Global Cardiovascular and Renal Outcomes of Reduced GFR


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ABSTRACT
The burden of premature death and health loss from ESRD is well described. Less is known regarding the burden of cardiovascular disease attributable to reduced GFR. We estimated the prevalence of reduced GFR categories 3, 4, and 5 (not on RRT) for 188 countries at six time points from 1990 to 2013. Relative risks of cardiovascular outcomes by three categories of reduced GFR were calculated by pooled random effects meta-analysis. Results are presented as deaths for outcomes of cardiovascular disease and ESRD and as disability-adjusted life years for outcomes of cardiovascular disease, GFR categories 3, 4, and 5, and ESRD. In 2013, reduced GFR was associated with 4% of deaths worldwide, or 2.2 million deaths (95% uncertainty interval [95% UI], 2.0 to 2.4 million). More than half of these attributable deaths were cardiovascular deaths (1.2 million; 95% UI, 1.1 to 1.4 million), whereas 0.96 million (95% UI, 0.81 to 1.0 million) were ESRD-related deaths. Compared with metabolic risk factors, reduced GFR ranked below high systolic BP, high body mass index, and high fasting plasma glucose, and similarly with high total cholesterol as a risk factor for disability-adjusted life years in both developed and developing world regions. In conclusion, by 2013, cardiovascular deaths attributed to reduced GFR outnumbered ESRD deaths throughout the world. Studies are needed to evaluate the benefit of early detection of CKD and treatment to decrease these deaths.
Understanding the true societal effect 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. Early CKD detection and management could defray costs related to eventual ESRD development and higher likelihood of CV disease.

Figure 1. Higher burden of GFR-attributable deaths and disability-adjusted life years (DALYs) by world region in 2013. (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.
Among super-regions, reduced GFR ranked eighth and was outranked by all metabolic risk factors except for low bone mineral density (17th). Reduced GFR was outranked by high fasting glucose (26.9%; 95% UI, 19.8 to 36.3), and high BP (49.1%; 95% UI, 43.2 to 55.2) have all increased (Supplemental Figure 1). Age-standardized DALY rates for the risk factors high BP (−16.5 mmHg; 95% UI, −20.0 to −12.5) and high total cholesterol (−27.5; 95% UI, −31.5 to −22.1) have decreased, whereas DALY rates associated with high fasting glucose have remained relatively constant (0.2%; 95% UI, −4.8 to 5.6).

Geographic Patterns for Reduced GFR Mortality in 2013
Among super-regions, reduced GFR ranked highest in Latin America and the Caribbean (fifth), with 7.0% of total attributed deaths and outranking metabolic risk factor high total cholesterol (seventh). Within the high-income super-region, reduced GFR ranked eighth and was outranked by all metabolic risk factors except for low bone mineral density (17th). Reduced GFR ranked lowest in sub-Saharan Africa (16th), but still outranked high total cholesterol (25th) with regards to deaths (Figures 2 and 3).

CV Disease Attributed to Reduced GFR
In 2013, globally 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% (95% UI, 24.6 to 43.8), whereas 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, with an age-standardized rate of 304.2 DALYs per 100,000 (Figure 4, Table 3). The developing world had a higher rate, as well as a smaller decrease in rate since 1990, when compared with 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 CV mortality rates in sub-Saharan Africa and South Asia tended to increase, as opposed to all other super-regions. The high-income super-region demonstrated the greatest decrease in mortality rate since 1990 (Table 2).

ESRD Deaths and CKD DALYs
Globally there were 956,246 (95% UI, 812,896 to 1,034,491) deaths because of 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% to 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 with the 9.8% increase within the developed world (Table 2).

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

Table 1. 2013 GFR-attributable deaths and DALY counts among all ages

<table>
<thead>
<tr>
<th>World Region</th>
<th>Mortality Counts (95% UI)</th>
<th>PAF% (95% UI)</th>
<th>DALYs Counts (95% UI)</th>
<th>PAF% (95% UI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>2,163,699 (1,959,711 to 2,387,042)</td>
<td>3.9 (3.6 to 4.3)</td>
<td>51,905,836 (46,245,898 to 57,573,443)</td>
<td>2.1 (1.9 to 2.3)</td>
</tr>
<tr>
<td>Developed</td>
<td>696,832 (615,822 to 797,400)</td>
<td>5.3 (4.7 to 6.1)</td>
<td>12,699,916 (11,026,556 to 14,497,193)</td>
<td>3.3 (2.9 to 3.7)</td>
</tr>
<tr>
<td>Developing</td>
<td>1,466,868 (1,256,422 to 1,633,677)</td>
<td>3.5 (3.0 to 3.9)</td>
<td>39,205,920 (33,942,972 to 43,716,898)</td>
<td>1.9 (1.7 to 2.1)</td>
</tr>
</tbody>
</table>

Data in parentheses indicate 95% uncertainty intervals.
At the global level, age-standardized CKD DALY rates have increased by 12.3%, but this increase largely occurred within the developing world (Table 3). In 2013, CKD DALY rates were highest in the Latin America and the Caribbean region (829 per 100,000), and lowest for Central Europe, Eastern Europe, Central Asia (398 per 100,000) and Southeast Asia, East Asia, and Oceania (393 per 100,000) (Figure 5, 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%]) (Table 3). The largest increases in age-standardized CKD DALY rates occurred in Latin America and the 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 Disease (GBD) Study 2013 ranks reduced GFR as the 12th leading risk factor for CV and ESRD deaths at the global level, and the 14th leading risk factor for DALYs among 79 risk factors in 2013.17 Within world regions such as high-income and Latin America and the 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, >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 GBD Study indicates that in 1990, the developed world demonstrated notably higher rates of total CV disease among all ages than in developing world regions. Over time, the burden of age-standardized fatal CV disease has markedly declined in the developed world, whereas it has largely remained stable within developing regions.18 These shifting patterns of total CV disease activity in the developed and developing worlds are driving the overall pattern of GFR-attributable CV DALY and death activity. There are likely three factors contributing to the change in prevalence of total CV disease 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.18–20 Second, the shift in diet toward 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 CV risk factor detection, treatment, and disease management within the developing world in the setting of a growing burden has led to sustained mortality rates.18,20,21 The differences between age-standardized and all age rates merit further research.

Our results showing 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.\textsuperscript{22} Importantly, when comparing the reduced GFR risk factor to other CV risk factors, such as high blood glucose, high BP, elevated total cholesterol, and smoking, reduced GFR and elevated fasting glucose had the lowest decrease in DALY rates within the past two decades.\textsuperscript{17} This finding suggests that building on the success of CV risk factor detection and treatment will require paying equal attention to more novel CV risk factors, such as reduced GFR, in the coming years, as well as their treatments.

Regarding ESRD deaths and CKD DALYs, recent meta-analyses have estimated >2 million individuals to have died prematurely in 2010 because of lack of access to dialysis, and that the majority of these deaths occurred within Southeast Asia and Africa.\textsuperscript{23,24} Similar to these estimates, our results indicate a high burden of CKD DALYs to have occurred in sub-Saharan Africa, but our results also highlight the very high burden of CKD DALYs in Mexico, most likely related to their extraordinarily high rate of diabetes mellitus.\textsuperscript{25} Despite high death rates to ESRD within world regions with no ESRD care access, the literature also describes the encouraging statistic of growth in dialysis provision over the past two decades. Studies indicate that this growth relates more to government expansion of dialysis programs rather than the increase in causative diseases of ESRD, such as diabetes and hypertension.\textsuperscript{24} Considering this, attention needs to be paid to ESRD prevention strategies alongside continued development of ESRD programs.

The potential public health benefits of CKD screening have been evaluated in the past.\textsuperscript{15,24–26} Cost-effectiveness CKD screening studies that fully incorporated fatal and nonfatal 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.\textsuperscript{16,29,30} These 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 countries, it is possible that CKD screening is of even higher importance in forestalling ESRD development, because RRT is limited in more than half of the world’s countries.\textsuperscript{24}

Evidence exists from randomized controlled trials of the benefit of statins in lowering CV morbidity.\textsuperscript{33} A recent major meta-analysis described that intensive BP control tended to reduce the relative risk of some CV outcomes, although not CV mortality or ESRD development.\textsuperscript{34} There is need for similar evidence demonstrating that diagnosing CKD early and slowing CKD progression lowers CV disease incidence and mortality. There are strong arguments that population-level CKD screening using urinary albumin and GFR measurement could potentially complement screening for hypertension and

![Figure 2. Developing world region has lower GFR-attributable age-standardized rates of deaths and DALYs over time. (A) Age-standardized mortality rate attributed to reduced GFR at the global, developed, and developing levels at six time points between 1990 and 2013. (B) Age-standardized DALY rate attributable to reduced GFR at the global, developed, and developing levels at six time points between 1990 and 2013.](www.jasn.org)
diabetes, the treatment of which would forestall CKD progression.\textsuperscript{33–35}

In developing countries, access to care is a barrier to chronic disease detection and treatment.\textsuperscript{26} Literature suggests that the prevalence of undiagnosed hypertension and diabetes is higher in developing than developed nations.\textsuperscript{26} Yet there are examples of efforts to detect and treat chronic diseases even within resource-limited settings. A nonprofit organization within Cambodia uses 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.\textsuperscript{38} Results from this organization indicate very favorable control of diabetes mellitus, hypertension, and CKD progression.\textsuperscript{39} Similar results have been published for chronic disease outreach programs in the Philippines and the Democratic Republic of Congo.\textsuperscript{40} Such screening and management interventions illustrate the importance and feasibility of chronic disease detection and management to delay progression, even in remote settings.

Within the developed region, although 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 early-stage CKD. These measures will also be necessary within developing nations, coupled with infrastructure development for treatment of ESRD.\textsuperscript{31,32}

Within certain regions, unique contributors to ESRD development require focused attention by that nation’s health care infrastructure. This concerns not only diabetes mellitus, hypertension, HIV, and other well known factors leading to kidney damage, but also the CKDus, the latter studied recently mainly in specific Latin American and Southeast Asian countries,\textsuperscript{41–45} with several hypothesized causes, including environmental exposures, toxins, and climate change. To date, there is no clear leading etiological factor.\textsuperscript{36} CKDu often targets young men to a higher degree than CKD caused by known factors,\textsuperscript{41–45} 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.\textsuperscript{36,37} 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, CKD prevalence data were only available for 44 countries; among these, 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 would involve incorporating albuminuria into the exposure definition for the population-attributable fractions (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.\textsuperscript{46} Thus, the estimates that we present might possibly underestimate the true burden of CV events associated with CKD. These limitations serve as steps for improvement of future estimations.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure3}
\caption{Fluctuating ranking of GFR risk factor by world region in 2013. Risk factor ranking for deaths in 2013 per 100,000 among seven super-regions. C, Central; E, East; HI, high-income; Latin Am, Latin America; MENA, Middle East and North Africa; PUFA, polyunsaturated fatty acids; S, South; SE, Southeast; Sub-Sah, sub-Saharan.}
\end{figure}
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 nonfatal burden for specific CV diseases as well as ESRD throughout the world and across time.

Reduced GFR-attributable CV deaths outnumber ESRD deaths at the global level, and the death rate from ESRD is increasing throughout the world and is a leading cause of death in world regions such as Latin America and the Caribbean. Efforts to forestall such rates will involve earlier detection of CKD. Affordable means of detecting early-stage CKD are available, as well as affordable means of treating early-stage CKD to delay progression.47 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 reduced GFR-attributable CV disease deaths. 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 2013 GBD Study 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 (Supplemental Appendix 1, Supplemental Table 3).17,48

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

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

where $R_{R_i}$ 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.49

Exposure An overview of the modeling method used for determining country-level prevalence of GFR categories <15 ml/min per 1.73 m² (not on dialysis), 15–29 ml/min per 1.73 m², and 30–59 ml/min per 1.73 m² is provided in Supplemental Appendices 2 and 5. We used these country-level prevalence estimates of reduced GFR categories as our exposure categories (Supplemental Tables 4–6).
### Table 3. CV and CKD DALYs attributable to reduced GFR in 2013

<table>
<thead>
<tr>
<th>World Regions</th>
<th>CV Disease</th>
<th>CKD Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GFR-Attributable Counts among All Ages</td>
<td>AS GFR-Attributable Rate per 100,000</td>
</tr>
<tr>
<td>Global</td>
<td>18,692,953 (16,347,710 to 21,874,776)</td>
<td>304.2 (266.7 to 354.0)</td>
</tr>
<tr>
<td>Developed</td>
<td>5,645,255 (4,902,452 to 6,477,730)</td>
<td>259.3 (226.4 to 298.3)</td>
</tr>
<tr>
<td>Developing</td>
<td>13,047,698 (11,057,015 to 15,643,702)</td>
<td>321.1 (274.1 to 384.1)</td>
</tr>
<tr>
<td>High-income</td>
<td>2,866,731 (2,392,244 to 3,394,840)</td>
<td>160.0 (134.1 to 189.3)</td>
</tr>
<tr>
<td>Central Europe, Eastern Europe, Central Asia</td>
<td>3,413,970 (2,937,079 to 3,983,708)</td>
<td>631.0 (543.4 to 733.4)</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>1,867,604 (1,562,751 to 2,234,589)</td>
<td>582.7 (492.2 to 683.4)</td>
</tr>
<tr>
<td>North Africa and Middle East</td>
<td>821,644 (689,936 to 1,000,608)</td>
<td>286.4 (240.1 to 347.3)</td>
</tr>
<tr>
<td>South Asia</td>
<td>4,735,628 (3,516,081 to 6,318,221)</td>
<td>462.5 (348.7 to 606.2)</td>
</tr>
<tr>
<td>Southeast Asia, East Asia, and Oceania</td>
<td>3,512,858 (2,561,677 to 4,657,418)</td>
<td>191.3 (138.9 to 256.9)</td>
</tr>
<tr>
<td>Latin America and Caribbean</td>
<td>1,474,518 (1,179,826 to 1,859,920)</td>
<td>350.6 (278.4 to 411.8)</td>
</tr>
</tbody>
</table>

Data in parentheses indicate 95% uncertainty intervals. Super-regions are comprised of the following regions: High-income: Asia Pacific, Australasia, Western Europe, Southern Latin America, North America; Central Europe, Eastern Europe, Central Asia; Central sub-Saharan Africa, Eastern sub-Saharan Africa, Southern sub-Saharan Africa, Western sub-Saharan Africa; North Africa and Middle East: North Africa, Middle East; South Asia: South Asia; Southeast Asia, East Asia; and Oceania: East Asia, Southeast Asia, Oceania. AS, age-standardized.
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Figure 5. Higher burden of GFR-attributable CKD (GFR categories 3, 4, 5, and maintenance dialysis) disability-adjusted life years (DALYs) by world region in 2013. CKD DALYs per 100,000 attributable to reduced GFR in 2013.
study, the collection, management, analysis, and interpretation of the data, or the preparation or approval of the manuscript.

A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org. A full list of participating REGARDS investigators and institutions can be found at http://www.regardsstudy.org.

DISCLOSURES

None.

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