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Full Review

The ascending rank of chronic kidney disease in the global burden of disease study

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ABSTRACT

General population-based studies, the chronic kidney disease (CKD) prognosis consortium and renal registries worldwide have contributed to the description of the scale of CKD as a public health problem. Since 1990, CKD has been included in the list of non-communicable diseases investigated by the Global Burden of Disease (GBD) study. The GBD represents a systematic, high-quality, scientific effort to quantify the comparative magnitude of health loss from all major diseases, injuries and risk factors. This article provides an outline of the place of CKD in the ranking of these diseases and the change over time. Whereas age-standardized death and disability-adjusted life years (DALYs) rates due to non-communicable diseases in general have been declining, such favourable trends do not exist for CKD. Altogether the GBD reports indicate increasing rates for death and DALYs due to CKD with huge variation across the globe. A substantial component of the observed increase in mortality attributable to CKD relates to that caused by diabetes mellitus and hypertension. For the increase in DALYs, CKD due to diabetes mellitus appears to be the main contributor. It is possible that these trends are in part due to new data becoming available or different coding behaviour over time, including greater specificity of coding. Although some feel there is evidence of overdiagnosis, it seems clear that in many regions CKD and its risk factors are a growing public health problem and in some of them rank very high as cause of years of life lost and DALYs. Therefore, public health policies to address this problem as well as secondary prevention in high-risk groups remain greatly needed.

Keywords: CKD, death rates, disability-adjusted life years, prevalence, years of life lost

INTRODUCTION

In 2002, chronic kidney disease (CKD) was classified into five stages [1] based on the presence of kidney damage (i.e. albuminuria) or decreased kidney function [i.e. glomerular filtration rate (GFR) <60 mL/min/1.73 m^2]. Ten years later, as both kidney function and kidney damage had been shown to independently affect the prognosis of CKD, the Kidney Disease: Improving Global Outcomes (KDIGO) modified this classification by proposing six categories of kidney function [estimated GFR (eGFR), G1–G5] and three categories of kidney damage (albuminuria, A1–A3). This resulted in 18 categories that have been labelled as low, moderately increased, high or very high risk of complications like drug toxicity, endocrine and metabolic outcomes, cardiovascular disease and mortality [2]. These and other complications of CKD have been recognized to induce an important disease burden both for individual patients and for societies.

In almost every recent paper dealing with the implications of CKD, the disease is referred to as an important public health problem. A number of general population-based studies have been instrumental in describing the scale of this public health problem by assessing and monitoring the health of communities and populations at risk, while the CKD prognosis consortium has provided significant input to the understanding of the joint contribution of albuminuria and decreased kidney function to patient prognosis. Finally, for the past few decades, renal registries have provided information on the access to appropriate, but costly, renal replacement therapy (RRT) for the treatment of end-stage kidney disease (ESKD).

European national surveys have shown CKD stage 3–5 prevalence to vary from 2.3% in Germany (in those aged 18–79

years) [3], 2.4% in Finland (in those aged 20–74 years) [4], 4.0% in Spain (in those aged 20–74 years) [4] to 5.2% in England in subjects of 16 years and older [5]. Outside Europe, the range in prevalence of CKD stage 3–5 derived from nationally representative samples is slightly wider: from 1.7% in China (in those aged 18 years and older) [6], 3.1% in adults from Canada [7], 5.8% in Australia (25 years and older) [8] to 6.7% in adults from the USA [9].

The CKD prognosis consortium has demonstrated that lower eGFR and higher albuminuria are risk factors for ESKD, acute kidney injury (AKI) and progressive CKD in both general and high risk populations, independent of each other and of cardiovascular risk factors [10]. In addition, they have provided evidence that both are also risk factors for cardiovascular morbidity as well as cardiovascular and all-cause mortality, regardless of age [11].

Renal registries, on the other hand, have shown that in 2013 the access to RRT across different nations varied greatly—from a prevalence of 66 per million population (pmp) in Indonesia to 3138 pmp in Taiwan, a nearly 50-fold difference [12]. In 2010, the total number of RRT patients worldwide amounted to 2.6 million, whereas the number of patients needing this treatment was estimated to be between 4.9 and 9.7 million, with the largest gap between need and supply of RRT in low-income countries, particularly in Asia and Africa [13].

The prevalence of both CKD stage 3–5 and that of RRT are expected to increase further, although for the USA recent NHANES data have shown that the increase in CKD stage 3–5 may only be very modest [14]. Nevertheless, a worldwide increase can be expected due to population ageing and the increasing prevalence of obesity, hypertension and diabetes mellitus in the general population. At the same time, worldwide use of RRT has been projected to more than double by 2030, with the largest growth in Asia [13]. This growing burden of RRT will likely be due to the continued improvement in survival on dialysis and transplantation [12, 15] and, in developing countries, to an increasing number of patients taken on to RRT.

Since 1990, CKD has been included in the list of non-communicable diseases investigated by the Global Burden of Disease (GBD) study. The GBD represents a systematic, high-quality, scientific effort to quantify the comparative magnitude of health loss from all major diseases, injuries and risk factors. This article aims to provide an outline of the place of CKD in the ranking of these diseases and the change over time.

GBD MEASURES AND ANALYTICAL METHODS

The methods involved in the GBD studies are complex, and this review will not attempt to cover them comprehensively [16–19]. The regions identified in the GBD study were the result of a collaboration of several hundred investigators reporting metrics such as adult and child mortality from across the world. Countries were divided into 21 regions according to similarity from an epidemiologic and geographical perspective [20]. Data availability and reliability varied widely between locations, therefore requiring several internal validity checks such as ensuring that the sum of individual cause of death numbers equalled the all-cause death totals [19].

The investigators have recognized important limitations of their data, such as insufficient information on certain causes of death from many countries. They therefore relied on complex statistical models to address gaps. For example, they used six different modelling strategies for causes of death depending on the quality and quantity of data available, and generated 95% confidence intervals to reflect the degree of uncertainty (95% UI) [19].

To summarize, they used the following steps to assess the quality of cause of death data:

(i) Adjustment of cause of death data from vital registration systems for incompleteness.
(ii) Development of maps to help translate causes of death in the collected data to the GBD 2013 cause list.
(iii) Identifying and redistributing 'garbage codes' (defined as 'codes for which deaths are assigned that cannot or should not be considered as the underlying cause of death').
(iv) Identifying data (such as verbal autopsy reports) where age or sex data were combined and using algorithms to split into specific age–sex groups.
(v) Smoothing fluctuations in cause of death data for small countries (where number of deaths for individual causes can fluctuate widely).
(vi) Exclusion of outliers on the basis of biological implausibility, where data from a country was highly inconsistent with other studies for that country (or from countries with similar sociodemographic profiles in the same region), and studies that led to abrupt changes in trends that could not be explained by contextual factors [16].

The mortality estimation processes used in the GBD studies are complex due to the widely varying degree of completeness of vital registration systems in different countries [21]. In the 2013 GBD, the methods used to identify cause of death were the same as those used in the 2010 GBD with the exception of some new datasets that became available to give information on 'deaths from CKD caused by glomerulonephritis' [16]. For those deaths that were medically certified, this was used as part of the process of identifying cause of death. Even with the introduction of standard International Classification of Diseases (ICD) coding, however, there remains considerable variation in coding practice and completeness globally. Where no death certification data were available, the investigators used a variety of sources such as surveillance systems, demographic research sites, surveys, censuses, disease registries, verbal autopsy data and police records. A summary of the 'site-years' of data are provided that show the principle sources for each cause of death. Where coding was available, CKD was identified by ICD-10 codes (E10.2, E11.2, E12.2, E13.2, I12.0, I12.9, I13.1, I13.2, I13.9, N02-N07, N15.0) and ICD-9 codes (250.4, 403–404, 581–583, 589) (Supplementary data, Table S1 for ICD terms). A further limitation of GBD in relation to CKD is that the latter was only defined as impaired GFR and did not take into account albuminuria.

To be able to make further meaningful comparison of the burden caused by different diseases, they calculated years of life lost (YLL, calculated by multiplying numbers of deaths by life expectancy at time of death in a reference population) due to premature death and disability-adjusted life years (DALYs) to reflect the degree of disability such as pain or functional limitations caused by each condition. Assessing the impact of different conditions by these metrics included the use of disability weights derived from general population surveys in five countries and an open Internet survey [22].

Finally, the GBD investigators calculated age-standardized death rates and DALY rates using the world population age standard (WHO 2001) updated to a standard population structure using population estimates for 2010–35 (World Population Prospects, United Nations) [16]. Data for the charts in the next section were obtained from the Institute for Health Metrics and Evaluation 'GBD Compare' calculator [23] except where referenced otherwise. Throughout this paper, death rate refers to deaths per 100 000 people and DALY rate to DALYs per 100 000 people.

GLOBAL, NATIONAL AND REGIONAL VARIATIONS IN CKD BURDEN OVER TIME

The change in CKD burden over time, globally and in different countries and regions as presented by the GBD, can be considered in terms of both mortality and morbidity and by absolute and relative measures. The GBD considers absolute measures by describing changes in the crude and age-standardized death rate and giving absolute estimates for DALYs and YLLs. In addition, they provide relative ones by ranking deaths, DALYs and YLLs.

Mortality: deaths, death rates and YLL

Global deaths due to all-cause CKD in 1990 were ∼409 000 (363 844–433 380) compared with 956 000 (812 896–1034 491) in 2013 [16]. The upper panel of Figure 1 illustrates the change in death rate attributed to CKD over time, globally and by 21 regions. It shows that globally death due to CKD is increasing (rising from ∼8 per 100 000 people to ∼13 per 100 000 people

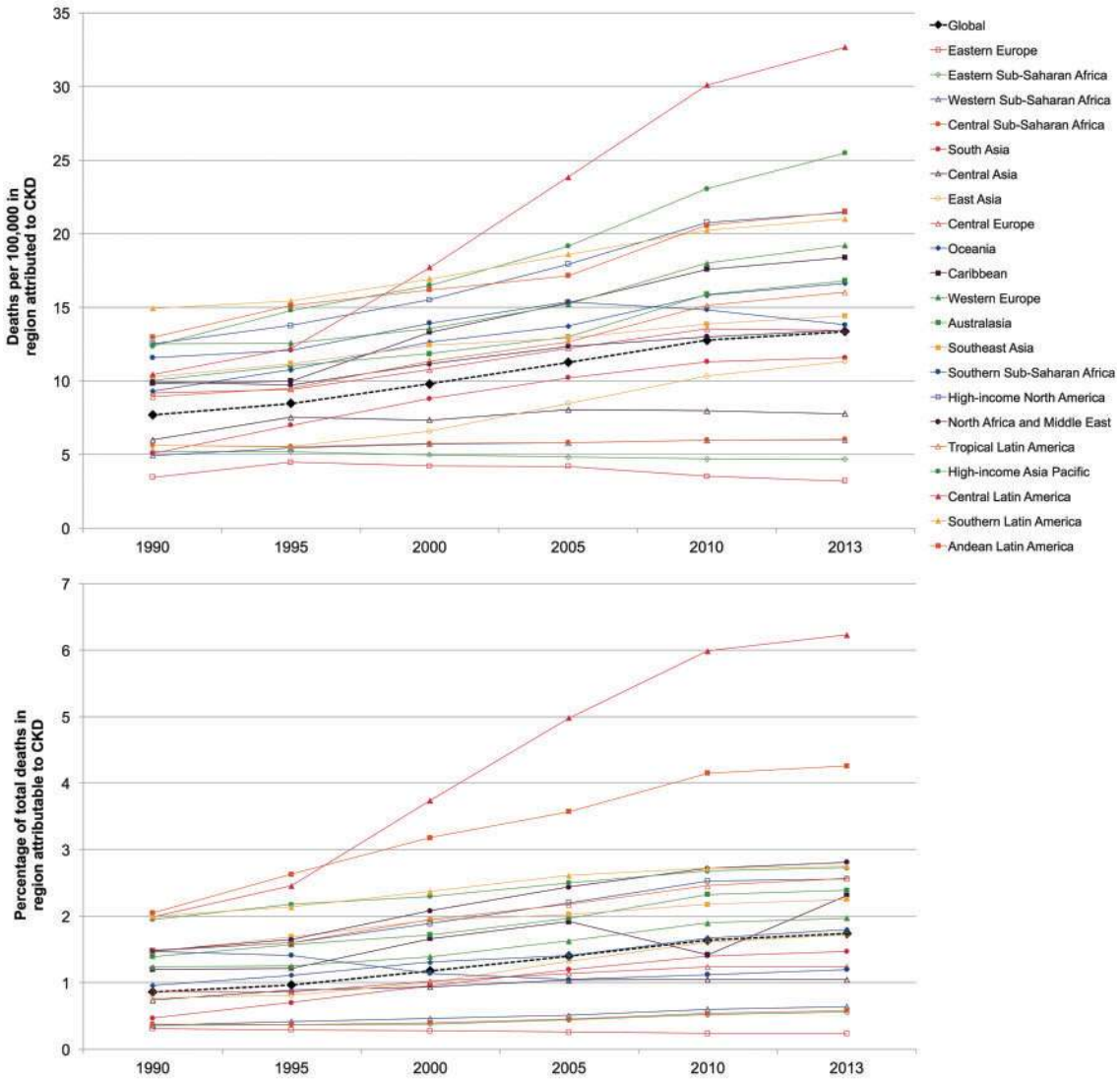

FIGURE 1: Crude death rate (upper panel) and percentage of total deaths attributed to CKD (lower panel) over time, by region. For clarity, the figure does not include 95% UIs.

between 1990 and 2013). However, these numbers hide considerable variation between the GBD regions. For some regions (such as Eastern Europe and Eastern and Central Sub-Saharan Africa), the death rate appears to have been static over this period. For others, particularly Latin America, high-income Asia Pacific and high-income North America, the absolute increase is remarkable. The most notable is Central Latin America (which includes Columbia, Costa Rica, El Salvador, Guatemala, Honduras and Mexico), where deaths have tripled from 10.4 per 100 000 people in 1990 to 32.7 per 100 000 people in 2013. Within Mexico itself, the change is even more striking (from 12.2 in 1990 to 47.1 in 2013, not shown in the figure). Age-standardized death rates by region show a similar but somewhat diluted pattern compared with the crude death rates, although with greater prominence for some regions, such as Oceania, and an even more noticeable difference between Central Latin America and other regions (Supplementary data, Figure S1) [23]. Table 1 shows the change in global age-standardized death rates for CKD according to cause. The GBD modelling suggests that the global increase in CKD mortality seen between 1990 and 2013 was 4.2 deaths per 100 000 people, of which 1.5 deaths (36%) were due to the increase in diabetes and hypertension-related CKD.

In relative terms, the GBD study shows the deaths attributable to CKD as a percentage of total deaths in a region (Figure 1, lower panel). Latin America still dominates the picture, with an increase in Central Latin America to over 6% of all deaths attributable to CKD in 2013, from ∼2% in 1990. Whereas globally CKD increased in the ranking of cause of death from 27th in 1990 to 13th in 2013, in Central Latin America over the same period it increased from 12th to 4th. Similarly, CKD increased in the global ranking of YLL from 36th in 1990 to 19th in 2013 but from 17th to 5th in Central Latin America [16].

Morbidity: DALYs

In absolute terms, the total number of global DALYs associated with CKD has increased from 19 million in 1990 to 33 million in 2013 [17]. The upper panel of Figure 2 illustrates the change in DALY rate due to CKD over time, globally and in the 21 regions. The trend in DALY rate shows a flatter pattern for many geographical areas compared with death rate, with an apparent decrease in Eastern Sub-Saharan Africa. On the other hand, there is a striking increase in DALY rate in Central Latin America since about 1995, resulting in having approximately twice the global DALY burden in 2013. Table 1 shows the change in age-standardized global DALY rate, overall and by CKD cause. The GBD data suggest that morbidity due to CKD is increasing globally and that CKD due to diabetes, hypertension and other causes are all contributing to this increase. Nevertheless, the greatest percentage increase is in CKD due to diabetes.

Similar to the pattern seen for mortality, the increasing percentage of DALYs due to CKD is most marked in Central Latin America (from 1.34% in 1990 to 3.66% in 2013, Figure 2, lower panel). There are also differences elsewhere. Western Europe, for example, recently shows a greater proportion of DALYs attributable to CKD than most other regions (2.4% in 2013). The steadily increasing pattern of CKD's relative position in the Caribbean was interrupted in 2010 by the dominance of the effects of the Haiti earthquake but appears to have resumed its previous rising pattern following that humanitarian disaster. In the global ranking of the number of DALYs, CKD increased as a cause from 28th in 1990 to 20th in 2013 [17]. The change in Central Latin America moved CKD from being the 18th cause of DALYs in 1990 to 7th in 2013. For Western Europe, this rank change was modest, from 15th in 1990 to 12th in 2013 [23].

Relative importance of CKD to YLLs and DALYs across nations

The GBD report also highlights the top 10 causes of YLLs and DALYs for each country [16]. There are 51 countries for which CKD was among either the top 10 causes of YLL (44 countries) or the top 10 causes of DALYs (28 countries) or both (20 countries) in 2013. These are shown in Table 2 with countries that appear in both lists shown in blue. These lists are again dominated by Latin America, with the Caribbean, North Africa and the Middle East being strongly represented in the top YLL list and Europe in the DALY list. Latin America is particularly prominent when considering the rank of CKD in each—it represents the second and third highest causes of YLL and DALYs in Mexico and Nicaragua.

Table 1. Global age-standardized death rate and age-standardized DALY rate (95% UI) due to CKD over time, total and by cause (per 100 000 people) (http://ghdx.healthdata.org/global-burden-disease-study-2013-gbd-2013-data-downloads)

	1990	2013	% change and direction
Age-standardized death rate			
CKD total	11.6 (10.4–12.3)	15.8 (13.5–17.1)	36% increase
CKD due to diabetes	1.4 (1.0–1.6)	2.9 (2.3–3.5)	107% increase
CKD due to hypertension	3.6 (2.8–4.4)	4.6 (3.3–5.6)	28% increase
CKD due to glomerulonephritis	2.5 (2.1–2.9)	1.8 (1.5–2.3)	28% decrease
CKD due to other causes	4.1 (3.3–4.8)	6.5 (4.9–7.5)	59% increase
Age-standardized DALY rate			
CKD total	443.4 (386.8–500.9)	497.3 (427.5–557.2)	12% increase
CKD due to diabetes	59.3 (48.9–70.9)	90.9 (77.1–105.9)	53% increase
CKD due to hypertension	116.7 (94.4–136.8)	121.1 (95.7–139.8)	4% increase
CKD due to glomerulonephritis	114.4 (100.0–130.5)	88.2 (74.0–103.2)	23% decrease
CKD due to other causes	153.0 (130.8–199.8)	197.2 (162.6–225.1)	29% increase

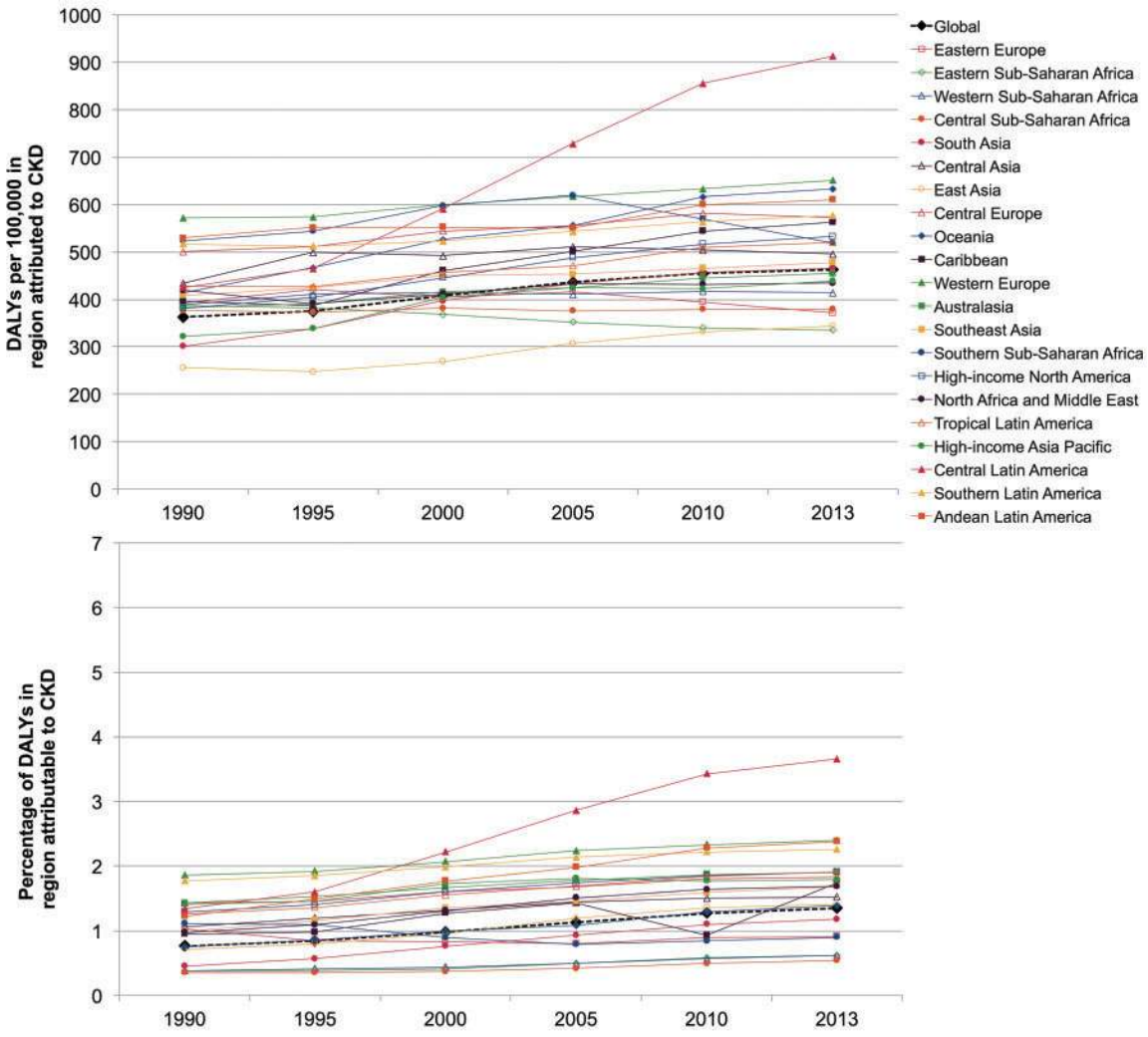

FIGURE 2: Crude DALY rate (upper panel) and percentage of DALYs attributed to CKD (lower panel) over time, by region. For clarity, the figure does not include 95% UIs.

INTERPRETATION

Whereas age-standardized death and DALY rates due to non-communicable diseases in general have been declining (median per cent change: −18.6 during 1990–2013 and −6.3 during 2005–13, respectively) [16, 17], such favourable trends do not exist for CKD. Altogether the different GBD reports indicate increasing rates for death and DALYs due to CKD, a substantial part of which results from CKD due to diabetes mellitus and hypertension-related CKD for death and from CKD due to diabetes mellitus for DALYs. Death and DALYs from CKD due to 'other causes' also increased substantially, the reasons for which are unclear. The contribution of AKI to CKD incidence and progression is one potential cause, although this cannot be inferred from these data [24]. As a result, for 51 countries in the world, CKD was among the top 10 causes of YLL, DALYs or both in 2013. On the other hand, death and disability as a result of CKD due to glomerulonephritis seem to be declining.

There is, however, substantial variation across the globe. The substantially worse outcomes in Central and other parts of Latin America compared with many other countries are striking, as are the other areas for which CKD appears in the top 10 causes of YLL and DALYs. Most notable among these are the Caribbean, Oceania, Mauritius, Thailand, and parts of North Africa and the Middle East. The increase in CKD in Latin America has been attributed to demographic changes (ageing population and rapid epidemiologic transition) as well as to an epidemic of obesity and type 2 diabetes [25]. Others have suggested that a significant contributor to the problem in Central Latin America is the high level of healthcare inequality, with the greatest burden of CKD mortality and morbidity being borne by those who are uninsured in Mexico's health system [26]. Similarly, diabetes, hypertension and obesity are cited as key, growing risk factors in the Arab world, resulting in calls for public health action [27, 28]. AKI has also been highlighted as an important contributory factor in this population [29].

As far as DALY rates due to CKD are concerned, Western Europe gave up its leading position around 2000 and now ranks second after Central Latin America. This may be due to Western Europe's relatively old population compared with most other areas. However, United Nations data projections estimate that for Latin America and the Caribbean, the

Table 2. Countries for which CKD was ranked in the top 10 for YLL and DALYs in 2013

Years of life lost		Disability-adjusted life years	
Region/country	CKD rank in country	Region/country	CKD rank in country
Andean Latin America		Andean Latin America	
Ecuador	7	Ecuador	8
Central Latin America		Central Latin America	
Mexico	2	Nicaragua	2
Nicaragua	3	Mexico	3
Costa Rica	4	Costa Rica	7
El Salvador	4	El Salvador	5
Panama	7	Panama	10
Venezuela	7	Venezuela	10
Tropical Latin America		Southern Latin America	
Paraguay	9	Chile	10
Caribbean		Caribbean	
Barbados	5	Barbados	7
Jamaica	6	Antiga and Barbuda	9
The Bahamas	7	Dominica	9
Dominica	8	Jamaica	9
Grenada	8	The Bahamas	9
TTO (Trinidad and Tobago)	8	TTO (Trinidad and Tobago)	8
Antiga and Barbuda	9		
Saint Lucia	9		
Cuba	10		
Dominican Republic	10		
VCT (St Vincent and the Grenadines)	10		
Suriname	10		
North Africa and Middle East		North Africa and Middle East	
Iraq	6	Iraq	9
Saudi Arabia	6		
Kuwait	7		
Palestine	7		
Libya	8		
Algeria	9		
Bahrain	9		
Egypt	9		
Jordan	9		
Lebanon	10		
Oman	10		
Tunisia	10		
Eastern sub-Saharan Africa		Eastern sub-Saharan Africa	
Mauritius	4	Mauritius	4
Seychelles	10		
Oceania		Oceania	
Fiji	7	Fiji	8
Samoa	7	Samoa	9
Marshall Islands	8	Marshall Islands	10
FSM (Federated States of Micronesia)	9		
High-income Asia Pacific			
Singapore	7		
Southeast Asia		Southeast Asia	
Thailand	7	Thailand	8
Maldives	9		
Malaysia	10		
Western Europe		Western Europe	
Greece	10	Israel	6
		Malta	9
		Portugal	9
		Greece	9
		Cyprus	10
		Germany	10
		Central Europe	
		Macedonia	10
		Montenegro	10

population will shift from just 11% aged 60 years or over in 2015 to 26% by 2050, causing significant concern for the prevalence and impact of CKD in these regions [30].

Methodological issues

The GBD study refers to a number of potential reasons as to why some causes of death—among them CKD—have shown such large changes in the number of global deaths. They point out that such changes may be because of new data, modifications of garbage coding algorithms and revised modelling strategies, and acknowledge that the breakdown into specific causes is challenging in practice where patients have more than one associated condition, such as those with both diabetes and hypertension. [16]. This important limitation was also recognised by Rhee and Kovesdy in their review of these trends. They stressed the potential for increased recognition and coding of CKD (using ICD-9 and ICD-10 codes for cause of death) to mask true changes in absolute and relative mortality and morbidity [31]. While it is very difficult to establish this for certain, it is possible that some of the change in CKD mortality could be attributed to greater specificity of coding over time in certain areas. For example, some CKD-related death may have previously been recorded as cardiovascular death, and the use of death certification and renal registry data to attribute cause of death to CKD may underestimate its true impact. GBD data may at least lend some support to this. Whereas global CKD age-standardized death rates have increased, the GBD study reports a substantial decrease in global age-standardized death rate from cardiovascular disease (from 375.5 deaths per 100 000 people in 1990 to 293.2 deaths per 100 000 people in 2013; median per cent change: −22 during 1990–2013) [16]. In Central Latin America, where the GBD study identified an ∼3-fold the increase in crude mortality due to cardiovascular disease (CVD) has been considerably more modest (from 102 per 100 000 in 1990 to 131 per 100 000 in 2013). In contrast, the age-standardized death rates for CVD decreased from 239 per 100 000 to 204 per 100 000 in 2013, whereas the age-standardized death rate for CKD in Central Latin America more than doubled, from 22 per 100 000 in 1990 to 48 per 100 000 in 2013 (Supplementary data, Figure S1). Moreover, the GBD calculator, which allows estimation of the percentage of cardiovascular deaths that are due to impaired GFR as risk factor, shows that ∼8.5% of global ischaemic heart disease deaths and 8% of stroke-related deaths are attributable to low GFR [23].

CKD as a public health problem

Now to come back to some of the issues raised in the introduction. GBD data support the claims that CKD, as currently defined, is a global public health problem. As it is unlikely that the changes observed are solely due to different coding behaviour, we may assume that for many countries the burden of CKD is increasing in both absolute and relative terms, resulting in greater morbidity and mortality. Some countries and regions currently have a substantial problem, with countries in Latin America, the Caribbean, North Africa and the Middle East, and Oceania particularly at risk.

On the other hand, dissenting opinions regarding labelling CKD as a disease have been expressed. Some nephrologists and general practitioners feel that there is evidence of overdiagnosis, given the large number of people with a CKD diagnosis who will never progress to symptomatic forms of kidney disease. They feel clinicians should be sceptical about the current definition of CKD and cautious about labelling, particularly older people [32].

What then should be the response of the global kidney and public health communities to these data? Given the trends identified, it seems unlikely that simply providing more RRT on demand is going to be the solution, although improving equity of access to RRT is clearly an important goal, particularly for countries in Central Latin America and other low-income countries. There is an urgent need for certain regions to develop their 'upstream' response to these issues if their health systems are going to survive. Such a response should be targeted both at the population level and at high-risk groups [4, 33], for example, tackling the threats of obesity, smoking and hypertension, addressing health inequalities and supporting efforts to prevent avoidable AKI at population level, as well as targeting those at high risk of CKD progression [34]. The GBD data suggest that the highlighted countries in Table 2 could be considered 'high-risk populations' and should become the focus of greater efforts to identify causal pathways and support public health nephrology interventions. This is likely to require substantial investment, strategic planning and political will, but will have co-benefits such as reducing the burden of other long-term conditions, which may be at least as important to population health gain as is the prevention of CKD. Efforts to increase the availability and impact of low-tech interventions through public health campaigns [such as dietary modification (including lowering high salt intake), smoking cessation and physical activity programmes] and primary care (such as treatment of hypertension) may yield greater health gain than increasing the availability of expensive high-cost technologies. As far as high-risk groups are concerned, it has been suggested that the treatment of diabetes and hypertension has improved in high-income countries, as RRT incidence rates for these two causes are decreasing. Future studies need to investigate which interventions are most effective in low- and middle-income countries [34].

In conclusion, GBD data suggest that both death rates and DALY rates due to CKD are increasing, albeit with substantial variation across the globe. It is possible that this is in part due to new data becoming available or different coding behaviour over time, including greater specificity of coding. However, although some feel there is evidence of overdiagnosis, it seems clear that in many countries and regions CKD is a growing public health problem and in some of them ranks very high as a cause of YLL and DALYs. Policies to address primary and secondary prevention remain greatly needed.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

CONFLICT OF INTEREST STATEMENT

The results presented in this paper have not been published previously in whole or part.

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