Worldwide cardiovascular and ESRD outcomes attributable to reduced GFR

Running Title: Reduced GFR-attributed health loss

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ABSTRACT

The burden of premature death and health loss from end-stage renal disease is well-described. Less is known regarding the burden of reduced glomerular filtration rate-attributable cardiovascular disease. The prevalence of reduced glomerular filtration rate categories 3, 4, and 5 (not on renal replacement therapy) was estimated for 188 countries at six time points from 1990 to 2013. Relative risks of cardiovascular outcomes by three strata of reduced glomerular filtration rate were calculated by pooled random effects meta-analysis. Results are presented as deaths for outcomes of cardiovascular disease and end-stage renal disease (ESRD), and disability-adjusted life years (DALYs) for outcomes of cardiovascular disease and CKD categories 3, 4, 5, and ESRD. In 2013, reduced glomerular filtration rate was associated with 4% of deaths worldwide, or 2.2 million deaths (95% uncertainty interval: 2.0 to 2.4M). More than half of these attributable deaths were cardiovascular deaths (1.2M; 95% UI: 1.1 to 1.4M), while 0.96M (95% UI: 0.81M, 1.0M) were end-stage renal disease deaths. Compared with metabolic risk factors, reduced glomerular filtration rate DALYs (14th) ranked under high-systolic blood pressure (1st), high body-mass index (3rd), high fasting plasma glucose (4th), and ranked similarly with high total cholesterol (13th). By 2013 cardiovascular deaths attributed to reduced GFR outnumbered ESRD deaths throughout the world. Studies are needed to evaluate the benefit of early chronic kidney disease detection and treatment to decrease these deaths.

INTRODUCTION

Chronic kidney disease (CKD) is prevalent within the general adult population.[1-4] Though general CKD screening is not performed in most countries, surveys consistently find that a sizeable proportion of the general adult population has some stage of CKD. In the United States, it is estimated that 13.1% of adults have CKD, and that CKD prevalence has been increasing over time.[1] A survey in Japan found 19.1% of the adult population have CKD.[2] Determining CKD burden within developing countries is more challenging. A recent meta-analysis of CKD prevalence of any stage in sub-Saharan Africa estimated a population prevalence of 13.9% among adults, though the analysis was limited by availability of few high-quality data sources.[3] A recent survey in two Indian cities found one in 12 individuals to have CKD, and among those with CKD almost 80% were assessed to be at high risk for a cardiovascular event.[4] These data indicate that CKD is common in diverse parts of the world.

The health and social effects of CKD patients who progress to end-stage renal disease (ESRD) are well-known.[5-7] The burden of health loss and premature mortality within the CKD population to cardiovascular (CV) disease is less known. Increasing severity of pre-dialysis reduced glomerular filtration rate (GFR) is associated with a higher likelihood of CV disease diagnoses, severity, and death.[8-11] Many studies have subsequently demonstrated a consistent association between reduced GFR and specific CV diagnoses of congestive heart failure, myocardial infarction, stroke, and peripheral vascular disease.[8,12-14] This independent contribution of reduced GFR to the fatal and nonfatal CV disease burden has not yet been quantified at a population-level.

Understanding the true societal impact of CKD requires evaluating the independent burdens of ESRD and reduced GFR-associated CV disease. Such data would guide national priorities regarding the benefit of early CKD detection.[15] Early CKD detection and management could defray costs related to eventual ESRD development and higher likelihood of CV disease development.[16] Thus, we aim to determine the burden of CV disease due to reduced GFR among 188 countries, compare this to the ESRD burden, and evaluate how this combined burden ranks among leading causes of health loss and premature death.

RESULTS

Global reduced-GFR mortality and DALYs in 2013

In 2013, 2.2 million deaths were associated with reduced GFR (Table 1, Figure 1).[17] Nearly 52 million DALYs were associated with reduced GFR (Table 1, Figure 2). These attributable deaths and DALYs account for 3.9% of total global deaths and 2.1% of total global DALYs in 2013, respectively (Table 1).

Changes in reduced GFR death and DALY rates since 1990

At the global level, among all ages, GFR-attributable median death and DALY counts have increased by 65.6% and 52.0%, respectively, whereas age-standardized rates of deaths and DALYs associated with reduced GFR have decreased by 10% and 8.1%, respectively (Tables 1-2, Figures 3-4). Compared with other metabolic risk factors, since 1990, among all ages, DALYs attributed to high fasting glucose (69.6%; UI: 60.9, 78.7); high total cholesterol (26.9%; UI: 19.8; 36.3); and high blood pressure (49.1%; UI: 43.2, 55.2) have all increased. Age-standardized DALY rates for the risk factors high blood pressure (-16.5; UI: -20.0, -12.5) and high total cholesterol (-27.5; UI: -31.5, -22.1) have decreased, whereas DALY rates associated with high fasting glucose remained relatively constant (0.2%; UI: -4.8, 5.6).

Geographic patterns for reduced GFR mortality in 2013

Among super-regions, reduced GFR ranked highest in Latin America/Caribbean (5th), with 7.0% of total deaths attributed and outranking metabolic risk factor high total cholesterol (7th). Within the High-income super-region, reduced GFR ranked 8th and was outranked by all metabolic risk factors except for low bone mineral density (17th). Reduced GFR ranked lowest in Sub-Saharan Africa (16th), though still out-ranked "high total cholesterol" (25th) for deaths (Figure 5).

Cardiovascular disease attributed to reduced GFR

Throughout the world in 2013, there were 1.2 million CV deaths attributed to reduced GFR, with an age-standardized rate of 20.8 deaths per 100,000 (Table 2). Since 1990, reduced GFR associated-CV deaths have increased by 33.8% (UI: 24.6, 43.8), while the age-standardized GFR-attributable rate has decreased by 28.6% (Table 2). The 2013 age-standardized CV mortality rate within the developing world (21.5 per 100,000) was slightly higher than in the developed world (19.2 per 100,000) (Table 2). Notably, the age-standardized CV mortality rate in the developing world has decreased slightly since 1990 (9.5% decline), whereas the developed world has demonstrated a 44% decline in age-standardized CV mortality (Table 2).

Reduced GFR was responsible for 18.7 million CV DALYs in 2013 among all ages, and an age-standardized rate of 304.2 DALYS per 100,000 (Table 3, Figure 6). The developing world region had a higher rate, as well as smaller decrease in rate since 1990 when compared to the developed world (Table 3).

Among super-regions, the highest age-standardized GFR-attributed CV mortality rates were estimated for Central Europe, Eastern Europe, Central Asia, and sub-Saharan Africa (Table 2). Since 1990, GFR-attributed cardiovascular mortality rates

in sub-Saharan Africa and South Asia tended to increase, as opposed to all other super-regions. The High-income world region demonstrated the greatest decrease in mortality rate since 1990 (Table 2).

ESRD deaths and CKD DALYs

Globally there were 956,246 (UI: 812,896, 1,034,491) deaths due to ESRD in 2013, with an age-standardized rate of 15.8 per 100,000 (Table 2). Since 1990, both the number of deaths (134.6%; 95% UI: 115.7%, 150.2%) and age-standardized mortality rate (36.9%) have increased (Table 2). The age-standardized mortality rate in the developing world was almost twice that of the developed, and has increased by 44.7% since 1990, compared to the 9.8% increase within the developed world (Table 2).

The super-region with highest ESRD mortality rate in 2013 was Latin America/Caribbean, with an ESRD mortality rate of 32/100,000, which is almost double the global rate (Tables 2, Figure 7). South Asia demonstrated the greatest increase in CKD deaths (82.9%) since 1990, though all developing super-regions demonstrated an increase in ESRD mortality (Table 2).

At the global level, age-standardized ESRD DALY rates have increased by 12.3%, but this increase largely occurred within the developing world (Table 3). 2013 ESRD DALY rates were highest in the Latin America and Caribbean region (829/100,000), and lowest for Central Europe, Eastern Europe, Central Asia (398/100,000) and Southeast Asia, East Asia, and Oceania (393/100,000) (Table 3). Age-standardized rates have decreased in three world regions since 1990 (Central Europe, Eastern Europe, and Central Asia (-6.7%), High-income (-0.7%), and North Africa and Middle East (-3.1%). The largest increases in age-standardized CKD DALY rates occurred in Latin America and Caribbean (39.1%) and South Asia (39.6%), driving the notable increase in the CKD DALY rate within the developing world in comparison to the developed world.

DISCUSSION

The Global Burden of Diseases, Injuries, and Risk Factors Study 2013 ranks reduced GFR as the 12th leading risk factor for death at the global level, and the 14th risk factor for DALYs among 79 risk factors in 2013.[18] Within world regions such as High-income and Latin America and Caribbean, the mortality ranking was as high as eighth and fifth, respectively. This analysis provides granular detail regarding the contribution of CV disease caused by reduced GFR to these rankings. In 2013, more than 2 million deaths and 52 million DALYs were associated with reduced GFR. More than half of attributable deaths were estimated to have occurred secondary to CV disease.

The Global Burden of Disease Study indicates that in 1990, the developed world demonstrated notably higher rates of total CV disease than developing world regions.[19,20] Over time, the burden of total fatal CV disease has markedly declined in the developed world, whereas it has increased within developing regions.[20] These shifting patterns of total CV disease activity in the developed and developing worlds are driving the overall pattern that we report of GFR-attributable CV DALY and death activity. There are likely three factors contributing to the increase in total CV disease mortality within the developing world. First, improved success in treating leading causes of premature mortality within resource-limited nations, mainly related to infectious diseases and maternal-perinatal mortality, has allowed individuals to reach more advanced age and thus develop conditions related to aging.[21] Second, the shift in diet towards greater intake of animal fat and high-caloric food has been documented within the developing world for at least the past decade, facilitating CV disease development. Third, limited implementation of cardiovascular risk factor detection, treatment, and disease management within the developing world in the setting of a growing burden led to sustained mortality rates.[20-22] The differences between age-standardized and all age rates merit further research.

Our results which show the attributable CV burden within the developed world may illustrate the success within regions such as North America and Western Europe in addressing risk factors for incident CV disease over the past decades.[23] Importantly, when comparing the reduced GFR risk factor to other CV risk factors such as high blood glucose, high blood pressure, elevated total cholesterol, and smoking, reduced GFR and elevated fasting glucose had the lowest decrease in DALY rates within the past two decades.[17] This finding suggests that building on the success of CV risk factor detection and treatment will require paying equal attention in the coming years to more novel CV risk factors, such as reduced GFR.

The potential public health benefits of CKD screening have been evaluated in the past.[15,25,26] Cost-effectiveness CKD screening studies that fully incorporated fatal and non-fatal CV outcomes as well as incident ESRD have concluded CKD screening within the general population to be cost-effective, in opposition to results of studies that only incorporated ESRD outcomes and fatal CV disease.[16,24,25] Our results are the first to quantify and compare ESRD and reduced GFR attributable CV outcomes

across developed and developing nations, and illustrate that ESRD represents less than half of health events attributable to reduced GFR, even within the developing world. This reiterates the importance of CV fatal and nonfatal disease incorporation into evaluations of the health and economic benefits of population CKD screening. Within low- and middle-income nations, it is possible that CKD screening is of even higher importance in forestalling ESRD development, since renal replacement therapy is limited in more than half of the world's countries.[26]

There is need for evidence demonstrating that slowing CKD progression lowers cardiovascular disease incidence and mortality. Despite this there are strong arguments for population-level CKD screening. CKD screening using even urinalysis could potentially improve screening for hypertension and diabetes, the treatment of which would forestall CKD progression.[27 28] Within developed nations, there are screening recommendations for diabetes and hypertension, but if CKD is advanced at the time of detection, management of diabetes and hypertension is more challenging.[29]

Within developing countries, access to care is a barrier to chronic disease detection and treatment.[19,30] Literature suggests that the prevalence of undiagnosed hypertension and diabetes is higher in developing than developed nations.[30] Yet there are examples of cost-effective efforts to detect and treat chronic diseases even within resource-limited settings. The non-profit organization MoPoTsyo employs a community health worker approach to screen rural Cambodian adults for diabetes, hypertension, obesity, and CKD and initiates treatment for these conditions, paired with diet and lifestyle modification and strict follow-up.[31] Results from this organization indicate very favorable control of diabetes mellitus, hypertension, and CKD progression.[32] Similar results have been published for chronic disease outreach programs in the Philippines and DR Congo.[33] Such novel screening and management interventions illustrate the importance and feasibility of chronic disease detection and management to delay progression even in remote settings.

CKD DALYs and ESRD deaths have been increasing globally because of increasing ESRD burden in developing nations.[34] This pattern is also likely multi-factorial. Possible additional contributors to those discussed above include the increasing global burden of obesity and diabetes mellitus, known leading causes of CKD.[35,36] Of concern is the limited infrastructure within many developing nations to provide maintenance renal replacement therapy or renal transplantation for individuals with advanced CKD, considering that such countries healthcare systems are already burdened with management of infectious diseases and malnutrition.[26,37]

Within the developed region, though CKD DALY rates have decreased slightly since 1990, mortality rates have not, which could be explained in part by increasing age at death. This is in notable contrast to the almost 45% reduction over that time period in CV disease deaths associated with reduced GFR within the developed world. Success in addressing this CKD burden will likely involve continued efforts at early diagnosis and treatment of hypertension, diabetes mellitus, and also early-stage

CKD. These measures will also be necessary within developing nations, coupled with infrastructure development for treatment of ESRD.[38,39]

Within certain regions, unique contributors to ESRD development require focused attention by that nation's healthcare infrastructure. This concerns not only usually considered diabetes mellitus, hypertension, HIV and other well-known factors leading to kidney damage — but also the *chronic kidney disease of unknown etiology* (CKDu). The later studied recently mainly in specific Latin American and Southeast Asian countries[40-44], with several hypothesized causes including environmental exposures, toxins, and climate change, but to date there is no clear etiological factor was revealed.[45] CKDu often targets young men to a higher degree than CKD caused by known factors,[40-44] and is now considered endemic in countries such as Sri Lanka, India, El Salvador and Nicaragua, and is the leading cause of hospital deaths in El Salvador.[45,46] The challenges surrounding the CKDu epidemic exemplify how methods for detecting and addressing CKD burden may have to extend beyond screening for traditional CKD risk factors within classically defined high-risk portions of the population in order to prevent ESRD deaths and CKD DALYs.

Making global estimates inherently requires assumptions and has limitations. First, the CKD prevalence data was only available for 44 countries and among the more than 1000 surveys, methods were often not optimal and within most countries, not all time points were included. The Bayesian methods provide the best estimates possible but are limited by the quality of the available data. Furthermore, inconsistency of data collection of time and world region could influence trends and geographic variation. An area for improvement of this analysis involve incorporating albuminuria into the exposure definition for PAF calculation. There is strong evidence in the literature demonstrating the independent association between albuminuria and CV events, in isolation of and in addition to reduced GFR.[47] Thus the estimates that we present might possibly underestimate the true burden of cardiovascular events associated with CKD. These limitations serve as steps for improvement of future estimations.

A significant strength of this study involves the relative risk determination for incident CV events by stage of kidney dysfunction in a global consortium. Further strengths involve our ability to estimate fatal and non-fatal burden for specific CV diseases as well as ESRD throughout the world and across time.

The death rate from ESRD is increasing throughout the world and is a leading cause of death in world regions such as Central Latin America. Efforts to forestall such rates will involve detecting CKD earlier. Affordable means of detecting early-stage CKD are available, as well as affordable means of treating early stage CKD to delay progression.[48] In order to evaluate whether such screening methods should be recommended for the general population, further cost-effectiveness analyses will need to be conducted that incorporate the 1.2 million CV disease deaths throughout the world attributable to reduced GFR. It will be difficult to alter death rates within the CKD population without such studies and screening efforts.

CONCISE METHODS

Study overview

This analysis follows the risk assessment framework used in the Global Burden of Disease (GBD) Study 2013 for 79 individual and combined risk factors, where prevalence of the exposure is determined, a theoretical minimum risk is defined, and the relative risk of a causally related health outcome is quantified.[18,49]

Population-attributable fractions (PAFs)

We calculated the CV fatal and nonfatal burden attributable to the categorical exposure of reduced GFR categories using the following equation:

$$PAF = \frac{\sum_{i=1}^{n} P_i(RR_i - 1)}{\sum_{i=1}^{n} P_i(RR_i - 1) + 1}$$

Equation 1. PAF based on categorical exposure

where RR_i is the relative risk for exposure level i, P_i is the proportion of the population in that exposure category, and n is the number of exposure categories.[50]

Exposure

An overview of the modeling method used for determining country-level prevalence of GFR categories <15ml/min/1.73m^2 (not on dialysis), 15-30 ml/min/1.73m^2, 30-60 ml/min/1.73m^2 is provided in the accompanying appendix (A.2.). We used these country prevalence estimates of reduced GFR categories as our exposure categories.

Relative risk determination

Relative risks of cardiovascular outcomes of ischemic heart disease and stroke per GFR exposure category were derived from cohort data included in the Chronic Kidney Disease Prognosis Consortium (14 cohorts, n = 135,484) with estimated kidney function based on serum creatinine and prospective assessment of fatal and nonfatal cardiovascular events (Supplemental Table 3).[51] The relative risk for peripheral vascular disease by stage of reduced renal function was determined from the Atherosclerotic Risk in the Communities (ARIC) cohort. We attributed 100% of ESRD incidence and mortality to reduced GFR (details provided in Appendix A.3. "Relative Risk determination").

Outcomes

CV outcomes of IHD, stroke, and PVD, ESRD deaths and CKD DALYs at the country/age/sex/year level were obtained from the Global Burden of Disease 2013 Study (Appendix A.4.)

World regions

The countries of which regions and super-regions are comprised are listed in Supplemental Table 1.

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FIGURE LEGENDS

Figure 1. **a. Age-standardized** deaths per 100,000 in 2013 attributed to reduced GFR
b. Age-standardized DALYs per 100,000 in 2013 attributed to reduced GFR

Figure 2. a. Age-standardized mortality rate attributed to reduced GFR at the global, developed, and developing levels at 6 time-points between 1990 and 2013
b. Age-standardized DALY rate attributable to reduced GFR at the global, developed, and developing levels at 6 time-points between 1990 and 2013

Figure 3. Risk factor ranking for deaths in 2013 per 100,000 among seven super-regions

Figure 4. Cardiovascular DALYs per 100,000 attributable to reduced GFR in 2013

Figure 5. Chronic Kidney Disease (CKD categories 3,4,5, and maintenance dialysis) DALYS per 100,000 attributable to reduced GFR in 2013