FIGHTING THE UNBEARABLE LIGHTNESS OF NEGLECTING KIDNEY HEALTH: THE DECADE OF THE KIDNEY*

**The "Decade of the Kidney™" is a global initiative of the American Association of Kidney Patients (AAKP), launched in 2019.*

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ABSTRACT

A brief comprehensive overview is provided of the elements constituting the burden of kidney disease (chronic kidney disease and acute kidney injury) . This publication can be used for advocacy emphasizing the importance and urgency of reducing this heavy and rapidly growing burden. Kidney diseases contribute to significant physical limitations, loss of quality of life, emotional and cognitive disorders, social isolation and premature death. Chronic kidney disease affects close to 100 million Europeans with 300 million being at risk, and is projected to become the fifth cause of worldwide death by 2040. Kidney disease also imposes financial burdens given the costs of accessing health care and inability to work. The extrapolated annual cost of all chronic kidney disease is at least as high as that for cancer or diabetes. In addition, dialysis treatment of kidney diseases imposes environmental burdens by necessitating high energy and water consumption and producing plastic waste. Acute kidney injury is associated with further increases of global morbidity, mortality and economic burden. Yet, investment in research for treatment of kidney disease lags behind that of other diseases. This publication is a call for European investment in research for kidney health. The innovations generated should mirror the successful EU actions against cancer over the last 30 years. It is also a plea to nephrology professionals, patients and their families, caregivers, and kidney health advocacy organizations, to draw during the Decade of the Kidney (2020-2030) the attention of authorities to realize changes in understanding, research and treatment of kidney disease.

Keywords: acute kidney injury, chronic kidney disease, dialysis, epidemiology, environment, health economy, kidney transplantation, mortality, non-communicable diseases, peritoneal dialysis

INTRODUCTION

The social and psychological impact of chronic kidney disease is seriously underestimated. The disease and its human and financial burdens are unknown to many, mainly due to unawareness, the intangible nature of how the kidneys function, and the difficulty of capturing public attention. Recently, a Belgian Member of the European Parliament, Hilde Vautmans, appropriately called chronic kidney disease "the most neglected common chronic disease"[1].

Chronic kidney disease mostly develops slowly without initial symptoms, and becomes progressively more debilitating at later stages, with little chances for reversal. In the most advanced stages (kidney failure; previously known as end-stage kidney disease), kidney replacement therapy (dialysis or transplantation) is the usual approach to support quality of life and keep the individual alive. Patients can also opt for comprehensive conservative care, assuring their quality of life but without kidney replacement. Kidney function can also suddenly decline (acute kidney injury)[2,3], which is strongly interconnected with chronic kidney disease. Patients with chronic kidney disease are more prone to develop acute kidney injury than the general population. Acute kidney injury in turn can worsen the course of chronic kidney disease or become the reason of subsequent incident chronic kidney disease[4].

This position paper is a call to action prepared by the European Kidney Health Alliance (EKHA), a non-governmental organization advocating for kidney patients at the level of the European Union (EU) and members state healthcare systems[5], and several other stakeholders including patients (see acknowledgements). The aim is to draw the attention of the authorities and the public to the urgent need to reduce the collective burden of kidney disease. In contrast to other fields in medicine, such as cardiology and oncology, limited progress has been made with respect to developing novel therapeutics for kidney disease in the last 3 decades. This inertia must urgently be overcome to generate overdue and long-awaited progress.

This call to action provides data to inform policy makers, administrators, regulators and payers. Media and society press, in parallel, can use this text to inform about the multiple burdens associated with kidney disease and the urgent need to acknowledge and address

these. However, education is not sufficient and should be coupled, first with prioritization of diagnosis, and, second, with streamlining of care trajectories through a collaborative effort between authorities and stakeholders. Where appropriate, we will make comparisons with other major health advocacy domains, to emphasize the need for gearing up financial and intellectual investment in kidney health.

A devastating disease

Individuals with chronic kidney disease suffer from countless limitations and symptoms which progressively impact their physical, mental and social functioning (video track with patient testimonies in[6]). Current dialysis and transplant options were rarely developed with a primary focus on the needs and preferences of patients and their care providers.

While kidney disease may have no specific symptoms in a number of patients (especially at early stages), it contributes to many challenges in others (table 1). Most of these, e.g. fatigue, sleep disorders and itching, are not fatal but they worsen progressively and heavily impact global functioning. Comfort is only rarely restored with treatment. Associated complications like cardiovascular disease and infection[7,8] trigger multiple hospitalizations and surgical interventions, not exceptionally twenty or more per disease course of one patient. Many patients must take more than 15-20 pills every day[9,10]. Physical appearance is negatively impacted by scars in the extremities and abdomen from vascular or peritoneal accesses for dialysis treatment. Immunosuppression following transplantation causes hair loss, gum hypertrophy and weight gain. Uncertainty about the future of their dialysis access or kidney graft, as well as restrictions of mobility and social life facilitate development of depression. Pain is common, due to complications (bone fractures, nerve lesions, gangrene, infections) but also to therapy (surgery, transcutaneous puncture every other day for hemodialysis access). Hemodialysis is frequently associated with hypotension, muscle cramps, thirst, anemia, mental changes, headache, vomiting and feeling drained; peritoneal dialysis with loss of appetite but nevertheless weight gain; in transplantation, immunosuppression causes muscle weakness, hirsutism, gout, tremors and mood swings. Hemodialysis also necessitates a number of time consuming treatments per week for several hours, with additional loss of time due to transport to and from in-center treatment.

Children and adolescents with kidney disease encounter growth retardation, and limitations in mobility and social and educational development which hamper psychological development. This may be worsened by time spent on dialysis which mostly takes place in the midst of adult fellow patients[11]. Among older patients, frailty and muscle wasting (sarcopenia) are common[12].

Unemployment is frequent among adults with chronic diseases. For individuals with advanced chronic kidney disease and those living with dialysis or transplants, who frequently suffer from several simultaneous comorbidities, unemployment rates of up to 75% have been reported[13-15]. This situation not only affects buying power but also lifestyle, self-image and mental health.

In summary, chronic kidney disease causes major and largely underestimated distress, which often resists to treatment, affects all age strata, modifies physical and emotional quality of life and limits socio-economic possibilities.

Far more frequent than assumed

Most lay people without direct exposure assume that kidney disease is limited to dialysis and transplantation. In fact, however, this group only constitutes the tip of the iceberg. The approximate ratio of individuals with chronic kidney disease not yet requiring dialysis or transplantation compared to those receiving dialysis or transplanted, is greater than 100 to 1 [16]. This ratio is higher in countries where access to dialysis or transplantation is limited by reliance on out of pocket payments, which restricts access for most who need it. In addition, chronic kidney disease is not a stand-alone condition but is part of a cluster of non-communicable and communicable diseases (figure 1), which during their evolution are frequently complicated by or further complicate kidney disease[17]. The most well-known causes of chronic kidney disease are hypertension, cardio-vascular disease and diabetes, but cancer, liver and auto-immune diseases as well as various infections and pre-eclampsia are also linked to chronic kidney disease. People living with chronic diseases represent one third of the European adult population and contribute to a large majority of annual European fatalities[18]. People surviving long enough with chronic disease have an increasing risk of developing either chronic kidney disease or acute kidney injury.

Chronic kidney disease is estimated to affect 700 to 850 million people worldwide, exceeding diabetes, chronic obstructive pulmonary disease and depression[16,19,20]. The 2017 Global Burden of Disease Study estimated prevalence of chronic kidney disease around 100 million Europeans with chronic kidney disease (among them 55.7 million people in EU-28 countries)[16]. In accordance to this, the Global Kidney Health Atlas of the International Society of Nephrology indicated its prevalence at 10.1% for Western Europe (equaling the global average), and 13.3% for Central and Eastern Europe[21]. However, although screening can easily be accomplished by two simple tests (serum creatinine and urinary albumin), a large majority of those affected remain unaware of their condition[22-24], also precluding prevention of progression and complications which is far more cost-effective than treating more advanced stages. In addition, even in presence of objectivated pathological parameters conform with chronic kidney disease (decreased kidney filtration or increased urinary albumin) , the condition id often overlooked by or underestimated by treating physicians.

The number of individuals with chronic kidney disease will continue to rise, mainly because of ageing of the population, but also due to intrinsic and not yet well-defined factors. With age, the incidence and prevalence of chronic kidney disease increase exponentially[25,26], which is mirrored by the year-by-year increase of age in the dialysis population[27]. Also the risk of acute kidney injury increases with age and frailty, and older patients surviving acute kidney injury show a higher risk for progression to chronic kidney disease and often require maintenance dialysis in subsequent months or years[28]. Next to ageing, also nutrition, unhealthy lifestyles and environmental factors contribute[29,30]

The numbers will further increase as advances in health care of underlying diseases successfully prolong survival and longevity thereby allowing chronic kidney disease to manifest. Some new therapies e.g. immunotherapy for cancer or cardiac interventions also carry inherent risks of kidney injury[31,32]. Increasing availability of kidney replacement therapy in lower income countries, will further increase the global population of people living with kidney failure, although these populations in lower income countries tend to be 1 or 2 decades younger than their European counterparts[33].

Briefly, a large section of the general population is at risk of chronic kidney disease. However, the large majority of both lay and medical population is unaware of this risk.

Participation in screening, prevention and early treatment is inadequate and should urgently be improved, especially in high-risk populations.

A killer disease

Worldwide, chronic kidney disease mortality for 2017 was estimated by the Global Burden of Disease Study at 1.2 million (more than HIV and tuberculosis and equal to traffic accidents) and a further 1.4 million deaths from cardiovascular disease, were attributed to reduced kidney function[16]. Annual mortality of chronic kidney disease in Europe is estimated at close to 130,000 [16]. Kidney disease rose to become the 10th leading global cause of death in 2019, and the 8th leading cause of death in high-income countries[34], and, concerningly, is projected to become the fifth leading cause of death by 2040, above all cancer types, Alzheimer, diabetes, HIV and tuberculosis[35]. Over the last 20 years mortality from chronic kidney disease has not improved, in contrast to most other chronic diseases[16]. The rise in chronic kidney disease as a cause of death may reflect the rising prevalence of chronic kidney disease globally related to population aging as well as improving access to diagnosis in lower income settings, but worryingly may also reflect the relative lack of progress in innovation which is holding kidney disease back compared with other chronic diseases.

Increased mortality is not limited to advanced chronic kidney disease but starts rising progressively when kidney filtration function falls below 50% of normal but also with normal filtration in the presence of albuminutia[7,36]. Additionally, presence of chronic kidney disease further increases mortality risk associated with other diseases like cardio-vascular disease or diabetes[37]. Premature death for most individuals with chronic kidney disease not yet in need of dialysis or transplantation is mainly due to high-risk comorbidities (cardio-vascular disease, cancer and infectious disease)[7,8,38,39]. Those reaching kidney replacement therapy, especially people living on dialysis, have similar or even worse survival chances than most people diagnosed with cancer[40,41] (figure 2). Compared to mortality rates of frequent malignancies, 5-year mortality of hemodialysis patients is only exceeded by 5-year mortality of pancreas and lung cancer. Mortality from kidney failure also exceeds that of acute myocardial infarction, diabetes, chronic heart failure, and stroke[41]. Expected remaining lifetime for advanced chronic kidney disease vs. the general population is more than halved across all age strata[41]. For 20 to 24-year-old dialysis patients, life expectancy is decreased by

approximately 70% (~ 40 years), not a surprise if one considers that dialysis replaces only a small fraction of the normal function of the kidneys. For individuals of the same age with a kidney graft the approximate reduction in life expectancy is by 25% (~15 years less)[42].

Briefly, an unacceptably high number of individuals die because of chronic kidney disease , and their survival chances are far below those of people without kidney failure, and comparable to or worse than people with other chronic diseases. These estimates do not include the burden of acute kidney injury, which in Europe alone is associated with an overall in-hospital mortality of more than 23%[43]. In the setting of intensive care, mortality from acute kidney injury ranges up to 65%[44], depending on its severity[45], and evolves into chronic kidney disease in about one third of its survivors[4].

These data corroborate the ominous impact of kidney disease on the lives of affected patients. More importantly, this negative effect is continuing to worsen over time.

Chronic kidney disease burden in the EU

Chronic kidney disease affected more than 55 million people living in the EU and caused almost 130,000 deaths only in 2019 (table 2). In addition, prevalence was similar to that of most other types of chronic disease including diabetes, cancer and cardiovascular disease (figure 3, panel A). Considering age-standardized rates over 29 years, that take into account changes in both age and population structure, mortality of chronic kidney disease has increased in contrast to a large array of other communicable and non-communicable diseases (figure 3, panel B). Importantly these data do not include acute kidney injury which contributes additional mortality.

Expensive to treat

Kidney replacement therapy (dialysis or transplantation) comes at a high societal cost and the share of global healthcare cost spent on kidney replacement therapy is proportionally 10-20 times higher than the number of patients treated[46]. Costs will rise further due to the projected growth in patient numbers[47].

The most used kidney replacement option, in-center hemodialysis, engenders the highest costs per patient[48] and in Europe, yearly reimbursement per country reaches up to 80,000

€/patient[49,50]. Although in countries with a lower gross domestic product (GDP), dialysis consumes less in absolute amounts, a larger percentage of general health care budget is spent[50], likely at the expense of other, more cost-effective health investments like screening and prevention[51]. Kidney transplantation is manifestly more cost-effective than dialysis at least in high-income countries[52], but not everybody is an eligible transplant candidate, and the transplantation rate is lagging behind in several European countries[53]. Costs of home dialysis (peritoneal dialysis and home hemodialysis) are intermediate between in-center hemodialysis and kidney transplantation but these options are also underexploited in Europe[54], in spite of patient preference[55,56] and better quality of life[57]. Many European countries even offer no specific financial regulations for home hemodialysis[50].

Individuals with chronic kidney disease who are not on dialysis or living with a functioning kidney transplant also represent a substantial source of expenditures, which largely is related to their higher number[58,59]. Costs per patient increase as chronic kidney disease becomes more severe[60,61]. Chronic kidney disease independently augments cost of many other chronic diseases by a factor of 2 or more[37,62].

Finding data of aggregated cost for comparisons with other diseases is extremely difficult. Whereas aggregated costs in Europe are available for cancer and diabetes mellitus[63,64], a similar assessment for chronic kidney disease necessitates extrapolation of data from several studies, taking into account costs of dialysis, transplantation, chronic kidney disease that is not dialyzed or transplanted, and indirect costs (hospitalization, primary care, mental care, transport etc.)[50,53,58,65-68] (supplemental data). Adding these up, overall costs for chronic kidney disease are at least in the same range if not higher as those for cancer and diabetes (figure 4). Inclusion of costs related to acute kidney injury would further substantially increase these estimated costs[69,70]. These data do also not include costs of productivity loss due to premature death, sick leave and unemployment and indirect costs due to services provided by family and friends.

Transnational health-economic assessments based on different studies from different countries, that were necessary for the current comparison, might be skewed due to differences in population, environment, definitions and timing. However, a German study[59] enables a comparison between expenditure for chronic kidney disease and that for cancer

on a single-country basis [63]. Here also, both expenditures were similar (25.5 billion € per year for cancer vs. 24.2 for chronic kidney disease), although the study did not include early chronic kidney disease stages and transplantation. These data thus corroborate our findings.

It is thus fair to assume that costs for kidney care are at least in the same range as those for cancer or diabetes. Unfortunately, aggregated European data for chronic kidney disease healthcare costs are lacking. Therefore, the creation of a registry of individual incidence and prevalence data for dialysis and transplantation covering all EU countries, also tracking costs and quality of care are needed. In addition, a comprehensive tracking system of prevalence of not dialyzed or transplanted chronic kidney disease and associated costs is desirable, especially for the later stages.

These costs could be reduced by promoting prevention and less costly therapeutic strategies (generic drugs, home dialysis), and reimbursement systems for real costs but also by pursuing more fair and transparent price setting of drugs and technical equipment.

Gaps in delivery of kidney care across Europe

The International Society of Nephrology (ISN) survey on country-level capacity for kidney care services was published in 2017 and 2019 as the first and second edition of the Global Kidney Health Atlas (ISN-GKHA)[71,72]. The Atlas highlighted significant barriers regarding delivery of optimal kidney care across countries and regions. Europe as a continent generally performed better than other parts of the world. However, there was a significant variability in workforce distribution (figure 5, supplemental figures 1 and 2) and other essential services, in particular significant limitations in surveillance systems and advocacy tools for both acute kidney injury and chronic kidney disease (figure 5). In addition, significant gaps were noted in the ability to fund services for patients with chronic kidney disease and provision of dialysis and transplantation, especially in Central and Eastern Europe (supplemental figures 3 and 4). Equitable funding services are pivotal to reduce the major health consequences of kidney disease.

An environmental challenge

All treatments for chronic kidney disease leave a considerable CO_2 footprint and cause substantial pollution due to frequent therapeutic interventions, hospitalizations, use of consumables, intake of large numbers of drugs requiring energy for production, and transport of goods and people. In addition, dialysis generates lots of plastic waste[73,74] and consumes enormous amounts of water, corresponding to more than 169 billion liters per year worldwide. Only 35% of water consumption is used for dialysis *per se* whereas 65% is reverse osmosis reject water that goes directly to the drain despite being perfectly drinkable[73].

Climate changes in turn impact kidney health, by promoting risk factors for acute kidney injury [dehydration due to drought and heatwaves, infectious and parasitic diseases after floods (leptospirosis, dysentery, malaria), extension of the spreading areas of tropical diseases (dengue, malaria)], and problems with interruption of dialysis, as storms, floods and hurricanes gain in frequency and severity[75].

Thus, the ecologic burden of kidney disease is substantial while disturbed ecology in turn threatens kidney health. All of these aspects are in urgent need of solutions.

The COVID-19 crisis: stressing the need to focus on kidney disease

The current COVID-19 pandemic is emblematic of the failure or at least delay in global recognition of the importance of kidney disease[76]. Initially, COVID-19 was seen as a pulmonary and infectious problem, while other chronic diseases remained under the radar for some time. The initial other conditions which came into focus as risk factors for severe disease were cardiovascular disease, diabetes and hypertension[77,78], all of which are prime causes of chronic kidney disease. The recognition that kidney disease (acute and chronic) is a leading risk factor for death came later. Ultimately, it appears that the population with chronic kidney disease, especially those living with dialysis or transplants, are among the highest risk groups for hospitalization and mortality[79-83]. Large scale European data only became available late after the end of the first wave, explaining why for early data Europe had to rely on the US Centers of Disease Control (CDC)[84] and China[77], as the CDC of the EU (ECDC) do not report on chronic diseases.

In view of the frequent cytokine storm in critically ill COVID-19 patients[85], a substantial number of acute kidney injury cases were to be expected, but insight into the real epidemiology and the negative prognostic impact of acute kidney injury lagged behind, with again the first data coming from outside Europe[86,87]. The world was scaling up access to ventilators and developing triage guidelines for access to intensive care, but remained unprepared for the rapid demand for acute dialysis facilities[88].

In addition, a large number of significantly invalidating problems affecting the patients with kidney disease often went unnoticed outside nephrology circles: 1) decreased transplantation rates from both deceased and living donors, due to a necessary focus shift of ICUs to COVID-care or with the intent to decrease infectious risk[89,90], increased the risk of transplant candidates dying on the waiting list; 2) shortage of dialysis supplies and protective material[88]; 3) postponement of arterio-venous fistula creation and peritoneal dialysis catheter insertions as non-essential interventions[91]; 4) severe COVID-19 outbreaks in the closed communities of in-center hemodialysis units[92], while patients on home dialysis were relatively protected[93]; and 5) heavy workload and infection risk for personnel in nephrology units with the potential of causing burn-out[94].

An additional difficulty was created by the almost systematic exclusion of patients with chronic kidney disease from trials of drug therapies and vaccinations for COVID-19, forcing the nephrology community into off-label use, while remaining in the dark about therapeutic efficacy[82,95,96]. This is illustrative of a more global concern as individuals with chronic kidney disease are in general excluded from clinical studies. This is likely one of the reasons for the disappointing progress in fighting chronic kidney disease. The COVID-19 vaccine being almost exclusively available in higher income settings is also a matter of major concern[97].

Briefly, the population with kidney disease was one of the most heavily affected risk groups by COVID-19, but the identification of this risk was delayed, partly due to insufficient awareness, attention and data capture.

Low investment in innovation

In view of the high burden of kidney disease and the paradoxical low investment in innovation[98], a common effort to find novel solutions is a primary need for all concerned.

However, the basic concept of hemodialysis has surprisingly barely changed since the original prototype developed by Willem (Pim) Kolff in 1942. Likewise, all other kidney replacement options, as well as the pharmacological approaches to delay progression to kidney failure, have not progressed at the same pace as those for diseases like cancer, HIV, cardio-vascular disease or diabetes. The advent of sodium-glucose transporter-2 (SGLT2) inhibitors has been the first innovation to delay progression of chronic kidney disease in decades[99,100], but many other therapies to modulate kidney function remain insufficiently explored.

It would be interesting to compare the EU efforts through research programs like Horizon 2020 or Horizon Europe which address kidney health as primary target to those addressing other diseases. Concerningly, kidney health does not even figure in the list of priority areas for EU health research and innovation[101] (supplemental table). Indirect information offers reason for concern. In response to an editorial stressing the importance of research investment in accordance to patient needs[102], global investment in HIV was more than 30 times higher than that for chronic diseases (including chronic kidney disease), despite the huge contrast in disability adjusted life years lost which were almost 20 times lower for HIV[103]. A UK analysis comparing research expenditure for cancer, coronary heart disease, Alzheimer and stroke versus their cost, showed a marked discrepancy, with more support for cancer compared to the other disorders[104]. According to the US National Institute of Health (NIH), despite much recent efforts (see below), kidney health still receives less research support than many other disorders[105]. It is clear that we do not suggest that there should be less investment in other diseases than chronic kidney disease, but we are convinced that more investment in chronic kidney disease is urgent.

In conclusion, in the case of kidney disease there is an imperative need to match cost and burden of disease to research and innovation investment. We also stress the need for transparency in European research funding allocation to allow comparison of investment in different diseases. In view of the current budgetary constraints, we also advocate that if therapies are the result of publicly funded research and innovation, those should not incur unreasonable societal costs or be bought and shelved[98]. Between 2005 and 2018, costs for oncologic drugs more than tripled[63], although the price does not appear to be related to clinical benefit[106]. Especially the skyrocketing price of orphan drugs, has recently been a

major matter of concern[107]. More transparency and consistency of oversight is required to achieve fair pricing and equitable access to innovative therapies[108].

Need for a change of paradigm

The most pressing actions required and the most alarming facts about kidney disease are summarized in table 3. All stakeholders (organizations, patients and professionals) should intensify advocacy about the urgent need to reduce the burden of kidney disease among broad layers of society, including administrators, regulators, policy makers, health care workers and the general population. Patients play a critical role by communicating their difficulties, distress and concerns and by defending their case.

In addition, in view of the staggering inertia in developing new therapeutic options for kidney disease (chronic and acute), we plead for a conceptual change in the paradigms regarding kidney therapies and research. The EU has a unique opportunity to play a leading and structuring role, motivating harmonized approaches among the member states. This approach is the only way to avoid complete dependency on other continents when it comes to therapeutic innovations.

In the US, joint action between the American Association of Kidney Patients (AAKP), the authorities and the nephrology professionals culminated in the Kidney Health Initiative (KHI), a public-private partnership to stimulate innovative drug and device development for kidney health.[47,109] One of the outcomes was the signing in July 2019 of an executive order to fundamentally change clinical kidney care[110], and also the call for innovation by the American Association for Kidney Patients (AAKP) during a "Decade of the Kidney™"[111].

Kidney disease and especially dialysis and transplantation have, next to health, important implications for economy, safety, ecology, education, research and innovation, which all are important EU competences[112]. Kidney health is linked to all EU-supported Sustainable Development Goals (SDGs) of the World Health Organization[113-115]. Consistent with the aims of the SDGs, the EU and the nephrology community have a responsibility to make people's lives better. We advocate that the European Commission and Parliament and the EU member states take a leading role in fighting kidney disease, mirroring the successful EU achievements over the last 30 years in cancer[116], especially because of the many parallels

between both conditions, as illustrated in this text. Unfortunate as it is, COVID-19 may serve as an eye-opener that a change of paradigm is needed.

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- Dutch Kidney Foundation (DKF) (TO)
- International Society of Nephrology (ISN) (AB, VL)

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CONFLICT OF INTEREST STATEMENT

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Table 1. Most important problems perceived by individuals with chronic kidney disease

Health-related quality of life (HRQOL)

- Frequent hospitalization and surgery
- Polypharmacy
- Physical appearance
- Uncertainty about future
- Time consuming therapies
- Immune deficiency
- Anemia

Functional

- Depression
- Anxiety
- Thirst
- Cognitive and physical dysfunction
- Frustration
- Restrained mobility
- Disturbed social life
- Burden to others
- Sexual dysfunction
- Frailty and sarcopenia
- Insomnia / Sleeplessness

Symptoms

- Pain
- Fatigue
- Sensory disturbances
- Lack of energy
- Muscle weakness
- Cramps
- Loss of appetite
- Taste and sleep disturbances
- Pruritus (itching)
- Restless legs
- Symptoms related to dialysis or transplantation

Health behavior & perception

- Social exclusion
- Dietary restraints and fluid intake restriction
- Incapacity for sport
- Transportation problems
- Limited travel possibilities
- Concerns about treatment unit (cleanliness, communication, quality of care)
- Unemployment, missed school
- Therapeutic costs

Table 2. Principal metrics of chronic kidney disease burden in the EU

Metric	2019 values		Change between 1990 and 2019, %	
	Number	Rate, per 100,000 population	in all-ages rate	in age-standardized rate
Prevalence	55,660,588 (52,242,530 to 59,161,862)	10,814.2 (10,150.1 to 11,494.4)	42.0 (39.3 to 44.8)	4.7 (3.5 to 6.0)
Mortality	126,377 (108,161 to 136,681)	24.6 (21.0 to 26.6)	99.5 (82.0 to 111.0)	10.5 (3.1 to 16.1)

All metrics presented as mean and 95% uncertainty interval. Change in all-ages rate considers differences between population size in 1990 and 2019, while change in age-standardized rate considers both differences in population size and population age structure. Source: Global Burden of Disease Study. Data available at: https://vizhub.healthdata.org/gbd-compare/.

Table 3. The most important actions required and the most imminent threats

ACTIONS REQUIRED

- Create awareness about kidney health
- Create harmonized pan-European early screening, diagnosis and prevention programs for kidney disease
- Include kidney health among EU health priorities and in all EU health communications
- Create registries for incidence and prevalence of dialysis and transplantation covering all EU countries
- Increase EU research investment in kidney disease to a level proportional to disease burden and cost
- Policy change towards sustainable kidney replacement options (home dialysis, transplantation)

MOST IMMINENT THREATS

- 10% of the general population suffers from chronic kidney disease and 30% is at risk
- Kidney disease impacts all levels of quality of life and imposes a major economic burden
- Complications of kidney disease kill most people before they reach dialysis or transplantation
- The 5-year survival of dialysis is lower than that of most cancers
- Only 20% of individuals on dialysis are waitlisted for kidney transplantation
- Mortality rates are increasing alarmingly and will continue to increase in the coming decades

CAPTIONS TO FIGURES

Figure 1: Relationship between other diseases and chronic kidney disease. The arrows indicate the direction of the interaction. With some diseases, the link is bidirectional. Several of these conditions have also mutual links on their own (e.g. diabetes mellitus and cardio-vascular disease) but this is not represented.

Figure 2: Percent 5-year survival of kidney replacement treatment modalities (red bars) (hemodialysis, peritoneal dialysis, transplantation after deceased donation and transplantation after living donation) or 5 years after the diagnosis of cancer (blue bars). Only malignancies with an incidence in excess of 3% of all cancers are illustrated. Orange bar: all cancers aggregated. Based on 2016 data[40,41].

Figure 3: Comparative burden of selected diseases in the EU. Panel A: Prevalence numbers 2019. Bars reflect prevalence in million persons. Panel B: Changes in age-standardized mortality rates. Bars and numeric labels at the bars reflect percent changes in age-standardized mortality rates between 1990 and 2019. Chronic kidney disease in orange. Source: Global Burden of Disease Study. Data available at: https://vizhub.healthdata.org/gbd-compare/.

Figure 4: Comparison of aggregated annual healthcare costs for Europe of cancer (light blue), diabetes mellitus (brown) and chronic kidney disease. Costs of chronic kidney disease are a composite of early chronic kidney disease (stages 1-2 not on dialysis or living with a functioning transplant - grey), more advanced stages of chronic kidney disease (stages 3-5 not on dialysis or living with a functioning transplant - orange), transplantation (red) and dialysis (dark blue). Sources and approaches for calculation: see supplemental data.

Figure 5: Country-level scorecard on availability of kidney care services across Europe comparing data from the International Society of Nephrology Global Kidney Health Atlas for the year 2019. Central and Eastern Europe (above) and Western Europe (below). Available services: green; unavailable services: red; N/A: not available. Funding for medications: public funding that is free at the point of delivery exclusive of private medical insurance or other sources. Advocacy group: organizations or foundations advocating the case of kidney disease at national or regional level. Nephrology workforce: total number of nephrologists and trainees in nephrology in a country per million population. Source: Global Kidney Health Atlas – https://www.theisn.org/initiatives/global-kidney-health-atlas/.

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REFERENCES

1. https://www.youtube.com/watch?v=fP-cmDZy7ac.
2. Hoste EAJ, Kellum JA, Selby NM, et al. Global epidemiology and outcomes of acute kidney injury. *Nature reviews Nephrology.* 2018;14(10):607-625.
3. Lameire NH, Bagga A, Cruz D, et al. Acute kidney injury: an increasing global concern. *Lancet.* 2013;382(9887):170-179.
4. Chawla LS, Kimmel PL. Acute kidney injury and chronic kidney disease: an integrated clinical syndrome. *Kidney international.* 2012;82(5):516-524.
5. http://ekha.eu/.
6. https://nierstichting.nl/professionals/webinar/.
7. Vanholder R, Massy Z, Argiles A, et al. Chronic kidney disease as cause of cardiovascular morbidity and mortality. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association.* 2005;20(6):1048-1056.
8. Matsushita K, Coresh J, Sang Y, et al. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. *The lancet Diabetes & endocrinology.* 2015.
9. Chiu YW, Teitelbaum I, Misra M, de Leon EM, Adzize T, Mehrotra R. Pill burden, adherence, hyperphosphatemia, and quality of life in maintenance dialysis patients. *Clinical journal of the American Society of Nephrology : CJASN.* 2009;4(6):1089-1096.
10. Parker K, Nikam M, Jayanti A, Mitra S. Medication burden in CKD-5D: impact of dialysis modality and setting. *Clinical kidney journal.* 2014;7(6):557-561.
11. Snauwaert E, Van Biesen W, Raes A, et al. A plea for more uremic toxin research in children with chronic kidney disease. *Pediatric nephrology.* 2018;33(6):921-924.
12. Ortiz A, Sanchez-Nino MD. Sarcopenia in CKD: a roadmap from basic pathogenetic mechanisms to clinical trials. *Clinical kidney journal.* 2019;12(1):110-112.
13. Danuser B, Simcox A, Studer R, Koller M, Wild P, Psychosocial Interest Group STCS. Employment 12 months after kidney transplantation: An in-depth bio-psycho-social analysis of the Swiss Transplant Cohort. *PloS one.* 2017;12(4):e0175161.
14. Dukic MZ, L. Employment in patients with renal replacement therapy. *SEEMED J.* 2019;3:11-20.
15. Julian Mauro JC, Molinuevo Tobalina JA, Sanchez Gonzalez JC. Employment in the patient with chronic kidney disease related to renal replacement therapy. *Nefrologia : publicacion oficial de la Sociedad Espanola Nefrologia.* 2012;32(4):439-445.
16. Collaboration GBDCKD. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2020;395(10225):709-733.
17. Zoccali C, Vanholder R, Massy ZA, et al. The systemic nature of CKD. *Nature reviews Nephrology.* 2017;13(6):344-358.
18. https://www.euro.who.int/__data/assets/pdf_file/0008/96632/E93736.pdf.
19. Jager KJ, Kovesdy C, Langham R, Rosenberg M, Jha V, Zoccali C. A single number for advocacy and communication-worldwide more than 850 million individuals have kidney diseases. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association.* 2019;34(11):1803-1805.
20. Bello AK, Johnson DW, Feehally J, et al. Global Kidney Health Atlas (GKHA): design and methods. *Kidney international supplements.* 2017;7(2):145-153.
21. https://www.theisn.org/focus/ckd?gclid=CjwKCAjwsan5BRAOEiwALzomX_3BfsC4QPZXCsl5HUVO5M-_90j2_FXANANQsI6nq2Dgjel_T5inLBoC0zYQAvD_BwE#health-atlas.
22. Plantinga LC, Tuot DS, Powe NR. Awareness of chronic kidney disease among patients and providers. *Advances in chronic kidney disease.* 2010;17(3):225-236.

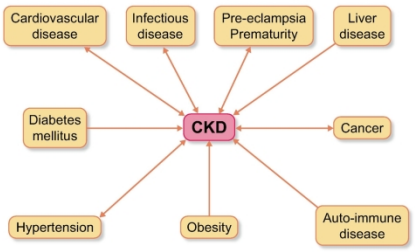
23. Whaley-Connell A, Shlipak MG, Inker LA, et al. Awareness of kidney disease and relationship to end-stage renal disease and mortality. *The American journal of medicine.* 2012;125(7):661-669.
24. Saunders MR, Kim SD, Patel N, Meltzer DO, Chin MH. Hospitalized patients frequently unaware of their chronic kidney disease. *J Hosp Med.* 2015;10(9):619-622.
25. Drey N, Roderick P, Mullee M, Rogerson M. A population-based study of the incidence and outcomes of diagnosed chronic kidney disease. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2003;42(4):677-684.
26. Raymond NT, Zehnder D, Smith SC, Stinson JA, Lehnert H, Higgins RM. Elevated relative mortality risk with mild-to-moderate chronic kidney disease decreases with age. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association.* 2007;22(11):3214-3220.
27. Canaud B, Tong L, Tentori F, et al. Clinical practices and outcomes in elderly hemodialysis patients: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Clinical journal of the American Society of Nephrology : CJASN.* 2011;6(7):1651-1662.
28. Ishani A, Xue JL, Himmelfarb J, et al. Acute kidney injury increases risk of ESRD among elderly. *Journal of the American Society of Nephrology : JASN.* 2009;20(1):223-228.
29. Bowe B, Artimovich E, Xie Y, Yan Y, Cai M, Al-Aly Z. The global and national burden of chronic kidney disease attributable to ambient fine particulate matter air pollution: a modelling study. *BMJ Glob Health.* 2020;5(3):e002063.
30. Vanholder R, Van Laecke S, Glorieux G, Verbeke F, Castillo-Rodriguez E, Ortiz A. Deleting Death and Dialysis: Conservative Care of Cardio-Vascular Risk and Kidney Function Loss in Chronic Kidney Disease (CKD). *Toxins.* 2018;10(6).
31. Cortazar FB, Marrone KA, Troxell ML, et al. Clinicopathological features of acute kidney injury associated with immune checkpoint inhibitors. *Kidney international.* 2016;90(3):638-647.
32. Valle JA, McCoy LA, Maddox TM, et al. Longitudinal Risk of Adverse Events in Patients With Acute Kidney Injury After Percutaneous Coronary Intervention: Insights From the National Cardiovascular Data Registry. *Circ Cardiovasc Interv.* 2017;10(4).
33. Harris DCH, Davies SJ, Finkelstein FO, et al. Increasing access to integrated ESKD care as part of universal health coverage. *Kidney international.* 2019;95(4S):S1-S33.
34. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.
35. Foreman KJ, Marquez N, Dolgert A, et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016-40 for 195 countries and territories. *Lancet.* 2018;392(10159):2052-2090.
36. Chronic Kidney Disease Prognosis C, Matsushita K, van der Velde M, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet.* 2010;375(9731):2073-2081.
37. Wan EYF, Yu EYT, Chin WY, et al. Burden of CKD and Cardiovascular Disease on Life Expectancy and Health Service Utilization: a Cohort Study of Hong Kong Chinese Hypertensive Patients. *Journal of the American Society of Nephrology : JASN.* 2019;30(10):1991-1999.
38. Stengel B. Chronic kidney disease and cancer: a troubling connection. *Journal of nephrology.* 2010;23(3):253-262.
39. Wang HE, Gamboa C, Warnock DG, Muntner P. Chronic kidney disease and risk of death from infection. *American journal of nephrology.* 2011;34(4):330-336.
40. https://seer.cancer.gov/csr/1975_2014.
41. 2016 Uc. https://www.usrds.org/2016/view/v2_13.aspx.
42. Kramer A, Boenink R, Noordzij M, et al. The ERA-EDTA Registry Annual Report 2017: a summary. *Clinical kidney journal.* 2020;13(4):693-709.
43. Susantitaphong P, Cruz DN, Cerda J, et al. World incidence of AKI: a meta-analysis. *Clinical journal of the American Society of Nephrology : CJASN.* 2013;8(9):1482-1493.

44. Bellomo R, Ronco C, Mehta RL, et al. Acute kidney injury in the ICU: from injury to recovery: reports from the 5th Paris International Conference. *Ann Intensive Care.* 2017;7(1):49.
45. Kellum JA, Sileanu FE, Bihorac A, Hoste EA, Chawla LS. Recovery after Acute Kidney Injury. *Am J Respir Crit Care Med.* 2017;195(6):784-791.
46. Vanholder R, Annemans L, Brown E, et al. Reducing the costs of chronic kidney disease while delivering quality health care: a call to action. *Nature reviews Nephrology.* 2017;13(7):393-409.
47. Himmelfarb J, Vanholder R, Mehrotra R, Tonelli M. The current and future landscape of dialysis. *Nature reviews Nephrology.* 2020;16(10):573-585.
48. Vanholder R, Davenport A, Hannedouche T, et al. Reimbursement of dialysis: a comparison of seven countries. *Journal of the American Society of Nephrology : JASN.* 2012;23(8):1291-1298.
49. van der Tol A, Lameire N, Morton RL, Van Biesen W, Vanholder R. An International Analysis of Dialysis Services Reimbursement. *Clinical journal of the American Society of Nephrology : CJASN.* 2019;14(1):84-93.
50. van der Tol A, Stel VS, Jager KJ, et al. A call for harmonization of European kidney care: dialysis reimbursement and distribution of kidney replacement therapies. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association.* 2020;35(6):979-986.
51. Howard K, White S, Salkeld G, et al. Cost-effectiveness of screening and optimal management for diabetes, hypertension, and chronic kidney disease: a modeled analysis. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2010;13(2):196-208.
52. Haller M, Gutjahr G, Kramar R, Harnoncourt F, Oberbauer R. Cost-effectiveness analysis of renal replacement therapy in Austria. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association.* 2011;26(9):2988-2995.
53. Vanholder R, Stel VS, Jager KJ, et al. How to increase kidney transplant activity throughout Europe-an advocacy review by the European Kidney Health Alliance. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association.* 2019;34(8):1254-1261.
54. Kramer A, Pippias M, Noordzij M, et al. The European Renal Association - European Dialysis and Transplant Association (ERA-EDTA) Registry Annual Report 2015: a summary. *Clinical kidney journal.* 2018;11(1):108-122.
55. Rubin HR, Fink NE, Plantinga LC, Sadler JH, Kliger AS, Powe NR. Patient ratings of dialysis care with peritoneal dialysis vs hemodialysis. *Jama.* 2004;291(6):697-703.
56. Ludlow MJ, Lauder LA, Mathew TH, Hawley CM, Fortnum D. Australian consumer perspectives on dialysis: first national census. *Nephrology.* 2012;17(8):703-709.
57. Wu AW, Fink NE, Marsh-Manzi JV, et al. Changes in quality of life during hemodialysis and peritoneal dialysis treatment: generic and disease specific measures. *Journal of the American Society of Nephrology : JASN.* 2004;15(3):743-753.
58. Kerr M, Bray B, Medcalf J, O'Donoghue DJ, Matthews B. Estimating the financial cost of chronic kidney disease to the NHS in England. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association.* 2012;27 Suppl 3:iii73-80.
59. Gandjour A, Armsen W, Wehmeyer W, Multmeier J, Tschulena U. Costs of patients with chronic kidney disease in Germany. *PloS one.* 2020;15(4):e0231375.
60. Honeycutt AA, Segel JE, Zhuo X, Hoerger TJ, Imai K, Williams D. Medical costs of CKD in the Medicare population. *Journal of the American Society of Nephrology : JASN.* 2013;24(9):1478-1483.

61. Elshahat S, Cockwell P, Maxwell AP, Griffin M, O'Brien T, O'Neill C. The impact of chronic kidney disease on developed countries from a health economics perspective: A systematic scoping review. *PloS one.* 2020;15(3):e0230512.
62. Cortaredona S, Ventelou B. The extra cost of comorbidity: multiple illnesses and the economic burden of non-communicable diseases. *BMC medicine.* 2017;15(1):216.
63. Hofmarcher T, Lindgren P, Wilking N, Jonsson B. The cost of cancer in Europe 2018. *Eur J Cancer.* 2020;129:41-49.
64. Williams R, Karuranga S, Malanda B, et al. Global and regional estimates and projections of diabetes-related health expenditure: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes research and clinical practice.* 2020;162:108072.
65. Mohnen SM, van Oosten MJM, Los J, et al. Healthcare costs of patients on different renal replacement modalities - Analysis of Dutch health insurance claims data. *PloS one.* 2019;14(8):e0220800.
66. https://www.era-edta-reg.org/files/annualreports/pdf/AnnRep2009.pdf.
67. Hill NR, Fatoba ST, Oke JL, et al. Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-Analysis. *PloS one.* 2016;11(7):e0158765.
68. Jommi C, Armeni P, Battista M, et al. The Cost of Patients with Chronic Kidney Failure Before Dialysis: Results from the IRIDE Observational Study. *Pharmacoecon Open.* 2018;2(4):459-467.
69. Kerr M, Bedford M, Matthews B, O'Donoghue D. The economic impact of acute kidney injury in England. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association.* 2014;29(7):1362-1368.
70. Silver SA, Long J, Zheng Y, Chertow GM. Cost of Acute Kidney Injury in Hospitalized Patients. *J Hosp Med.* 2017;12(2):70-76.
71. Bello AK, Levin A, Tonelli M, et al. Assessment of Global Kidney Health Care Status. *Jama.* 2017;317(18):1864-1881.
72. Bello AK, Levin A, Lunney M, et al. Status of care for end stage kidney disease in countries and regions worldwide: international cross sectional survey. *Bmj.* 2019;367:l5873.
73. Agar JW. Green dialysis: the environmental challenges ahead. *Seminars in dialysis.* 2015;28(2):186-192.
74. Blankestijn PJ, Bruchfeld A, Capasso G, et al. Lancet Countdown paper: what does it mean for nephrology? *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association.* 2019;34(1):4-6.
75. Barraclough KA, Blashki GA, Holt SG, Agar JWM. Climate change and kidney disease-threats and opportunities. *Kidney international.* 2017;92(3):526-530.
76. Vanholder R, Lameire N. COVID-19 and policy changes for kidney disease: the need for a 'decade of the kidney'. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association.* 2021;36(1):8-11.
77. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *The New England journal of medicine.* 2020;382(18):1708-1720.
78. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. *Jama.* 2020;323(13):1239-1242.
79. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature.* 2020;584(7821):430-436.
80. Clark A, Jit M, Warren-Gash C, et al. Global, regional, and national estimates of the population at increased risk of severe COVID-19 due to underlying health conditions in 2020: a modelling study. *Lancet Glob Health.* 2020;8(8):e1003-e1017.
81. Jager KJ, Kramer A, Chesnaye NC, et al. Results from the ERA-EDTA Registry indicate a high mortality due to COVID-19 in dialysis patients and kidney transplant recipients across Europe. *Kidney international.* 2020.

82. Council E-E, Group EW. Chronic kidney disease is a key risk factor for severe COVID-19: a call to action by the ERA-EDTA. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association.* 2021;36(1):87-94.
83. Gansevoort RT, Hilbrands LB. CKD is a key risk factor for COVID-19 mortality. *Nature reviews Nephrology.* 2020;16(12):705-706.
84. https://www.cdc.gov/mmwr/volumes/69/wr/mm6913e2.htm.
85. Batlle D, Soler MJ, Sparks MA, et al. Acute Kidney Injury in COVID-19: Emerging Evidence of a Distinct Pathophysiology. *Journal of the American Society of Nephrology : JASN.* 2020;31(7):1380-1383.
86. Pei G, Zhang Z, Peng J, et al. Renal Involvement and Early Prognosis in Patients with COVID-19 Pneumonia. *Journal of the American Society of Nephrology : JASN.* 2020;31(6):1157-1165.
87. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *Jama.* 2020.
88. Goldfarb DS, Benstein JA, Zhdanova O, et al. Impending Shortages of Kidney Replacement Therapy for COVID-19 Patients. *Clinical journal of the American Society of Nephrology : CJASN.* 2020;15(6):880-882.
89. Manara AR, Mumford L, Callaghan CJ, Ravanan R, Gardiner D. Donation and transplantation activity in the UK during the COVID-19 lockdown. *Lancet.* 2020;396(10249):465-466.
90. Alasfar S, Avery RK. The impact of COVID-19 on kidney transplantation. *Nature reviews Nephrology.* 2020;16(10):568-569.
91. Brown EA, Perl J. Increasing Peritoneal Dialysis Use in Response to the COVID-19 Pandemic: Will It Go Viral? *Journal of the American Society of Nephrology : JASN.* 2020;31(9):1928-1930.
92. Watnick S, McNamara E. On the Frontline of the COVID-19 Outbreak: Keeping Patients on Long-Term Dialysis Safe. *Clinical journal of the American Society of Nephrology : CJASN.* 2020;15(5):710-713.
93. Quintaliani G, Reboldi G, Di Napoli A, et al. Exposure to novel coronavirus in patients on renal replacement therapy during the exponential phase of COVID-19 pandemic: survey of the Italian Society of Nephrology. *Journal of nephrology.* 2020;33(4):725-736.
94. Sever MS, Ortiz A, Maggiore U, Bac-Garcia E, Vanholder R. Mass Disasters and Burnout in Nephrology Personnel: From Earthquakes and Hurricanes to COVID-19 Pandemic. *Clinical journal of the American Society of Nephrology : CJASN.* 2021.
95. Combe C, Kirsch AH, Alfano G, et al. At least 156 reasons to prioritise COVID-19 vaccination in patients receiving in-centre haemodialysis. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association.* 2021.
96. https://britishrenal.us13.list-manage.com/track/click?u=ba16832efb8ed279407c624e8&id=8b21384214&e=7c5781d482.
97. Lucero-Prisno DE, Ogunkola IO, Imo UF, Adebisi YA. Who Will Pay for the COVID-19 Vaccines for Africa? *Am J Trop Med Hyg.* 2021.
98. Wieringa FP, Sheldon M. The Kidney Health Initiative innovation roadmap for renal replacement therapies: Building the yellow brick road, while updating the map. *Artificial organs.* 2020;44(2):111-122.
99. Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. *Diabetologia.* 2018;61(10):2108-2117.
100. Wanner C, Marx N. SGLT2 inhibitors: the future for treatment of type 2 diabetes mellitus and other chronic diseases. *Diabetologia.* 2018;61(10):2134-2139.
101. https://ec.europa.eu/info/research-and-innovation/research-area/health-research-and-innovation_en.
102. The Lancet Diabetes E. Diabetes and NCD research: meeting the needs of the patient. *The lancet Diabetes & endocrinology.* 2016;4(11):873.

103. Allen L. Non-communicable disease funding. *The lancet Diabetes & endocrinology.* 2017;5(2):92.
104. Luengo-Fernandez R, Leal J, Gray A. UK research spend in 2008 and 2012: comparing stroke, cancer, coronary heart disease and dementia. *BMJ open.* 2015;5(4):e006648.
105. https://report.nih.gov/categorical_spending.aspx.
106. Vivot A, Jacot J, Zeitoun JD, Ravaud P, Crequit P, Porcher R. Clinical benefit, price and approval characteristics of FDA-approved new drugs for treating advanced solid cancer, 2000-2015. *Ann Oncol.* 2017;28(5):1111-1116.
107. https://www.ahip.org/wp-content/uploads/IB_OrphanDrugs-1004.pdf.
108. Moon S, Mariat S, Kamae I, Pedersen HB. Defining the concept of fair pricing for medicines. *Bmj.* 2020;368:l4726.
109. Zoccali C, Vanholder R, Wagner CA, et al. Funding kidney research as a public health priority: challenges and opportunities. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association.* 2020.
110. https://www.whitehouse.gov/presidential-actions/executive-order-advancing-american-kidney-health/.
111. https://aakp.org/decade-of-the-kidney/.
112. https://europa.eu/citizens-initiative/faq-eu-competences-and-commission-powers_en.
113. Luyckx VA, Tonelli M, Stanifer JW. The global burden of kidney disease and the sustainable development goals. *Bull World Health Organ.* 2018;96(6):414-422D.
114. https://ec.europa.eu/info/strategy/international-strategies/sustainable-development-goals_en.
115. Luyckx VA, Al-Aly Z, Bello AK, et al. Sustainable Development Goals relevant to kidney health: an update on progress. *Nature reviews Nephrology.* 2021;17(1):15-32.
116. https://ec.europa.eu/health/sites/health/files/major_chronic_diseases/docs/30years_euaction_cancer_en.pdf.



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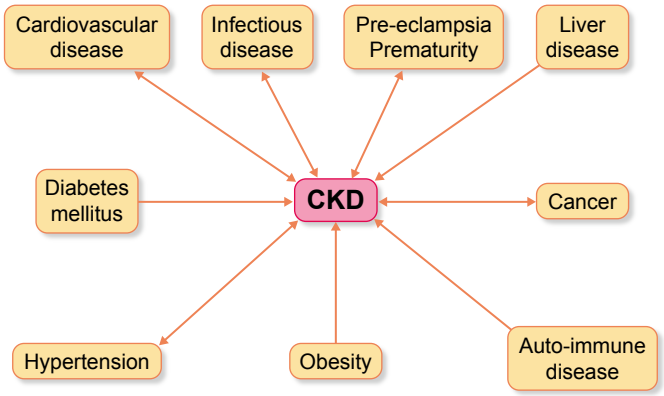

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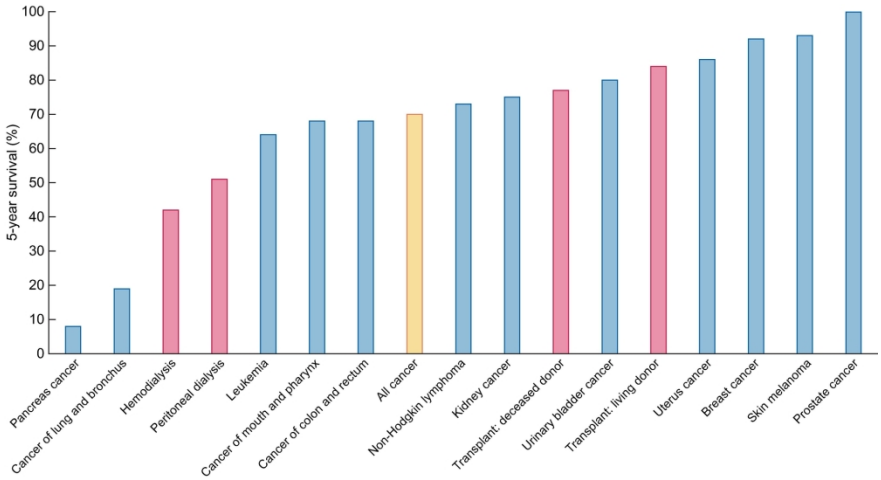

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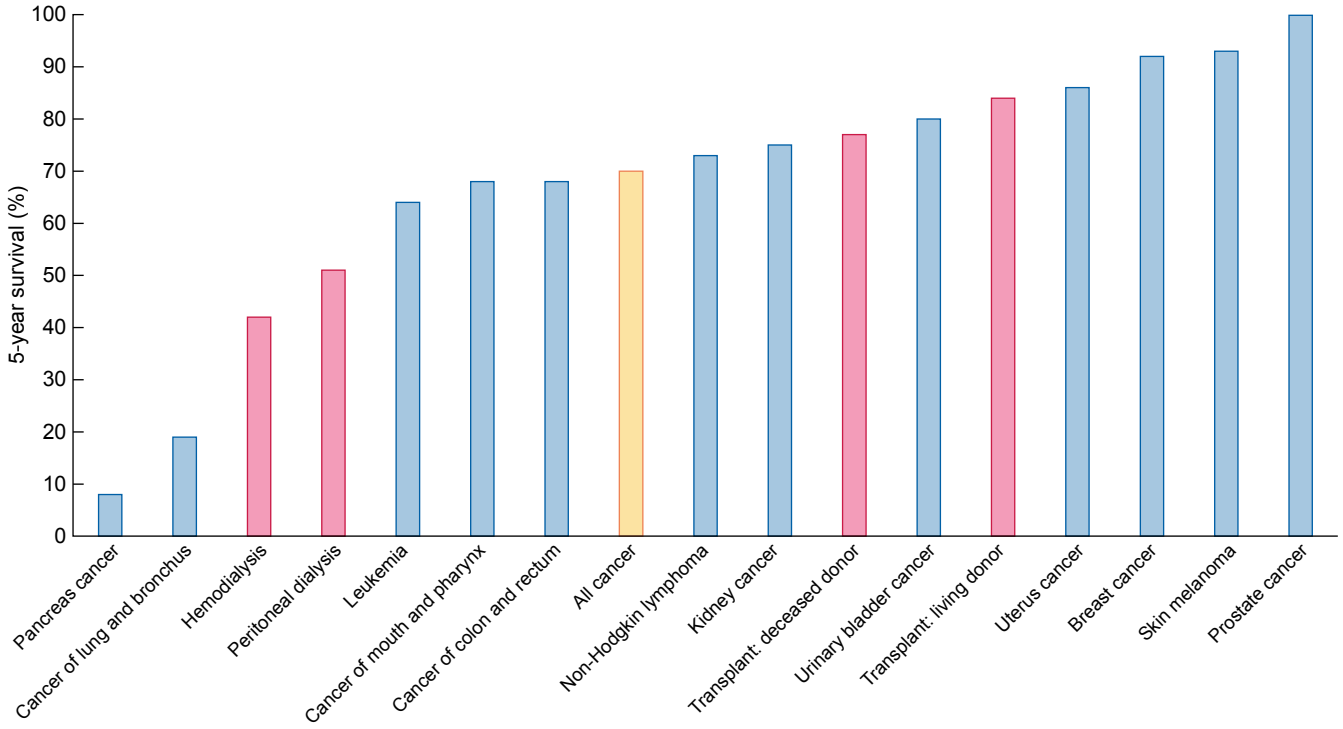

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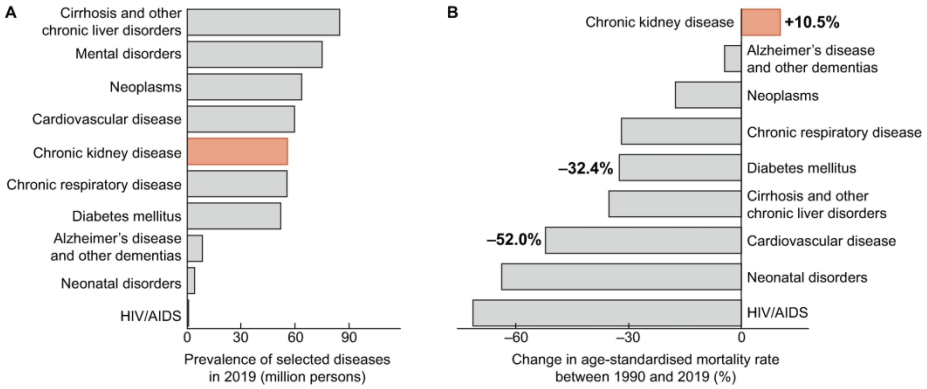

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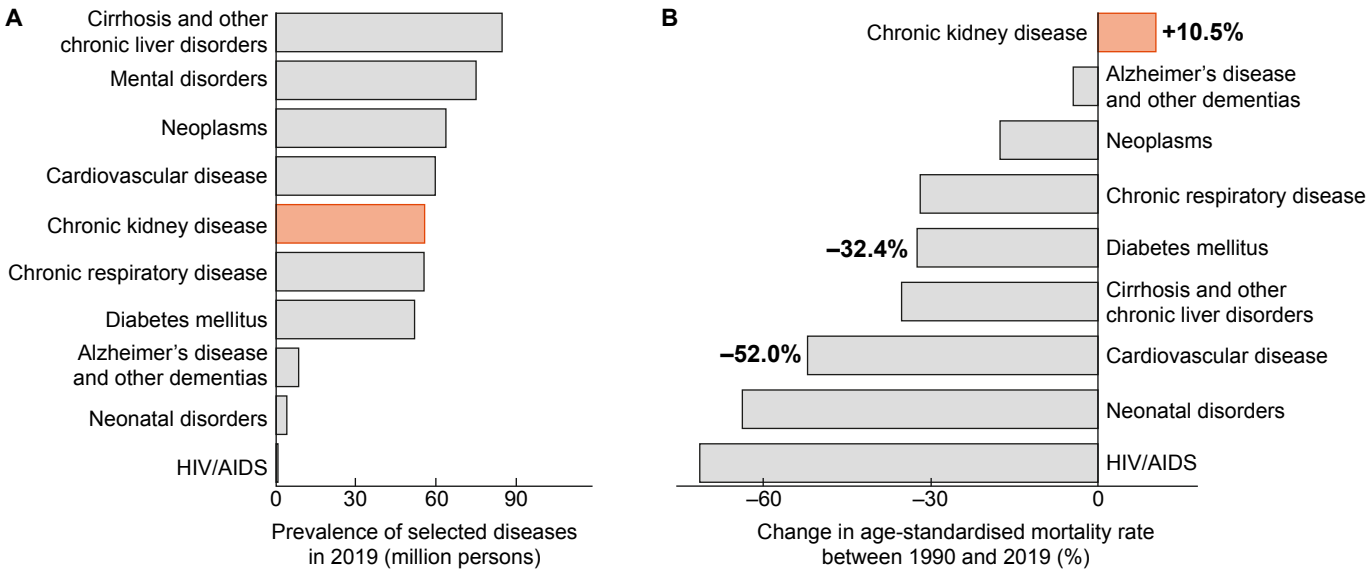

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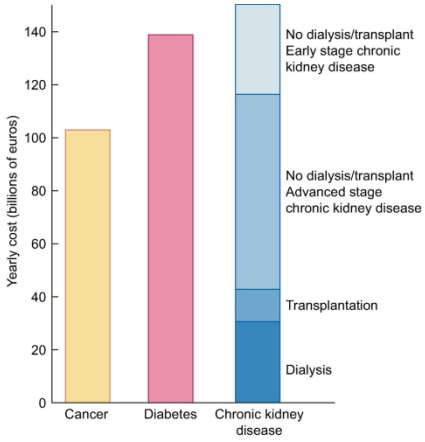

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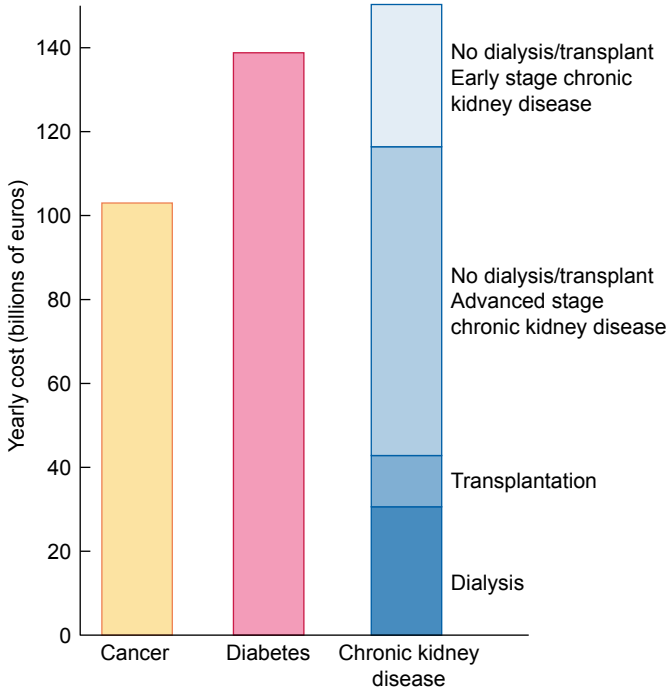

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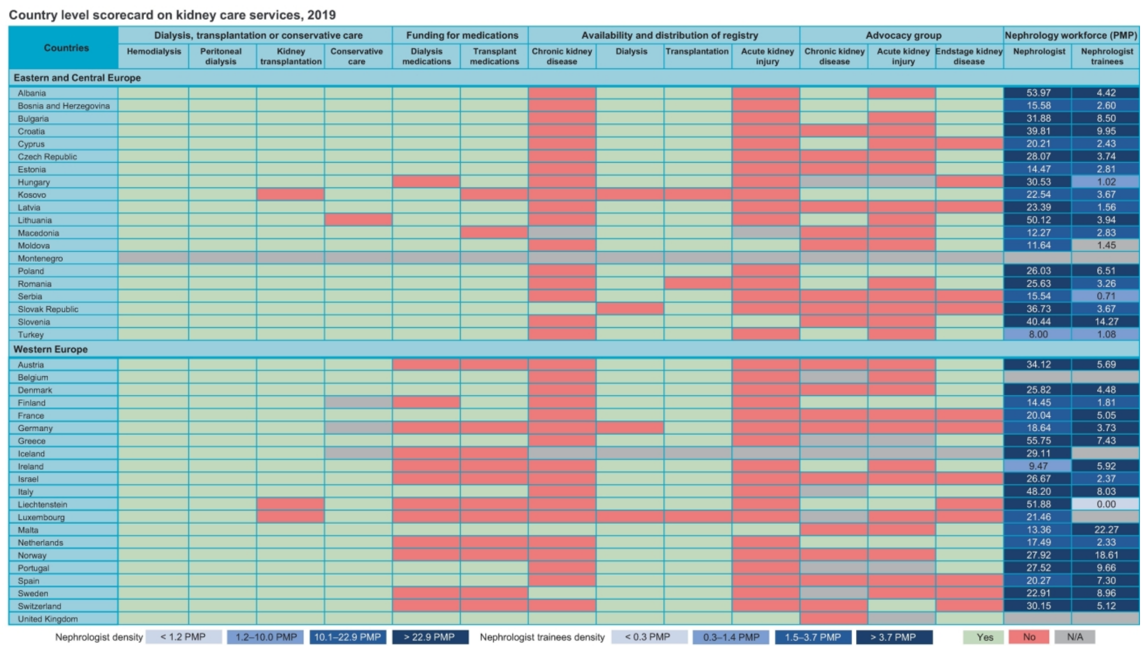

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Country level scorecard on kidney care services, 2019

Countries	Dialysis, transplantation or conservative care				Funding for medications		Availability and distribution of registry				Advocacy group			Nephrology workforce (PMP)	
	Hemodialysis	Peritoneal dialysis	Kidney transplantation	Conservative care	Dialysis medications	Transplant medications	Chronic kidney disease	Dialysis	Transplantation	Acute kidney injury	Chronic kidney disease	Acute kidney injury	Endstage kidney disease	Nephrologist	Nephrologist trainees
Eastern and Central Europe															
Albania														53.97	4.42
Bosnia and Herzegovina														15.58	2.60
Bulgaria														31.88	8.50
Croatia														39.81	9.95
Cyprus														20.21	2.43
Czech Republic														28.07	3.74
Estonia														14.47	2.81
Hungary														30.53	1.02
Kosovo														22.54	3.67
Latvia														23.39	1.56
Lithuania														50.12	3.94
Macedonia														12.27	2.83
Moldova														11.64	1.45
Montenegro															
Poland														26.03	6.51
Romania														25.63	3.26
Serbia														15.54	0.71
Slovak Republic														36.73	3.67
Slovenia														40.44	14.27
Turkey														8.00	1.08
Western Europe															
Austria														34.12	5.69
Belgium															
Denmark														25.82	4.48
Finland														14.45	1.81
France														20.04	5.05
Germany														18.64	3.73
Greece														55.75	7.43
Iceland														29.11	
Ireland														9.47	5.92
Israel														26.67	2.37
Italy														48.20	8.03
Liechtenstein														51.88	0.00
Luxembourg														21.46	
Malta														13.36	22.27
Netherlands														17.49	2.33
Norway														27.92	18.61
Portugal														27.52	9.66
Spain														20.27	7.30
Sweden														22.91	8.96
Switzerland														30.15	5.12
United Kingdom															

Nephrologist density: < 1.2 PMP | 1.2–10.0 PMP | 10.1–22.9 PMP | > 22.9 PMP

Nephrologist trainees density: < 0.3 PMP | 0.3–1.4 PMP | 1.5–3.7 PMP | > 3.7 PMP

Yes | No | N/A