

1 **Worldwide disparity in the relation between CKD prevalence and**  
2 **kidney failure risk**

3 Marieke HC van Rijn<sup>1,2</sup>, MSC, Natalia Alencar de Pinho<sup>2</sup>, PhD, Jack F Wetzels<sup>1</sup>, MD, Jan  
4 AJG van den Brand<sup>1</sup>, PhD, Benedicte Stengel<sup>2</sup>, PhD

5  
6 <sup>1</sup>Department of Nephrology, Radboud Institute of Health Sciences, Radboud University Medical  
7 Center, Nijmegen, The Netherlands.

8 <sup>2</sup>Univ. Paris-Saclay, UVSQ, Univ. Paris-Sud, Inserm, Clinical Epidemiology team, CESP, Villejuif, France

9  
10 Corresponding author:

11 Name : Benedicte Stengel  
12 University : CESP, Clinical Epidemiology Team  
13 Address : 16, avenue P. Vaillant Couturier  
14 94 807 Villejuif cedex  
15 E-mail : benedicte.stengel@inserm.fr  
16 Tel : 33 1 45 59 50 39

17  
18  
19  
20 Word count: 3193

21 Abstract: 249

22 Text: 2943

23  
24 Sources of support

25 Marieke HC van Rijn was supported by grants from the Radboud Institute for Health Sciences and the  
26 Dutch Kidney Foundation (150KK109).

27  
28 Running head : CKD prevalence and kidney failure risk

29  
30 Key words : chronic kidney disease, kidney replacement therapy, disparity, international comparison,  
31 ecologic study

1 **Abstract**

2 **Introduction**

3 The incidence of kidney replacement therapy (KRT) for kidney failure varies internationally much  
4 more than chronic kidney disease (CKD) prevalence. This ecologic study investigated the relation of  
5 CKD prevalence to KRT and mortality risks by world region.

6 **Methods**

7 We used data from Global Burden of Disease and KRT registries worldwide with linear models to  
8 estimate the percentages of variance in KRT incidence and all-cause mortality explained by age-  
9 adjusted prevalence of CKD stages 3-5, overall and by gender, in 61 countries classified in three  
10 regions: high-income (n=28), Eastern and Central Europe (n=15), and Other (n=18).

11 **Results**

12 The incidence of KRT ranged from 89 to 378 per million population in high-income regions, 32–222 in  
13 Central and Eastern Europe, and 22–493 in the Other region; age-adjusted CKD prevalence ranged  
14 respectively from 5.5 to 10.4%, 7.6–13.7%, and 7.4–13.1%. The relation between these indicators  
15 was positive in high-income countries, negative in Central and Eastern Europe, and null in the Other  
16 region. Age-adjusted CKD prevalence explained 40% of the variance in KRT incidence ( $P<0.001$ ) in  
17 high-income countries. The explained variance of age-adjusted mortality was close to zero in high-  
18 income countries and positive at 19% ( $P=0.10$ ) in Central and Eastern Europe and at 11% ( $P=0.17$ ) in  
19 the Other region. Results were consistent by gender.

20 **Conclusion**

21 This study raises awareness on the significant part of the gaps in KRT incidence across countries not  
22 explained by the number of individuals with CKD, even in high-income countries where access to KRT  
23 is not limited.

24

# 1 **Introduction**

2 Over the past two decades, knowledge about the epidemiology of chronic kidney disease (CKD) and  
3 its complications has advanced substantially worldwide.(1-6) The increasing availability of national  
4 registries of kidney replacement therapy (KRT) for kidney failure and the work by the Global Burden  
5 of Disease (GBD) consortium in recent years to search for and standardize CKD prevalence data from  
6 the many available population-based studies have made it possible to obtain a global picture of CKD  
7 burden from moderate to advanced stages.(7-9) The most striking finding from these estimates is  
8 that the disparities across countries are much greater for KRT incidence than for CKD prevalence.

9 The Global Kidney Health Atlas, led by the International Society of Nephrology (ISN), recently  
10 provided a comprehensive overview of the capacity of health systems to deliver care for kidney  
11 failure worldwide.(10) This capacity remains a major determinant of the variations observed in KRT  
12 incidence in low- and middle-income countries. Large variations in KRT incidence may also exist,  
13 however, across countries where access to KRT is not restricted. Hallan et al first pointed out this  
14 discrepancy in 2006, showing that KRT incidence in the United States was 3 times higher than in  
15 Norway, despite similar CKD prevalence. They suggested that faster progression to kidney failure  
16 rather than a higher number of individuals at risk likely explains this difference.(11) Since then, two  
17 studies have investigated potential explanatory factors for differences in CKD progression across  
18 countries.(12, 13) Nevertheless, no overview is available of the gaps in KRT incidence between  
19 countries with their links to CKD prevalence within and across world regions, although it would help  
20 in understanding the possible sources of variations.

21 We therefore studied the relations of CKD prevalence with the incidence of KRT for kidney failure  
22 and with all-cause and CKD-related mortality rates across countries, by region, both overall and by  
23 gender, and estimated the proportion of variance in these three latter health indicators that is  
24 explained by CKD prevalence.

# 1 **Methods**

## 2 **Data sources**

### 3 **Chronic kidney disease prevalence**

4 Crude (all ages) and age-standardized CKD prevalences in 2016, expressed as percentages, were  
5 extracted overall and by gender from the Global Health Data exchange, GBD Results Tool website  
6 (<http://ghdx.healthdata.org/gbd-results-tool>). In the GBD Study, CKD is defined by an estimated  
7 glomerular filtration rate < 60 ml/min/1.73m<sup>2</sup> or a need for KRT. Data that inform GBD estimates  
8 include microdata or tabulated data obtained from publications (systematic literature reviews), as  
9 well as other relevant data sources such as vital registrations, hospital data, and disease registries  
10 (citations available on <http://ghdx.healthdata.org/gbd-2017/data-input-sources>). Prevalence is  
11 estimated with a compartmental model that allows data to be incorporated for various  
12 epidemiological indicators, such as incidence and mortality rates, through an integrative Bayesian  
13 meta-regression.(14) It is based on (one or multiple) individual (national representative or local)  
14 studies or other data sources within a country. When there is no data for that country available,  
15 modeling may consider information from other countries with similar epidemiological backgrounds.  
16 Prevalence estimates were age-standardized by the GBD 2017 world standard population.(15)

17

### 18 **Incidence of kidney replacement therapy for kidney failure**

19 Kidney replacement therapy included dialysis or pre-emptive kidney transplantation and its incidence  
20 was expressed per million population (pmp). We used data gathered by the United States Renal Data  
21 System (USRDS) from national KRT registries worldwide willing to contribute data to the international  
22 comparison chapter of this report. We extracted data for the crude incidence of KRT for the year  
23 2016, overall and by gender, from the USRDS website  
24 ([https://www.usrds.org/2018/view/v2\\_11.aspx](https://www.usrds.org/2018/view/v2_11.aspx)). Age-adjusted estimates were not available.(7)

1 **All-cause mortality**

2 Age-standardized all-cause and CKD-related mortality rates per 100 000 population, overall and by  
3 gender, from 2016 were extracted from the World Health Organization (WHO), Global Health  
4 Estimates website ([http://origin.who.int/healthinfo/global\\_burden\\_disease/estimates/en/](http://origin.who.int/healthinfo/global_burden_disease/estimates/en/)).(16)  
5 WHO 2016 mortality rates are based on the latest available national-level information about  
6 mortality and causes of death at the beginning of 2018. WHO also uses estimates from the 2016 GBD  
7 Study for countries without usable vital registration data or other nationally representative sources  
8 of information for causes of death.(17) CKD-related mortality included deaths from diabetes-related  
9 CKD and from CKD due to other causes. Mortality rates were age-standardized according to the WHO  
10 2001 standard population.(18)

11

12 **Global Burden of Disease regional classification system**

13 The 61 countries or regions included in this study, because of the availability of KRT incidence, were  
14 classified into three regions or categories, using GBD super regions, defined by a combination of  
15 geographic location and country GDP, and based on cause of death patterns  
16 (<http://www.healthdata.org/terms-defined>), as follows: (14)

17 • High-income regions: high-income Asia Pacific (Japan, South Korea, and Singapore),  
18 Australasia (Australia and New Zealand), Western Europe (Andorra, Austria, Belgium, Cyprus,  
19 Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg,  
20 Malta, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, and the United Kingdom),  
21 Southern Latin America (Argentina, Chile, and Uruguay) and North America (Canada and the  
22 United States)

23 • Central and Eastern Europe: Lithuania, Slovakia, Latvia, Hungary, Russia, Bulgaria, Romania,  
24 Belarus, Serbia, Albania, Bosnia and Herzegovina, Macedonia, and Ukraine

25 • Other regions: Latin America (Jalisco [Mexico], Brazil, Peru, Colombia, and Guatemala), North  
26 Africa and Middle East (Qatar, Saudi Arabia, Kuwait, Iran, Turkey, and Jordan), South, East,

1 and Southeast Asia (Hong Kong, Malaysia, Taiwan, Thailand, Philippines, Indonesia, and  
2 Bangladesh), and Southern Sub-Saharan Africa (South Africa).

3

#### 4 **Statistical Analysis**

5 Estimates of CKD prevalence (%), KRT incidence (pmp), and all-cause and CKD-related mortality (per  
6 100 000 population) were tabulated and are presented as median and ranges according to region, as  
7 described above (high-income, Central and Eastern Europe, or Other), overall and by gender. To  
8 study the relations with KRT incidence, we plotted crude KRT incidence rates against crude and age-  
9 adjusted CKD prevalence, by region, overall and by gender, and for the relations with mortality risk,  
10 age-adjusted all-cause or CKD-related mortality rates against age-standardized CKD prevalence, again  
11 by region, overall and by gender. In addition, we used linear regression models to estimate the  
12 proportion of variance (R-squared) in KRT incidence and mortality rates explained by CKD prevalence.  
13 We tested the linearity assumption for all regression models, which was not satisfied for the analysis  
14 of the association with mortality rates and required log-transformation. Other model assumptions  
15 (normality of residuals, link function, and homoscedasticity) were checked with the Global Validation  
16 of Linear Models Assumptions “glvma” package. Analyses were performed in R version 3.4.2.

17

## 1 **Results**

### 2 **Geographic variations in age-standardized CKD prevalence, by gender and region**

3 The age-standardized prevalence of CKD stages 3-5 ranged from 5.5% to 10.4% (median 6.3%) in the  
4 high-income region, 7.6% to 13.7% (median 8.7%) in Central and Eastern Europe, and 7.4% to 13.1%  
5 (median 10.7%) in the Other region (Supplementary Table 1A). The prevalence of CKD was higher in  
6 women than in men in all countries except Sweden (Supplementary Table 1B).

7

### 8 **Geographic variations in *kidney replacement therapy incidence*, by gender and region**

9 Overall, KRT incidence rates were highest in Taiwan (493 pmp), the USA (378 pmp), Mexico (355  
10 pmp) and Thailand (345 pmp) and lowest in South Africa (22 pmp), Ukraine (32 pmp), Bangladesh,  
11 and Belarus (51 pmp). The median KRT incidence was 155 pmp, ranging from 89 to 378 in the high  
12 income region, 107 pmp ranging from 32 to 222 in Central and Eastern Europe, and 140 pmp, ranging  
13 from 22 to 493 in the Other region. The incidence was higher in men than women in all countries but  
14 one, with sex ratios ranging from 1.04 in Bulgaria to 2.5 in Estonia. In Jordan more women (70 pmp)  
15 than men (51 pmp) received treatment for KRT.

16

### 17 **Geographic variations in age-adjusted all-cause *and CKD-related* mortality rate, by gender**

18 The age-standardized all-cause mortality rate per 100 000 ranged from 299 in Japan to 555 in  
19 Argentina in the high-income region (median 360), from 525 in Estonia and Bosnia Herzegovina to  
20 798 in Russia in Central and Eastern Europe (median 647), and from 523 in Qatar to 1213 in South  
21 Africa in the Other region (median 640) (Supplementary Table 2A). All-cause mortality rates were  
22 higher in men than in women in all countries, with sex ratios ranging from 1.15 in Kuwait to 2.2 in  
23 Lithuania. The age-standardized CKD-related mortality rate ranged from 2.5 to 42.4 per 100 000 in  
24 the high-income region, from 3.5 to 17 in Central and Eastern Europe, and from 2.6 to 45.2 in the  
25 Other region.

1 **Ecologic associations between age-adjusted CKD prevalence and KRT incidence**

2 In the high-income region, there was a positive and statistically significant relation between the age-  
3 adjusted prevalence of CKD and KRT incidence (Figure 1). CKD prevalence explained 40% of the  
4 variation in KRT incidence, while 60% remained unexplained. Relations were similar when crude CKD  
5 prevalence was used (Supplementary Figure 1). In a subset of the 23 (of the 28 studied) high-income  
6 countries with available KRT incidence data stratified by gender, the percentage of explained  
7 variance was slightly lower in men than women (49% vs 56%, Supplementary Table 3). In Central and  
8 Eastern Europe, KRT incidence was negatively and statistically significantly related to both the crude  
9 and age-adjusted prevalence of CKD and did not differ by gender. In contrast, in countries from the  
10 Other region, crude CKD prevalence was positively and significantly related to KRT incidence  
11 (explained variance = 37%;  $P = 0.007$ ), but the relation was null with age-standardized prevalence.

12 Although differences in KRT incidence between countries with similar CKD prevalence were usually  
13 larger across than within regions, substantial intraregional variations were also observed. Western  
14 Europe is the region with the smallest differences across countries, but KRT incidence was  
15 nonetheless 3 times higher in Greece than in Iceland despite their similar CKD prevalence. In South,  
16 East, and Southeast Asia, KRT incidence varied from 1 to 10, for small differences in CKD prevalence.

17

18 **Ecologic associations between age-adjusted CKD prevalence and mortality risk**

19 In the high-income region, CKD prevalence explained a very low percentage of the variation in  
20 mortality (2%), while it tended to explain a higher but still not significant percentage in Central and  
21 Eastern Europe and in the Other region (Figure 2). This percentage was similar for both genders in  
22 the high-income and Other regions, but differed strongly by gender, 47% in men vs 0% in women, in  
23 Central and Eastern Europe (Supplementary Table 3). Regarding CKD-related mortality, the  
24 association was positive and statistically significant ( $p=0.016$ ) in high-income countries, negative ( $p =$   
25  $0.042$ ) in Central and Eastern Europe, and positive, but nonsignificant ( $p>0.10$ ) in the Other region  
26 (Supplementary Figure 2)



# 1 Discussion

2 We confirm the well-known greater gaps in KRT incidence than in CKD prevalence between countries  
3 in all of the GBD regions. The main novelty of this study is to highlight the high percentage of  
4 variation in KRT incidence not explained by the prevalence of CKD even in high-income countries  
5 (60%) where access to dialysis is not restricted. For similar CKD prevalence, KRT incidence rate can be  
6 up to three times higher from one country to another, as between Iceland and Greece. These results  
7 also show an unexpected negative association between these two kidney health indicators in Central  
8 and Eastern Europe, together with a weak, but positive association of CKD prevalence with all-cause  
9 mortality. An overview of these ecologic associations we observed can help raise global awareness  
10 about the issues and challenges regarding kidney failure prevention and care .

11

12 Our results extend worldwide the observation of significant discrepancies in the KRT-to-CKD ratio  
13 between countries, as described previously between Norway and the US white population.(11) Only  
14 a small fraction of individuals with CKD eventually progress to kidney failure, but if the variation in  
15 the number of individuals with CKD were the only explanation for that of KRT incidence, the ratio of  
16 KRT incidence to CKD prevalence would be similar across countries, and the percentage of variance  
17 explained would be 100%. In high-income countries, this percentage was 40%, which suggests that  
18 differences in the distribution of CKD risk factors play a substantial role in the variation of kidney  
19 failure incidence between countries. Nonetheless, although a meta-analysis of 19 general  
20 population-based studies from 13 European countries did find variations in CKD prevalence across  
21 these countries, differences in major CKD risk factors, including diabetes, hypertension, and obesity,  
22 did not appear to explain them well.(6, 8, 19-21) The negative relation or lack of association observed  
23 in Central and Eastern Europe and in the Other region, in contrast, cannot be interpreted as the  
24 absence of an impact of CKD risk factors, most especially as CKD prevalence is higher in these regions  
25 than in high-income countries.(6, 8, 19-21) In Central and Eastern Europe, the association of higher  
26 CKD prevalence with lower KRT incidence together with higher all-cause mortality may instead reflect

1 the combination, at the population level, of poor population health with a health care system with  
2 inadequate capacity. Several CKD risk factors are well established, including genetic, socioeconomic,  
3 and environmental risk factors, as well as poor maternal and fetal health. A landmark article  
4 reporting the conclusions of an ISN CKD summit on Global Kidney Health in 2016 updated these  
5 factors, which are summarized in the Table.(1, 22) These risk factors might be attenuated by  
6 promoting healthy lifestyles, improved education of the public and of health practitioners, and  
7 strategies to improve maternal and fetal health.

8 Although heterogeneity in the prevalence of CKD risk factors explains part of the variance in KRT  
9 incidence, this study shows that a significant part of this variance remains unexplained. Several  
10 hypotheses can be generated including variations across countries in risk factors for CKD progression  
11 or in access to KRT, as listed in the Table. Hallan et al first suggested that slower progression to  
12 kidney failure rather than a smaller number of individuals could account for the lower incidence of  
13 KRT in Norway than in the US.(11) Two recent meta-analyses of CKD cohort studies have investigated  
14 this hypothesis with individual-level data.(12, 13) The European CKD Burden Consortium, which used  
15 a joint model to compare estimated glomerular filtration rate (eGFR) decline and mortality risk across  
16 nine cohorts from five European countries, showed that baseline patient profiles and CKD  
17 progression rates differed substantially between studies.(12, 13) These variations in CKD progression,  
18 however, persisted despite adjustment for baseline eGFR, age, sex, albuminuria, comorbidities, and  
19 use of renin-angiotensin system inhibitors. The international network of CKD cohorts (iNET-CKD) has  
20 also observed different baseline profiles and highly heterogeneous risks of CKD progression, KRT  
21 incidence, and mortality among individuals with CKD participating in eight cohort studies around the  
22 globe.(12, 13) This study also observed that adjustment for several patient characteristics and  
23 laboratory markers did not substantially attenuate the differences in outcomes. Its finding that the  
24 magnitude of the associations of individual-level predictors with clinical outcomes varied  
25 substantially across studies suggests that the setting and/or differences in populations may influence  
26 these differences. Another iNET-CKD study finding of considerable heterogeneity in blood pressure

1 control and antihypertensive prescription patterns in CKD worldwide also indicates that clinical  
2 practices may have an effect.(23, 24)

3 Finally, because kidney failure incidence is assessed from dialysis and transplantation registries,  
4 factors linked to the management of transition to kidney failure and/or access to KRT may play a  
5 major role in the gaps observed between countries. (Table) It is well-known that access to KRT is  
6 influenced by local policies, and that several countries such as the United States, Japan, South Korea,  
7 or Taiwan, have very liberal criteria for acceptance on dialysis, while many European countries,  
8 Australia and New Zealand have a less liberal acceptance policy, and most African, Asia, and central  
9 or Eastern European countries have very limited access. An ecologic study of 46 countries reported  
10 that gross domestic product (GDP) per capita and percentage of GDP spent on health care were  
11 independently associated with KRT incidence.(3, 4, 10, 13, 25) It also showed that in more developed  
12 countries, the private for-profit share of hemodialysis facilities was also associated with higher KRT  
13 incidence, This study and ours raise the issue of overtreatment related to early-start dialysis in  
14 countries with extremely high KRT incidence. In France, eGFR level at dialysis start explained a  
15 substantial part of the variations in KRT incidence between regions.(26) Variations in the availability  
16 of conservative therapy may also have an impact in the elderly population, as suggested by the  
17 Global Kidney Health Atlas study.(10, 27) Overall, these meta-analyses highlight the complexity of the  
18 relations between CKD and KRT risk and the need for further investigation.

19 This study has several strengths including the large number of countries spread over the different  
20 GBD super regions with standardized estimates of kidney health indicators. Another strength is that  
21 we were able to assess the relations between CKD prevalence and KRT incidence by gender in many  
22 of these countries. We also looked at the relation between CKD prevalence and all-cause and CKD-  
23 related mortality risk, a major competing risk for KRT in CKD.

24 The study also has a number of limitations. First, it is an ecologic study, and the associations  
25 observed at the country level may be different at the individual level. Further studies comparing the  
26 relationship of CKD to kidney failure risk at the individual level are needed to identify potentially

1 modifiable risk factors and racial disparities. Second, the use of KRT registry data did not enable us to  
2 describe the association of CKD prevalence with kidney failure risk because KRT registries cannot  
3 capture patients who progress to kidney failure but do not have access to KRT, refuse dialysis, or  
4 receive conservative care. Moreover, age-standardized KRT incidence was not available. Third, CKD  
5 prevalence may have been affected by the use of different creatinine assays or GFR estimation  
6 equations across studies,(6, 8, 19-21) although the GBD correction methods should have reduced  
7 these disparities by standardizing these estimates. Fourth, the available reference population for  
8 age-standardization was different for the WHO and the GBD statistics. However, while this may have  
9 had an impact on mortality rate and CKD prevalence estimates, it should not have affected the  
10 associations we observed. Finally, the aggregation of countries with very diverse CKD epidemiology in  
11 one single “Other” group may be controversial, but the small number of these countries precluded a  
12 more detailed stratification.

13 In conclusion, this ecologic study highlights the large proportion of the global variation in KRT  
14 incidence that is apparently not explained by the number of individuals with CKD. While differences  
15 in health care resources are an obvious explanation of disparities in access to KRT, at least partly, in  
16 low- and middle-income countries, other hypotheses should be assessed for high-income countries,  
17 such as variations in clinical practice patterns intended to slow CKD progression and/or manage the  
18 transition to KRT. (28, 29) The issue of dialysis overtreatment is scarcely discussed and may receive  
19 greater attention from both the patients and public health perspective. International comparisons at  
20 both patient and provider levels are necessary to investigate the relative impact of individual  
21 characteristics, physician practices, and local policies on the incidence of KRT.

1 **Disclosure**

2 Marieke HC van Rijn (None), Natalia Alencar de Pinho (None), Jack F Wetzels (None) , Jan AJG van  
3 den Brand (None), Benedicte Stengel (None)

4 **None**

5 **Acknowledgments**

6 Marieke HC van Rijn was supported by grants from the Radboud Institute for Health Sciences and the  
7 Dutch Kidney Foundation (150KK109). We thank Joe Coresh for his helpful comment in this study and  
8 Jo-Ann Cahn for her editorial assistance.

## 1   **References**

- 2   1.       Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, et al. Chronic kidney disease: global  
3   dimension and perspectives. *Lancet*. 2013;382(9888):260-72.
- 4   2.       Nitsch D, Grams M, Sang Y, Black C, Cirillo M, Djurdjev O, et al. Associations of estimated  
5   glomerular filtration rate and albuminuria with mortality and renal failure by sex: a meta-analysis.  
6   *Bmj*. 2013;346:f324.
- 7   3.       Thomas B, Matsushita K, Abate KH, Al-Aly Z, Arnlov J, Asayama K, et al. Global Cardiovascular  
8   and Renal Outcomes of Reduced GFR. *J Am Soc Nephrol*. 2017;28(7):2167-79.
- 9   4.       Caskey FJ, Jager KJ. A population approach to renal replacement therapy epidemiology:  
10   lessons from the EVEREST study. *Nephrology, dialysis, transplantation : official publication of the*  
11   *European Dialysis and Transplant Association - European Renal Association*. 2014;29(8):1494-9.
- 12   5.       Liyanaage T, Ninomiya T, Jha V, Neal B, Patrice HM, Okpechi I, et al. Worldwide access to  
13   treatment for end-stage kidney disease: a systematic review. *Lancet*. 2015;385(9981):1975-82.
- 14   6.       Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, et al. Global Prevalence of  
15   Chronic Kidney Disease - A Systematic Review and Meta-Analysis. *PLoS one*. 2016;11(7):e0158765.
- 16   7.       United States Renal Data System. 2018 USRDS annual data report: Epidemiology of Kidney  
17   Disease in the United States. National Institutes of Health, National Institute of Diabetes and  
18   Digestive and Kidney Diseases, Bethesda, MD, 2018
- 19   8.       Mills KT, Xu Y, Zhang W, Bundy JD, Chen CS, Kelly TN, et al. A systematic analysis of  
20   worldwide population-based data on the global burden of chronic kidney disease in 2010. *Kidney Int*.  
21   2015;88(5):950-7.
- 22   9.       Bikbov B, Perico N, Remuzzi G, on behalf of the GBDGDEG. Disparities in Chronic Kidney  
23   Disease Prevalence among Males and Females in 195 Countries: Analysis of the Global Burden of  
24   Disease 2016 Study. *Nephron*. 2018;139(4):313-8.
- 25   10.      Bello AK, Levin A, Lunney M, Osman MA, Ye F, Ashuntantang GE, et al. Status of care for end  
26   stage kidney disease in countries and regions worldwide: international cross sectional survey. *Bmj*.  
27   2019;367:l5873.
- 28   11.      Hallan SI, Coresh J, Astor BC, Asberg A, Powe NR, Romundstad S, et al. International  
29   comparison of the relationship of chronic kidney disease prevalence and ESRD risk. *J Am Soc Nephrol*.  
30   2006;17(8):2275-84.
- 31   12.      Bruck K, Jager KJ, Zoccali C, Bello AK, Minutolo R, Ioannou K, et al. Different rates of  
32   progression and mortality in patients with chronic kidney disease at outpatient nephrology clinics  
33   across Europe. *Kidney Int*. 2018;93(6):1432-41.
- 34   13.      Orlandi PF, Huang J, Fukagawa M, Hoy W, Jha V, Oh KH, et al. A collaborative, individual-level  
35   analysis compared longitudinal outcomes across the International Network of Chronic Kidney Disease  
36   (iNETCKD) cohorts. *Kidney Int*. 2019;96(5):1217-33.
- 37   14.      Global Burden of Disease Injury, Incidence Prevalence, Collaborators. Global, regional, and  
38   national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195  
39   countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study  
40   2017. *Lancet*. 2018;392(10159):1789-858.
- 41   15.      Global Burden of Disease Injury, Incidence Prevalence, Collaborators. Global, regional, and  
42   national incidence, [ prevalence, and years lived with disability for 354 diseases and injuries for 195  
43   countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study  
44   2017. *Lancet*. 2018;392(10159):1789-858.
- 45   16.      Global Health Estimates 2016: Disease burden by Cause A, Sex, by Country and by Region,  
46   2000-2016. Geneva, World Health Organization; 2018.
- 47   17.      World Health Organization. WHO methods and data sources for global causes of death 2000-  
48   2016. Global Health Estimates Technical Paper. Geneva. 2018.
- 49   18.      Ahmad OB, Boschi-Pinto C, Lopez AD, Murray CJ, Lozano R, Inoue M. Age standardization of  
50   rates: A new who standard. GPE Discussion Paper Series: No31. World Health Organization 2001.

- 1 19. Bruck K, Stel VS, Gambaro G, Hallan S, Volzke H, Arnlov J, et al. CKD Prevalence Varies across  
2 the European General Population. *J Am Soc Nephrol*. 2015.
- 3 20. Stel VS, Bruck K, Fraser S, Zoccali C, Massy ZA, Jager KJ. International differences in chronic  
4 kidney disease prevalence: a key public health and epidemiologic research issue. *Nephrology,*  
5 *dialysis, transplantation : official publication of the European Dialysis and Transplant Association -*  
6 *European Renal Association*. 2017;32(suppl\_2):ii129-ii35.
- 7 21. De Nicola L, Zoccali C. Chronic kidney disease prevalence in the general population:  
8 heterogeneity and concerns. *Nephrology, dialysis, transplantation : official publication of the*  
9 *European Dialysis and Transplant Association - European Renal Association*. 2016;31(3):331-5.
- 10 22. Levin A, Tonelli M, Bonventre J, Coresh J, Donner JA, Fogo AB, et al. Global kidney health  
11 2017 and beyond: a roadmap for closing gaps in care, research, and policy. *Lancet*.  
12 2017;390(10105):1888-917.
- 13 23. Pecoits-Filho R, Fliser D, Tu C, Zee J, Bieber B, Wong MMY, et al. Prescription of renin-  
14 angiotensin-aldosterone system inhibitors (RAASi) and its determinants in patients with advanced  
15 CKD under nephrologist care. *J Clin Hypertens (Greenwich)*. 2019;21(7):991-1001.
- 16 24. Alencar de Pinho N, Levin A, Fukagawa M, Hoy WE, Pecoits-Filho R, Reichel H, et al.  
17 Considerable international variation exists in blood pressure control and antihypertensive  
18 prescription patterns in chronic kidney disease. *Kidney Int*. 2019;96(4):983-94.
- 19 25. Caskey FJ, Kramer A, Elliott RF, Stel VS, Covic A, Cusumano A, et al. Global variation in renal  
20 replacement therapy for end-stage renal disease. *Nephrology, dialysis, transplantation : official*  
21 *publication of the European Dialysis and Transplant Association - European Renal Association*.  
22 2011;26(8):2604-10.
- 23 26. Couchoud C, Guihenneuc C, Bayer F, Stengel B, Registry R. The timing of dialysis initiation  
24 affects the incidence of renal replacement therapy. *Nephrology, dialysis, transplantation : official*  
25 *publication of the European Dialysis and Transplant Association - European Renal Association*.  
26 2010;25(5):1576-8.
- 27 27. Davison SN, Levin A, Moss AH, Jha V, Brown EA, Brennan F, et al. Executive summary of the  
28 KDIGO Controversies Conference on Supportive Care in Chronic Kidney Disease: developing a  
29 roadmap to improving quality care. *Kidney Int*. 2015;88(3):447-59.
- 30 28. Dienemann T, Fujii N, Orlandi P, Nessel L, Furth SL, Hoy WE, et al. International Network of  
31 Chronic Kidney Disease cohort studies (iNET-CKD): a global network of chronic kidney disease  
32 cohorts. *BMC nephrology*. 2016;17(1):121.
- 33 29. Mariani L, Stengel B, Combe C, Massy ZA, Reichel H, Fliser D, et al. The CKD Outcomes and  
34 Practice Patterns Study (CKDopps): Rationale and Methods. *Am J Kidney Dis*. 2016;68(3):402-13.

1 **Table Potential sources of international variations in the relation**  
2 **between CKD prevalence and the risk to progress to kidney failure**  
3 **requiring KRT**

4  
5 **Variation in methods to estimate CKD prevalence**

- 6 • Sampling method and sample representativeness of country population
- 7 • Creatinine assay and GFR estimating equation

8 **Variations in life expectancy and distribution of CKD risk factors**

9 *Life expectancy*

- 10 • Competing risk of mortality

11 *Heterogeneity in the prevalence of CKD risk factors*

- 12 • Ethnicity, race
- 13 • Genetic risk factors
- 14 • Environmental risk factors
  - 15 – socioeconomic factors and working conditions
  - 16 – lifestyle, diet, and access to clean water
  - 17 – obesity, diabetes, and hypertension
  - 18 – nephrotoxic medications, herbal remedies, and environmental nephrotoxins
  - 19 – infections
- 20 • Poor maternal and fetal health (low birth weight, premature birth)

21 *Acute kidney injury as a risk factor for CKD*

22 **Variation in risk factors for CKD progression (GFR decline) to kidney failure**

- 23 • Variation in risk factors for CKD progression
  - 24 – Albuminuria
  - 25 – Diabetes, hypertension
  - 26 – Lifestyle (smoking status, physical activity)
- 27 • Acute-on-chronic kidney disease as a risk factor for CKD progression
- 28 • Heterogeneity in clinical practices
  - 29 – Use of ACEI/ARB, blood pressure control
  - 30 – Dietary counseling (sodium, protein)

31 **Variations in access to kidney replacement therapy**

- 32 • Variations in health resources
  - 33 – Gross domestic product (GDP)
  - 34 – Health expenditure as % GDP
  - 35 – Private vs public share of health expenditure
  - 36 – Fee for service
  - 37 – Out of pocket expenses
- 38 • Practice pattern regarding initiation of kidney replacement therapy
  - 39 – GFR at dialysis initiation (early *versus* late dialysis start)
  - 40 – Conservative therapy for elderly CKD patients



- 1 ACEI: angiotensin-converting-enzyme inhibitors, ARB: angiotensin receptor blockers, CKD: Chronic
- 2 kidney disease, GFR: glomerular filtration rate, KRT: kidney replacement therapy
- 3

1 **Figure legends**

2

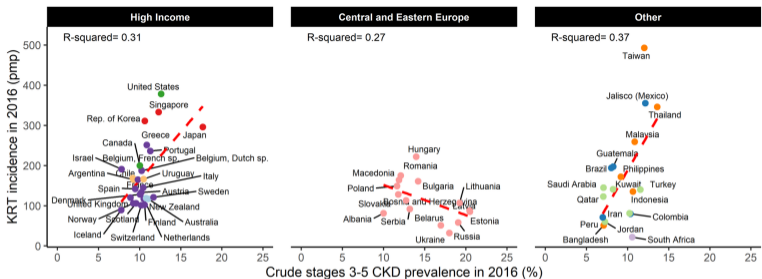
3 Figure 1: Incidence of KRT incidence according to age-standardized CKD prevalence, by region.

4 Legend: KRT, kidney replacement therapy; pmp, per million population; CKD, chronic kidney disease.

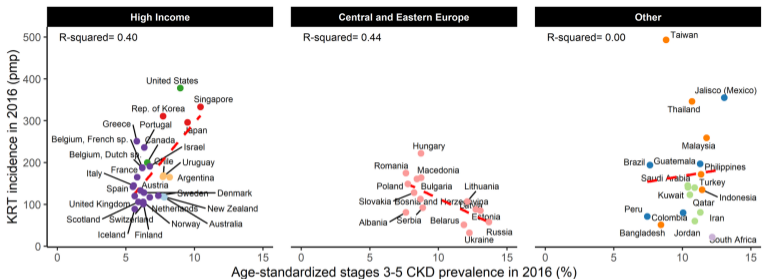
5

6 Figure 2: Age-standardized all-cause mortality according to age-standardized CKD prevalence, by  
7 region.

8 Legend: CKD, chronic kidney disease.

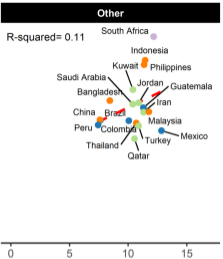
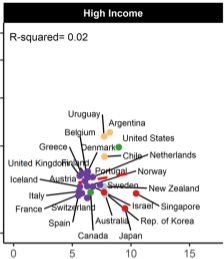


- Australasia
- High-income Asia-Pacific
- High-income North America
- Western Europe
- Southern Latin America
- Central and Eastern Europe
- Latin America
- North Africa and Middle East
- South, East and Southeast Asia
- Southern Sub-Saharan Africa



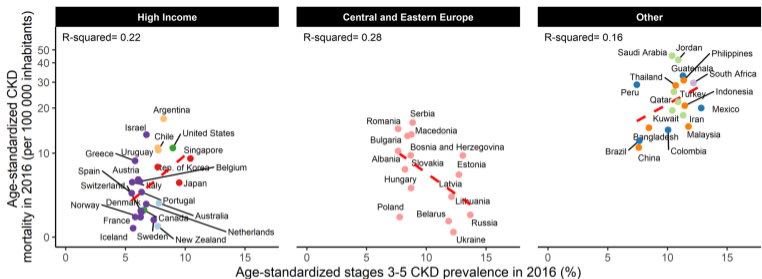
- Australasia
- High-income Asia-Pacific
- High-income North America
- Western Europe
- Southern Latin America
- Central and Eastern Europe
- Latin America
- North Africa and Middle East
- South, East and Southeast Asia
- Southern Sub-Saharan Africa

Age-standardized all-cause mortality in 2016 (per 100 000 inhabitants)



Age-standardized stages 3-5 CKD prevalence in 2016 (%)

- Australasia
- Central and Eastern Europe
- High-income Asia-Pacific
- Latin America
- High-income North America
- North Africa and Middle East
- Western Europe
- South, East and Southeast Asia
- Southern Latin America
- Southern Sub-Saharan Africa



- Australasia
- High-income Asia-Pacific
- High-income North America
- Western Europe
- Southern Latin America
- Central and Eastern Europe
- Latin America
- North Africa and Middle East
- South, East and Southeast Asia
- Southern Sub-Saharan Africa