%) participants with no CKD (as defined by GFR and albuminuria categories) and EMPA-REG Outcome enrolled 3322 (47.8%) participants with no CKD for a total of 20 156 participants with no CKD between the three trials.

basement membrane through increased susceptibility to endo-proteolysis [55, 56]. In clinical trials, treatment with SGLT2 inhibitors resulted in chronic stable eGFR slopes in low-risk groups (e.g. albuminuria category A1 with eGFR category G1–G4). Participants in these categories who received placebo had decreased eGFRs at the expected rate of 0.9–1.0 ml/min/1.73 m²/year, which is not different from the age-associated decreases in eGFR and concordant with their low risk of progression or absence of CKD [57–62] (Fig. 7). These data fit the hypothesis that the age-associated loss of eGFR can be slowed down or even stopped, at least for 2–3 years, in people without CKD or with a low risk of CKD progression. It can be hypothesized from these data that SGLT2 inhibitors may function as an antiaging therapy in these populations and probably beyond. Although less well-characterized, GLP-1 receptor agonists are also promising for the prevention of CKD, especially in individuals with type 2 diabetes mellitus or overweight/obesity [63].

Therapy for CKD can address the primary cause of CKD and/or a common pathway (Fig. 8). Given the accumulating evidence of shared pathogenic pathways between diverse causes of CKD and biological kidney aging, we propose that the aging concept should be incorporated into the common pathway. Drugs targeting it should be labelled as kidney age-delaying therapy (KADT), kidney gerosuppressor therapy (KiGST) or a similar term that points to the role of shared aging pathways by age-associated cardiovascular, kidney and potentially other organ conditions.

CKD management in the elderly

Case identification programs for early detection of CKD should be offered for those >60 years of age [41] in addition to other high-risk individuals. Case identification should rely on both eGFR and UACR. Sarcopenia is common in the elderly and may result in overestimated creatinine-based eGFR and mask a low eGFR. This may underlie the 3-fold increased risk of death in older normoalbuminuric people with eGFR >105 ml/min/1.73 m² [48] as well as the high risk of persons with the so-called glomerular hypofiltration syndrome [64].

Cystatin-based eGFR may better estimate risk when sarcopenia is suspected.

New-generation kidney-protective medications can be started to delay CKD progression and associated cardiovascular consequences. Such programs would be integrated into individualized care plans with a multidisciplinary approach to manage multimorbidity, frailty, polypharmacy, high rates of adverse outcomes, mental health, fatigue and other age-related symptoms. Additionally, some causes of CKD are more frequent in the elderly, such as amyloidosis, monoclonal gammopathies, obstructive uropathy, paraneoplastic syndromes and vasculitis.

Treatment strategies for older patients with CKD should align with those applied to the general population, minimizing cardiovascular events and reducing the risk of progression to kidney failure. Newer therapeutic agents, such as SGLT2 inhibitors, non-steroidal MRAs and GLP-1 receptor agonists, are promising for the effective management of CKD in older and even frail individuals [65]. The mean age of participants in pivotal trials was >60–67 years and 16% were >74–78 years of age, the range representing different trials [27, 61, 66].

Non-pharmacological interventions such as nutritional and exercise therapies should also be emphasized. These interventions enhance the effects of pharmacotherapy and, importantly, contribute to the maintenance of cognitive function and overall quality of life [67].

Kidney failure management in the elderly

All treatment options, including KRT (dialysis or transplantation) and conservative management approaches, should be discussed with older patients with kidney failure and tailored to the individual through patient-centred decision-making [67]. Various factors beyond age, frailty and cognitive function must be considered when deciding on KRT.

The acceptance of KRT in the elderly varies across countries (Fig. 5A and B) [68]. People ≥75 years of age represent 43% of men and 51% of women starting KRT in Japan [69, 70] (Fig. 9A),

Conceptual framework: interaction of kidney aging and other causes of CKD

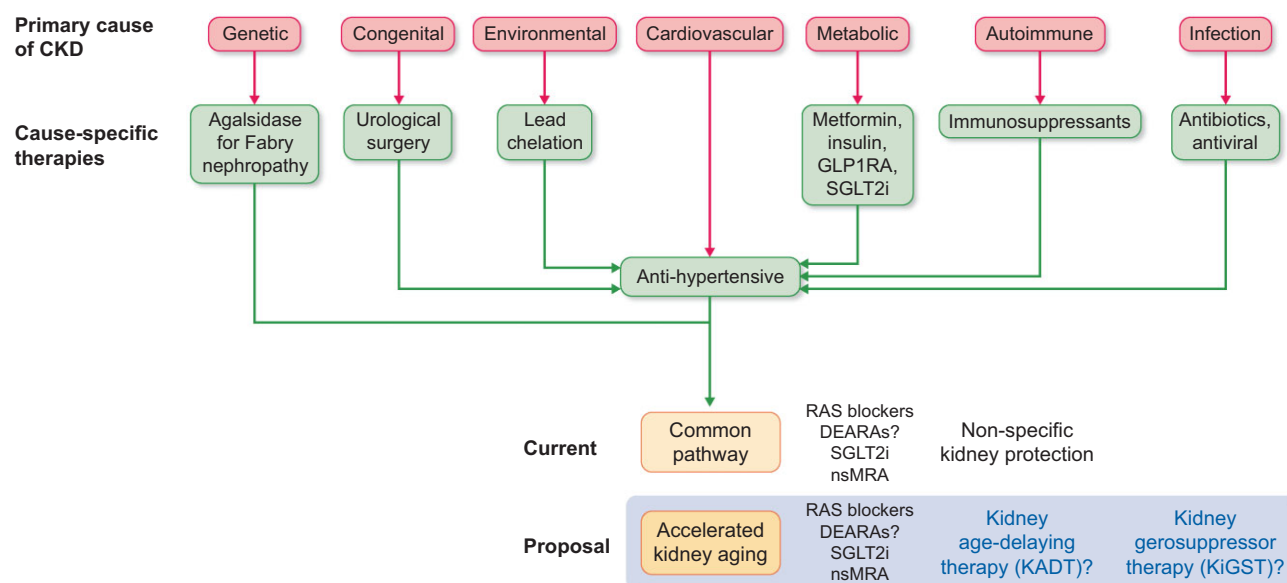


Figure 8: Conceptual framework for the interaction between kidney aging and other causes of CKD. An interaction is expected between kidney aging and other causes of CKD, since the latter most frequently occur in the elderly. In this regard, only a minority of persons with type 2 diabetes mellitus develop CKD and the prevalence of CKD in people with type 2 diabetes mellitus increases with age. We propose to conceptualize therapy into therapy aimed at the primary cause of CKD and therapy aimed at a common pathway shared by multiple causes of CKD, sometimes referred to as non-specific therapy for CKD. Given the evidence for wider target organ protection by kidney protective therapies developed so far, the evidence for common pathways of tissue injury between organs and between specific kidney conditions and accelerated aging and that gerosuppressor effects of drugs such as SGLT2 inhibitors have been described, we propose to refer to this therapy as KADT, KiGST or similar terms.

27% of men and women starting KRT in Europe (Fig. 9B) and even less in some European countries (e.g. 15% in Scotland, where the incidence per million persons is equally low) (Fig. 5A, B) [42].

In Japan, the average age at incident KRT (mostly dialysis) has increased since 1983 and was 70.9 years in 2020 [69, 70]. In contrast, in Europe it has been stable over the past 15 years (≈ 66 years) (Fig. 9C, Supplementary Fig. S1) and is heterogeneous between countries. The mean age at the start of KRT ranged from 59.3 to 72 years in 2022 among countries and territories with an incidence >100 persons/year [42]. In 17 countries and territories it was >1 year older than in 2012, but in 7 it was >1 year younger, including Aragon, Denmark, the four UK countries and The Netherlands, with the largest decrease observed for Northern Ireland and Wales (3.5 and 3.1 years younger in 2022, respectively), likely reflecting evolving attitudes towards KRT in the healthcare system and/or the population [42, 71, 72].

Lower residual kidney function during the first 2 years of haemodialysis is associated with an increased risk of death for up to 50 months following the initiation of dialysis [73]. This adds to a growing body of evidence that interventions to preserve residual kidney function in these patients should be tested in clinical trials [73], following the lead of peritoneal dialysis, for which kidney-protective drugs delayed the decrease in GFR [74]. Maintenance of residual kidney function may facilitate home dialysis or incremental dialysis in the elderly as well as preservation of additional kidney functions, such as the synthesis of gerosuppressors (e.g. Klotho).

In addition to KRT, comprehensive conservative kidney failure management should be offered as a viable option during the

shared decision-making process to collaboratively determine a treatment approach that respects the values and wishes of the patient while explicitly informing that this approach will likely decrease life expectancy, a key preferred outcome for people >65 years of age [72], and avoiding 'god panels' [75]. Issues surrounding conservative therapy (instead of KRT) for the elderly with advanced CKD include the need for adequate resources, including multidisciplinary teams with both nephrology and palliative care skills, the lack of evidence regarding the different models of conservative care and gaps in cultural and ethical/legal aspects [76, 77].

Interventions that maintain or improve quality of life, including pain management and palliative care services when appropriate, should be offered for both patients on KRT and on conservative care [36].

Kidney rejuvenation

Chronological kidney age is not modifiable, but biological kidney age is. Rejuvenation interventions have been proposed to delay aging and the onset of age-associated decline and disease to extend lifespan and health [78, 79]. They include metabolic manipulation, heterochronic parabiosis, pharmaceutical administration and senescent cell ablation. Partial reprogramming by the Yamanaka factors (Oct4, Sox2, Klf4 and cMyc) *in vivo* can erase the epigenetic markers that have accumulated over time and lead to an aging phenotype. This may restore cell health and resilience of the kidney through cellular rejuvenation programming to reverse disease, injury and associated disabilities [80]. The kidneys offer a unique opportunity for first-in-human rejuvenating strategies, given the increasing age of cadaveric

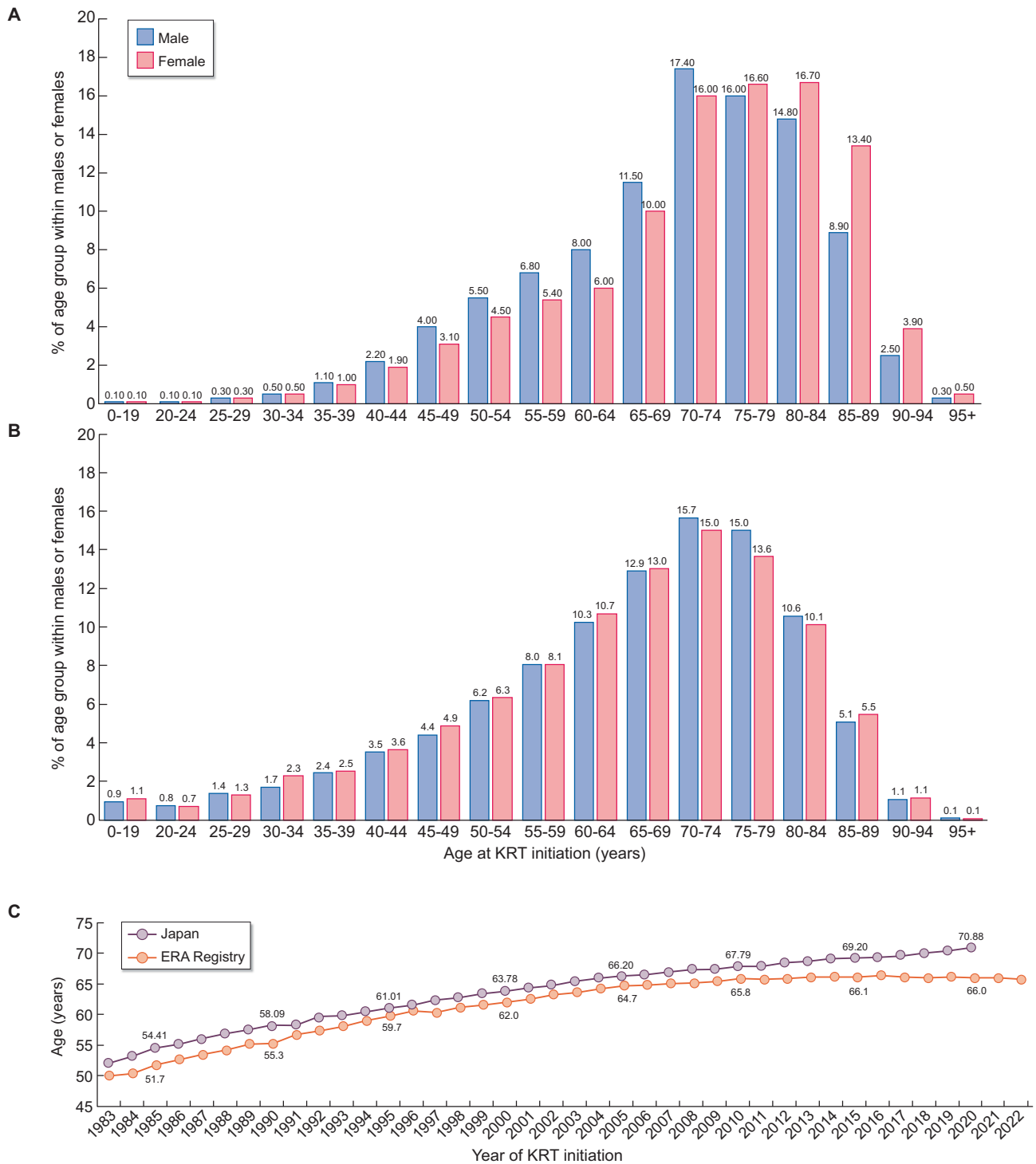


Figure 9: Trend in average age at incident KRT and age distribution by sex in Japan and Europe. Age distribution at incident KRT by sex in **(A)** 2020 in Japan [69, 70] and **(B)** 2022 in the ERA Registry [42]. Note that KRT data in Japan correspond to dialysis. Pre-emptive transplantation represents $\approx 1\%$ of incident KRT patients. **Supplementary Fig. S1A** displays an overlay of both sets of data. **(C)** Trend in average age at incident KRT in Japan and in the ERA Registry. Japanese data refer to the dialysis modality of KRT [69, 70]. ERA Registry data correspond to all data available and is in line with those of the six countries that provided data for the full period, shown in **Supplementary Fig. S1B**.

kidney donors and the opportunity for *ex vivo* perfusion before kidney transplantation. This would help address the organ shortage by potentially rescuing kidneys now considered too old to be transplanted [81].

CALL TO ACTION

On 15 September 2024, based on the above considerations, the ERA and JSN agreed on a call to action to address the growing burden of kidney disease in the elderly and aging societies (box). Overall,

we feel that more should be done to promote the prevention and early diagnosis (and treatment) of CKD.

Box JSN and ERA call to action: Achieving Kidney Health in Aging/Aged Societies

- Encourage comprehensive data collection on kidney disease in the aging/aged population.
- Define kidney health in the elderly.
- Elucidate the mechanisms of kidney aging and accumulate knowledge on therapeutic options.
- Establish treatment goals and recommend appropriate therapeutic options for kidney disease in the elderly.
- Publish future recommendations for research on kidney disease in the elderly.
- Provide guidance for the at-risk elderly for prevention of CKD.

SUPPLEMENTARY DATA

Supplementary data are available at [Nephrology Dialysis Transplantation Journal](#) online.

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Fig. 2A was drawn by Tatiana Melissa Naranjo Castaño.

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AUTHORS' CONTRIBUTIONS

A.O. wrote the draft. All authors contributed key intellectual content and approved the final version.

DATA AVAILABILITY STATEMENT

All data are available in the articles and its supplementary material.

CONFLICT OF INTEREST STATEMENT

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