Worldwide Epidemiology of Diabetes-Related End-Stage Renal Disease, 2000–2015

Hui-Teng Cheng,[1,2] Xiaoqi Xu,[3] Paik Seong Lim,[4,5] and Kuan-Yu Hung[2,6]

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OBJECTIVE

The annual risk among patients with diabetes of reaching end-stage renal disease (ESRD) is largely unknown worldwide. This study aimed to compare the incidence of diabetes-related ESRD by creating a global atlas during 2000–2015.

RESEARCH DESIGN AND METHODS

The annual incidence of ESRD among patients with diabetes was calculated as the quotient of the number of incident ESRD patients with diabetes divided by the total number of patients with diabetes after subtraction of the number with existing ESRD. The estimated ESRD prevalence and annual incidence were validated with use of the data provided by Fresenius Medical Care, Germany, and previously reported data, respectively.

RESULTS

Data were obtained from 142 countries, covering 97.3% of the world population. The global percentage of the prevalent ESRD patients with diabetes increased from 19.0% in 2000 to 29.7% in 2015 worldwide, while the percentage of incident ESRD patients due to diabetes increased from 22.1% to 31.3%. The global annual incidence of ESRD among patients with diabetes increased from 375.8 to 1,016.0/million with diabetes during 2000–2015. The highest average rates were observed in the Western Pacific Region. Comparatively, the rates of incident ESRD among European patients with diabetes ranged from one-half (309.2 vs. 544.6) to one-third (419.4 vs. 1,245.2) of the rates of the Western Pacific population during 2000–2015.

CONCLUSIONS

Great and nonrandom geographic variation in the annual rates among patients with diabetes of reaching ESRD suggests that distinct health care, environmental, and/or genetic factors contribute to the progression of diabetic kidney disease. Measures to prevent and treat diabetes-related ESRD require better patient susceptibility stratification.

The population of patients with diabetes has increased worldwide in recent decades, from 108 million in 1980 (1) to 463 million in 2019 (2). Current projection indicate that this number will exceed 700 million in 2045 (2). The prevalence of diabetes varies widely among countries, ranging from 22.0% in Kuwait to 5.6% in the U.K. in 2019 (2). Diabetes can damage the kidney and other major organs. The most serious consequence is end-stage renal disease (ESRD), in which affected patients require a renal replacement therapy (RRT), such as hemodialysis, peritoneal dialysis, or kidney transplantation, for survival (3). Long-standing projections suggest that the global

[1]Department of Internal Medicine, National Taiwan University Hospital Hsin-Chu Biomedical Park Branch, Zhubei City, Taiwan
[2]Department of Internal Medicine, National Taiwan University Hospital Hsin-Chu Branch, Hsin-Chu City, Taiwan
[3]Clinical Research and Scientific Affairs, Medical Affairs, Fresenius Medical Care Asian Pacific, Hong Kong, China
[4]Fresenius Kidney Care, Taiwan Branch, Taiwan
[5]Division of Renal Medicine, Tungs Taichung Metroharbour Hospital, Taichung, Taiwan
[6]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

Corresponding authors: Hui-Teng Cheng, hcheng@wustl.edu, and Kuan-Yu Hung, kyhung@ntu.edu.tw

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increase in patients with diabetes has contributed to the ever-increasing ESRD prevalence (4,5), although the latter is also affected by rapidly aging populations (5), improved survival rates (6,7), and government subsidies for RRT in many countries (8–10). Paradoxically, many developed countries observed a stable or decreasing number of incident ESRD since 2010 (11,12), possibly owing to a decrease in diabetes-related ESRD. In the U.S., Burrows et al. (13) observed a remarkable 33% decrease in the age-standardized ESRD incidence among patients with diabetes from 2000 to 2014 (260.2 vs. 173.9 per 100,000 patients with diabetes). In Finland, Finne et al. (14) also observed a lower ESRD incidence among patients with diabetes diagnosed during 2000–2011 relative to those diagnosed during 1990–1994 (35.8 vs. 60.1 per 100,000 patient-years). Notably, the risk of ESRD among patients with diabetes in the 2000s was five- to sevenfold higher in the U.S. than in Finland.

Only a few developed countries have reported the incidence of ESRD among patients with diabetes (15,16). Two large multinational renal registries, the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) Registry and the United States Renal Data System (USRDS), reported percentages of incident ESRD patients due to diabetes that ranged from 66.7% in Malaysia (11) to 12.0% in Albania in 2016 (17). Notably, this wide gap could not be explained by the difference in diabetes prevalence between these two countries (16.6% and 12.0%, respectively) (18). Comparisons of the proportions of patients with diabetes who develop ESRD are needed to better understand the diabetes-related renal failure. We hypothesize that these proportions varied substantially across the geographic regions and that a nonrandom variation implied a fundamental difference in factors such as appropriateness of disease care, environmental risk exposure, and genetic susceptibility. A better understanding of the relative global importance of diabetes in ESRD pathogenesis may also advance our knowledge about the underlying mechanisms, enable the more efficient allocation of limited health care resources, and allow the development of better prevention and treatment strategies.

RESEARCH DESIGN AND METHODS

Estimation of the Annual Incidence of ESRD Among Patients With Diabetes

Five parameters are required to calculate the incidence of ESRD among patients with diabetes (i.e., the annual rate of patients with diabetes who enter ESRD, or incidence of diabetes-related ESRD): *1*) prevalence of diabetes, *2*) incidence of ESRD, *3*), percentage of incident ESRD patients with diabetes, *4*) prevalence of ESRD, and *5*) percentage of prevalent ESRD patients with diabetes. The annual incidence was then calculated with the following model formula: number of incident ESRD patients with diabetes/(number of patients with prevalent diabetes − number of prevalent ESRD patients with diabetes).

The number of incident ESRD patients with diabetes was calculated as the number of incident ESRD patients multiplied by the percentage of incident ESRD patients with diabetes. The number of prevalent ESRD patients with diabetes was calculated as the number of prevalent ESRD patients multiplied by the percentage of prevalent ESRD patients with diabetes. The resulting values were converted to counts per million population (pmp) for comparability among countries.

Definitions of Parameters, Data Sources, and Methodologies Used to Estimate the Unavailable Data

Global diabetes prevalence data during 1980–2014 were available from the World Health Organization (WHO) Global Health Observatory data repository (19), which defined diabetes as having a fasting blood glucose concentration ≥7.0 mmol/L or being on diabetes medication. The data included only people aged ≥18 years and were reported in terms of percentages of the populations. Both type 1 and type 2 diabetes were included in this study. Linear regression models based on the data from 2010 to 2014 were used to estimate the data in 2015.

The other four parameters were acquired from regional (Europe and Latin America) and national renal registries and from reliable literature. For identification of these sources, PubMed and Google were searched without language restriction with use of queries that combined individual country names with the following words or phrases: renal registry/registries, kidney failure, end-stage renal disease, end-stage kidney disease, dialysis, hemodialysis/hemodialysis, peritoneal dialysis, RRT, kidney disease, prevalence, incidence, kidney/renal transplantation/transplant. All renal registries, reviews, book chapters, clinical or epidemiological studies on kidney diseases or ESRD, and news articles by journalists were eligible for data extraction.

The ESRD prevalence was defined as the number of patients who were receiving hemodialysis or peritoneal dialysis and the number of patients who had received kidney transplantation, although it should be better described as the prevalence of "treated" ESRD. The incidence of ESRD was defined as the number of new patients who initiated hemodialysis or peritoneal dialysis or received kidney transplantation within the defined year, which is better described as the incidence of "treated" ESRD. The reported data were defined as those extracted from regional or national renal registries or from peer-reviewed journal articles or book chapters.

The following methods were used for estimation of data for countries that did not report ESRD prevalence or incidence. First, we estimated the prevalence or incidence by the reported values of other years using either a linear regression or exponential curve model (if multiple data points were available). The model type was selected based on face validity (no negative values or extreme values), R^2 values, incidence or prevalence trend, and trends in neighboring countries. If the year(s) to be estimated were surrounded by years with available data, at least four data points were included into the model whenever possible. Otherwise, at least six data points were included whenever possible. The estimates were based on years close to the targeted years. Second, if incidence data were available in the literature or by estimation and only one prevalence data point was available, the prevalence in other years was estimated according to the incidence trend. This was supported by an observed linear correlation between reported prevalence and incidence data (see Supplementary Material for European countries, U.S., Latin American countries, Saudi Arabia, South Africa, Taiwan, Japan, and South Korea). Third, if no incidence data and only one prevalence data point were available, the

prevalence in other years was estimated according to the trend of an adjacent or nearby country in the same region. Selection of the index country was based on the following criteria in the specified order: geographic proximity, availability of reliable data (from renal registry, literature, or news articles, in this order), comparability of economic status (such as gross national income per capita), and similarity of nephrology care (e.g., density of nephrologists). The same rules were applied to estimate the incidence from the reported prevalence.

Nearly all sub-Saharan African countries had no data of ESRD incidence available. We were only able to estimate the incidence of all new ESRD cases, rather than only treated cases, by the "gap%" estimated by Liyanage et al. (20) (for details see the section on Benin and other sub-Saharan African countries in Supplementary Table 1). It is defined as the percentage of ESRD patients who required but did not receive RRT.

The percentage of prevalent ESRD patients with diabetes was defined as the percentage of prevalent ESRD patients diagnosed with diabetes before or after entry to ESRD. The percentage of incident ESRD patients with diabetes was defined as the percentage of incident ESRD patients diagnosed with diabetes before reaching ESRD. If the percentage data for ESRD patients were not available in any way, we adopted the frequency of diabetes among patients with chronic kidney disease (CKD), using the stage as late as possible, as a less stringent but close estimate of the percentage of diabetes among incident ESRD patients. These estimates might have been less than the true proportion of incident ESRD patients with diabetes because CKD patients with diabetes are more likely to progress to ESRD.

We estimated the missing values of the diabetes mellitus percentages (DM%) using one of the following methodologies in the given order. First, they were estimated from a linear regression or exponential curve model established with use of available data points (if more than two were available). Second, if only one data point of the DM% among the prevalent ESRD patients together with the DM% of incident ESRD patients was available, the DM% in prevalent ESRD patients was estimated from that in incident ESRD patients, giving the existence of the linear correlation between these two percentages (see Supplementary Material for European countries, U.S., Saudi Arabia, Taiwan, Japan, and South Korea). Similarly, the DM% in incident ESRD patients was estimated from the trend of the prevalent ESRD patients if only one data point of the DM% among incident ESRD patients and the DM% of prevalent ESRD patients was available. Third, the DM% were estimated based on the trends of another country in the same region if the percentage data were only available in prevalent or incident ESRD patients. Fourth, the percentage of prevalent ESRD patients with diabetes directly adopted the percentage of incident patients, or vice versa, if no reliable reference data from another country were available. Fifth, the percentage adopted the data directly from an adjacent country if no reported data were available. The WHO regions and the World Bank income groups were defined according to the WHO (https://www.who.int/healthinfo/global_burden_disease/definition_regions/en/).

Validation of the Estimation

We retrieved the literature that reported the data of the proportion of patients with diabetes who progress to ESRD. We also compared the estimates of the ESRD prevalence with the data in 2012, 2007, and 2002 provided by Fresenius Medical Care, Germany.

Statistical Analysis

We used SPSS, version 18 (Chicago, IL), and the built-in statistical tools in Microsoft Excel to perform the linear regression model, the exponential curve fitting, and statistical analyses including calculation of the R^2 of the models, the Pearson correlation coefficient, and one-way ANOVA and the Scheffe post hoc analysis. P value <0.05 was considered significant.

RESULTS

We obtained data from 146 countries (as indicated in Supplementary Table 1) and completed tabulation for 142 countries in the years 2000, 2003, 2007, 2010, 2011, 2013, and 2015. These data represented 97.3% of the world population in 2015, according to the United Nations. The reported data revealed a strong correlation between the ESRD prevalence and incidence as well as between the percentage of prevalent ESRD in patients with diabetes and of incident ESRD in patients caused by diabetes (Supplementary Tables 2 and 3). These findings supported the estimation of either the prevalence or incidence, or either percentages, from its counterpart if data were lacking for one parameter.

Global Trend of the Contribution of Diabetes to Prevalent and Incident ESRD

The global percentage of prevalent ESRD patients with diabetes increased from 19.0% in 2000 to 29.7% in 2015, and increasing trends were observed in 103 of 142 countries (72.0%) (Table 1, Supplementary Table 4, and Supplementary Fig. 1). However, significant variation was observed among geographic regions (Supplementary Table 5). The most rapid increase rates occurred in the Western Pacific and Eastern Mediterranean Regions (Table 1 and Supplementary Table 6). In contrast, the slowest increases were observed in Europe, where 40.5% (17 of 42) of the countries observed no change in this parameter over time compared with only 25.4% of the countries worldwide (z test, $P < 0.001$). Within any given year, the percentages of prevalent ESRD patients with diabetes did not differ statistically across the four income groups (Supplementary Table 5). This percentage increased at a significantly slower rate in high-income countries relative to upper-middle-income and lower-middle-income countries (Supplementary Table 7).

The percentage of incident ESRD patients due to diabetes increased steadily worldwide, from 22.1% in 2000 to 31.3% in 2015 (Table 1, Supplementary Table 8, and Supplementary Fig. 2). Increasing trends were observed in most countries (63.4%) and particularly in the Western Pacific (92.3%, z test, $P = 0.036$) and American regions (90.9%, z test, $P = 0.010$). Countries in these regions had already reported high percentages of incident diabetes-related ESRD in the early 2000s and much more rapid increases relative to other countries (Supplementary Table 9). Both African and European countries had the lowest percentages of incident ESRD patients caused by diabetes in the early 2000s and reported slower rates of increase over time (Supplementary Table 10). Consequently, the percentages in these regions remained the lowest throughout the

Table 1—Percentage of prevalent ESRD patients or incident ESRD patients with diabetes worldwide from years 2000 to 2015

		Percentage of prevalent ESRD patients with diabetes							Yearly change				
	N	2000	2003	2007	2010	2011	2013	2015	rate (slope)	95% CI	Up	Down	No
WHO regions													
World	142	19.0	20.8	23.8	25.7	26.1	27.3	29.8	0.69	0.61–0.77	103	3	36
African Region	37	16.3	16.5	17.9	20.3	20.4	23.5	28.3	0.71	0.32–1.11	21	3	13
Region of the Americas	22	22.0	26.1	30.1	32.4	30.6	32.7	34.6	0.77	0.53–1.02	21	0	1
Eastern Mediterranean Region	20	22.2	24.8	29.3	31.9	35.1	32.8	38.7	1.03	0.74–1.33	15	0	5
European Region	42	13.7	14.5	17.0	17.9	17.9	18.7	18.8	0.37	0.28–0.46	25	0	17
South-East Asia Region	8	28.6	29.4	33.2	33.2	34.6	35.3	36.4	0.53	0.41–0.65	8	0	0
Western Pacific Region	13	28.1	33.5	37.8	40.8	41.8	43.5	44.1	1.07	0.86–1.28	13	0	0
World Bank income groups													
High income	50	21.4	23.1	25.9	27.2	27.6	28.8	29.9	0.57	0.52–0.61	35	0	15
Upper-middle income	36	17.1	19.7	24.3	26.6	26.3	27.5	30.1	0.84	0.70–0.98	31	0	5
Lower-middle income	32	19.2	21.5	24.2	26.1	27.6	27.8	30.5	0.72	0.62–0.81	22	1	9
Low income	24	16.9	17.0	18.2	20.8	20.3	23.3	28.4	0.67	0.26–1.08	15	2	7
		Percentage of incident ESRD patients with diabetes							Yearly change				
	N	2000	2003	2007	2010	2011	2013	2015	rate (slope)	95% CI	Up	Down	No
WHO regions													
World	142	22.1	24.3	26.9	28.1	28.8	29.6	31.4	0.59	0.52–0.65	90	8	44
African Region	37	14.9	15.0	15.7	15.9	16.5	19.6	22.4	0.42	0.08–0.76	23	3	11
Region of the Americas	22	26.4	30.9	35.2	38.2	36.4	38.0	40.7	0.88	0.61–1.14	20	0	2
Eastern Mediterranean Region	20	23.0	25.7	28.4	30.4	33.8	33.4	35.8	0.85	0.67–1.02	15	0	5
European Region	42	20.6	21.8	24.3	24.2	25.6	24.3	24.9	0.29	0.12–0.47	14	5	23
South-East Asia Region	8	27.7	30.3	32.6	32.9	32.6	32.1	34.0	0.35	0.15–0.55	6	0	2
Western Pacific Region	13	35.2	42.1	47.5	51.7	51.1	53.3	53.9	1.24	0.89–1.58	12	0	1
World Bank income groups													
High income	50	26.5	28.7	30.9	31.9	32.6	32.6	34.2	0.48	0.39–0.57	26	3	21
Upper-middle income	36	21.7	24.8	29.2	30.6	31.0	32.0	33.7	0.78	0.63–0.92	26	2	8
Lower-middle income	32	20.2	23.0	25.8	27.6	29.0	29.0	31.1	0.70	0.60–0.80	22	1	9
Low income	24	16.1	16.3	16.8	17.1	17.2	20.5	22.5	0.37	0.07–0.67	16	2	6

The yearly change rate is the slope calculated by linear regression model. The final three columns show the number of countries with a trend increasing (up), decreasing (down), or without change (no) (the slope with 95% CI across zero).

study period. Furthermore, the income level had a differential effect on the percentages each year, and this difference was most pronounced between high- and low-income countries (Table 1 and Supplementary Table 5), with increasing trends observed in 52.0% of high-income countries vs. 72.2%, 68.7%, and 66.7% of upper-middle-income, lower-middle-income, and low-income countries, respectively (all $P < 0.001$, z test). Notice that 13 countries, 11 in sub-Saharan Africa, adopted the CKD data to approximate the percentage of incident ESRD patients due to diabetes: Botswana, Cameroon, Chad, Côte d'Ivoire (Ivory Coast), Ethiopia, Ghana, Guinea, Madagascar, Myanmar, Senegal, Sri Lanka, Tanzania, and Togo.

International Variation in the ESRD Incidence Among Patients With Diabetes

The ESRD incidence data in three African countries, namely, Algeria, South Africa, and Zimbabwe, were derived from patients receiving treatment, and the African region that included only these three countries had the lowest incidence over time. For the rest of 34 WHO-defined African countries and Somalia (defined as an Eastern Mediterranean country), the ESRD incidence rates were derived from patients requiring RRT. As a result, the African Region, the low-income group, and the lower-middle-income group posted substantially higher ESRD incidence than all other countries (Table 2, Supplementary Table 11, and Supplementary Fig. 3), and the increase in the ESRD incidence rates was among the fastest (Supplementary Tables 12 and 13). A dramatic increase in the ESRD incidence was observed in Southeast Asia during the study period (Taiwan, Thailand, and Nepal were among the highest), leading to the second highest (nearly the highest) incidence of ESRD in 2015 (Table 2).

Between 2000 and 2015, the global annual incidence of ESRD among patients with diabetes increased from 375.8 to 1,016.0 per million patients with diabetes (Table 3, Fig. 1, and Supplementary Table 14). This incidence was modest in the European Region, ranging from approximately half of that in the Western Pacific Region in 2000 to one-third in 2015. The Western Pacific Region and Europe also exhibited the fastest and slowest annual increases in the ESRD incidence among patients with diabetes, respectively; the latter was significantly slower than the global rate of change. From 2000 to 2011, the highest average annual rate of increase was observed in the Western Pacific Region. The incidence of ESRD among patients with diabetes was remarkably high in the low-income and lower-middle-income countries, which also reported high annual rates of increase in this incidence. A sensitivity analysis, which included only the three African countries (Algeria, South African, and Zimbabwe) whose estimation of the ESRD incidence was based on new

Table 2—ESRD incidence rates and prevalence (in people pmp) worldwide from years 2000 to 2015

		ESRD incidence rates in pmp							Yearly change				
	N	2000	2003	2007	2010	2011	2013	2015	rate (slope)	95% CI	Up	Down	No
WHO regions													
World	142	101.3	121.8	156.0	177.8	190.0	215.6	241.8	9.13	7.76–10.50	108	3	31
World*	107	96.0	112.8	129.4	139.6	144.4	148.9	154.6	3.88	3.33–4.42	74	3	30
African Region	37	113.0	141.3	219.7	265.6	293.7	363.8	456.3	21.63	15.24–28.02	36	0	1
African Region*	3	26.2	32.0	38.4	45.7	48.5	55.1	60.2	2.25	1.92–2.57	3	0	0
Region of the Americas	22	95.9	115.1	134.1	146.9	159.4	186.2	172.9	5.71	4.03–7.40	14	1	7
Eastern Mediterranean Region	20	93.9	111.5	128.2	148.8	158.2	193.9	188.4	6.74	4.85–8.63	16	0	4
Eastern Mediterranean Region*	19	97.9	112.2	119.5	123.7	123.6	131.3	141.5	2.49	1.80–3.18	15	0	4
European Region	42	101.8	114.7	131.9	143.8	141.9	131.4	139.0	2.48	0.83–4.13	23	2	17
South-East Asia Region	8	75.0	97.7	123.8	144.0	163.9	161.8	190.6	7.40	6.18–8.62	8	0	0
Western Pacific Region	13	103.5	131.5	151.9	156.0	167.5	181.9	193.0	5.53	4.45–6.62	11	0	2
World Bank income groups													
High income	50	129.1	142.6	160.4	167.6	168.9	165.9	172.0	2.82	1.74–3.89	32	2	16
Upper-middle income	36	87.5	114.6	134.2	149.8	160.8	173.2	185.5	6.31	5.68–6.93	24	1	11
Upper-middle income*	32	78.9	105.4	121.4	134.3	143.1	151.3	155.5	5.02	4.15–5.89	20	1	11
Lower-middle income	32	72.9	95.5	144.5	181.7	198.9	240.8	298.0	14.32	10.75–17.90	29	0	3
Lower-middle income*	21	49.8	60.4	74.7	87.4	94.3	110.3	116.6	4.53	3.78–5.28	18	0	3
Low income	24	102.3	124.5	194.7	236.0	266.2	349.2	396.3	19.58	14.05–25.10	23	0	1
Low income*	4	62.1	74.4	92.2	105.6	110.6	120.7	130.3	4.55	4.37–4.73	4	0	0
		ESRD prevalence in pmp							Yearly change				
	N	2000	2003	2007	2010	2011	2013	2015	rate (slope)	95% CI	Up	Down	No
WHO regions													
World	142	303.5	362.6	446.4	510.8	532.1	569.9	615.9	20.83	20.45–21.20	128	0	14
African Region	37	8.3	14.2	23.7	32.8	36.7	46.3	60.5	3.27	2.36–4.18	35	0	2
Region of the Americas	22	330.5	384.8	537.8	611.7	644.5	754.6	767.7	31.13	26.70–35.56	19	0	3
Eastern Mediterranean Region	20	241.0	301.2	373.3	426.6	446.6	469.7	495.4	17.20	15.64–18.76	18	0	2
European Region	42	468.0	557.6	658.3	747.6	771.8	774.3	855.5	25.09	21.53–28.66	36	0	6
South-East Asia Region	8	370.9	444.8	539.1	647.1	677.8	774.2	858.1	32.02	26.87–37.17	7	0	1
Western Pacific Region	13	620.7	731.0	865.4	981.1	1,019.2	1,115.7	1,202.4	38.29	35.58–41.00	13	0	0
World Bank income groups													
High income	50	610.5	721.2	838.6	950.2	981.4	1,021.9	1,080.9	31.49	29.06–33.91	46	0	4
Upper-middle income	36	231.6	294.2	417.9	494.3	521.6	580.8	648.2	27.81	26.12–29.50	33	0	3
Lower-middle income	32	126.5	145.2	192.2	216.5	231.3	265.2	300.1	11.33	9.22–13.44	29	0	3
Low income	24	7.6	8.2	10.7	12.4	12.9	18.4	20.0	0.82	0.46–1.18	20	0	4

The yearly change rate was the slope calculated by linear regression model. The final three columns show the number of countries with a trend increasing (up), decreasing (down), or without change (no) (the slope with 95% CI across zero). *Data excluding the countries whose ESRD incidence rates were estimated by the number of new patients in need of RRT instead of those being treated.

patients under treatment, instead revealed the lowest incidence of diabetes-related ESRD in the African Region (Table 3). This incidence was similar among all four income groups over time (Table 3 and Supplementary Table 5). However, a significantly slower annual rate of increase in this incidence was observed in the low-income group relative to the other groups (Table 3 and Supplementary Table 15). Similarly, the annual rate of increase in this incidence in the Eastern Mediterranean Region slowed considerably when Somalia was not included (Table 3 and Supplementary Table 16).

The incidence of ESRD from the population with diabetes was reported from 19 countries or territories during 2000–2015 (Supplementary Table 17). Twenty-eight data points were comparable plus 16 studies focusing on type 1 diabetes or special subgroups. The differences ranged from −58.9% to 0.4% of the reported data. Four outliers showed a higher discrepancy, from −70.2% to −80.2%.

Cross Validation of the ESRD Prevalence and the Fresenius Data

From 2000 to 2015, the global ESRD prevalence doubled from 303.5 to 615.9 pmp (Table 3 and Supplementary Table 18). The ESRD prevalence data for 2012, 2007, and 2000 provided by Fresenius Medical Care matched the reported data from the corresponding years (Kolmogorov-Smirnov test, $P > 0.05$ in all 3 years) (Supplementary Tables 19–21). In 2012, 72 of 85 countries (84.7%) had differences in absolute counts within 200 pmp (Supplementary Fig. 5) and 76 (89.4%) reported differences of <50% relative to the Fresenius data (Supplementary Fig. 6). Similar patterns were observed for the differences in counts or percentages in the data from 2007 and 2002 (Supplementary Figs. 7–10). Conversely, the model-based estimates of ESRD

Table 3—Annual incidence of ESRD among patients with diabetes worldwide and by the WHO regions or the World Bank income groups from years 2000 to 2015

		Annual incidence of ESRD among patients with diabetes in pmp							Yearly change				
	N	2000	2003	2007	2010	2011	2013	2015	rate (slope)	95% CI	Up	Down	No
WHO regions													
World	142	375.8	467.6	606.7	671.3	712.7	858.7	1,016.0	39.37	28.28–50.45	90	8	44
World*	107	366.9	457.4	541.6	576.8	580.4	599.2	625.2	16.49	12.06–20.92	61	8	38
African Region	37	384.7	469.1	743.8	862.3	992.1	1,443.5	1,995.9	95.44	45.50–145.37	31	0	6
African Region*	3	65.0	75.9	87.8	101.1	105.2	122.4	143.4	4.81	3.32–6.30	3	0	0
Region of the Americas	22	452.6	530.6	638.2	712.0	711.3	790.1	782.7	23.31	19.38–27.24	12	2	8
Eastern Mediterranean Region	20	317.1	373.4	429.9	494.9	552.5	669.9	662.2	24.46	17.11–31.82	12	3	5
Eastern Mediterranean Region*	19	330.3	375.4	402.7	415.9	438.7	453.4	488.7	9.49	7.53–11.46	11	3	5
European Region	42	309.2	361.2	416.7	424.8	427.5	399.5	419.4	6.76	1.61–11.90	19	2	21
South-East Asia Region	8	345.7	601.5	767.8	821.5	697.7	662.4	770.2	22.19	−0.21 to 44.58	4	1	3
Western Pacific Region	13	544.6	763.1	950.0	1,033.4	1,097.5	1,205.4	1,245.2	45.81	38.80–52.81	12	0	1
World Bank income groups													
High income	50	479.7	579.1	671.2	681.4	671.6	679.3	709.4	13.77	6.98–20.56	25	3	22
Upper-middle income	36	312.7	408.3	501.2	565.6	593.1	628.7	689.4	24.19	22.38–26.00	25	2	9
Upper-middle income*	32	284.0	388.0	477.3	539.5	551.8	578.2	589.9	20.52	15.75–25.28	21	2	9
Lower-middle income	32	250.0	342.6	531.5	655.2	734.1	939.3	1,277.4	61.91	38.20–85.62	20	2	10
Lower-middle income*	21	229.8	293.2	364.5	422.3	443.9	476.1	517.4	18.96	18.42–19.50	12	2	7
Low income	24	421.7	491.2	731.0	830.0	949.6	1,470.1	1,796.3	84.58	40.46–128.70	19	2	3
Low income*	4	340.1	352.7	366.4	379.5	386.4	411.3	421.7	5.33	3.86–6.80	3	1	0

The numbers are people per million patients with diabetes. The yearly change rate was the slope of annual rate against year calculated by the linear regression model. The final three columns show the number of countries with a trend increasing (up), decreasing (down), or without change (no) (the slope with 95% CI across zero). *Data excluding the countries whose ESRD incidence rates were estimated by the number of new patients in need of RRT instead of those being treated.

prevalence closely matched the Fresenius data of ESRD prevalence in all 3 years (Kolmogorov-Smirnov test, $P > 0.05$) (Supplementary Tables 18–20). In 2012, based on the model, 40 of 44 countries (90.9%) had differences within 200 pmp (Supplementary Fig. 11) and 35 (79.5%) had differences within 100 pmp. Moreover, the estimates of ESRD prevalence in 31 countries (70.5%) differed from the Fresenius data by <50% (Supplementary Fig. 12), and similar results were obtained for 33 of 50 (66.0%) and 40 of 55 (72.7%) countries in 2007 and 2002, respectively (Supplementary Figs. 13–16). Only Bangladesh, China, India, Myanmar, Sri Lanka, and Vietnam presented reported or estimated prevalence values that were 200% higher than the Fresenius data in all 3 years.

CONCLUSIONS

This study yielded three major findings. First, the proportion of prevalent ESRD patients with diabetes continued to rise worldwide. The slowest annual increase in this proportion was observed in Europe, but nearly threefold increase was reported in the Eastern Mediterranean and Western Pacific regions. Second, the importance of diabetes as a risk factor for ESRD was observed both in high-income countries and in increasing numbers of developing and underdeveloped countries. Third, substantial geographic variation was observed in the incidence of ESRD among patients with diabetes. Remarkably, the incidence in Western Pacific countries was twice the world average and thrice that of the lowest incidence observed in Europe.

Our findings reveal that the expansion of populations with diabetes among the ESRD patients is a global phenomenon, and it does not appear to be stoppable anytime soon. Special consideration should be given to the challenges of providing care to an ESRD population with a higher proportion of patients with preexisting diabetes. We should appreciate the fact that diabetes is becoming the dominant risk factor for ESRD in developing and underdeveloped countries—not just as seen in the developed countries. Interestingly, decrease of the percentage of incident ESRD patients due to diabetes was seen in five European countries and three African countries (Table 1), even though their diabetes prevalence kept increasing as in all other countries. Risk stratification based on geographic origins may be needed to identify populations with diabetes that should be targeted more aggressively to prevent the initiation of renal complications or halt further deterioration.

Our survey for the incidence of ESRD among populations with diabetes with a global perspective may help disclose a mechanism in determining the progression of diabetic kidney disease. The international variation was enormous, yet the pattern was nonrandom. One potential explanation is the competing risks between death and kidney failure in patients with diabetes (21). Our equation included only patients treated with RRT and did not consider those who died of cardiovascular or renal complications before reaching ESRD. This incidence may be deceptively lower in countries where a higher proportion of patients with diabetes died before reaching ESRD due to lack of appropriate care or delayed initiation of RRT or soon after reaching ESRD due to lack of RRT or voluntary choice of conservative treatment. Proper care including blood pressure control, blockade of renin-angiotensin system, awareness of CKD itself, and timely

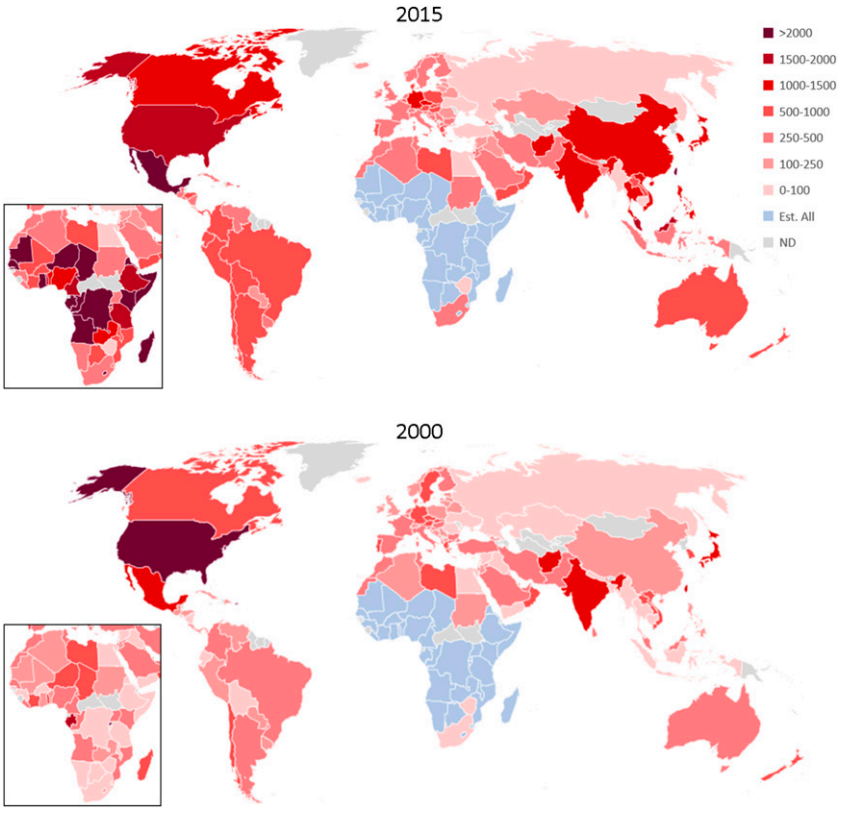

Figure 1—The annual incidence of ESRD among patients with diabetes in 2015 and 2000, in people pmp. "Est. all" marks the sub-Saharan African countries whose ESRD incidence was estimated by all ESRD patients requiring RRT instead of by those being treated. The inset maps show the results. ND, no data.

referral to a nephrologist can halt the progression of diabetic kidney disease, but they were inadequate in many underdeveloped countries (22). As the aging population is more vulnerable to the progression to ESRD, the developed countries with a higher proportion of older patients with diabetes should have more patients with diabetes entering ESRD. However, our analysis of data from countries in Western Europe versus those in industrialized area of Asia (Japan, Taiwan, South Korea) basically excluded the possible effects of age, sex, and RRT access. These findings suggest the existence of distinct environmental factors and/or genetic origin.

Tobacco smoking is known to increase the risks of mortality and vascular complications in patients with diabetes (23). However, reports describe a smoking prevalence of ~17.4% among patients with diabetes in the U.K. (24) and 28.1% among their counterparts in Japan (25). This small discrepancy is far less than the 10-fold difference in the annual rate of incident ESRD among patients with diabetes between these countries. The effects of climate (26) or air pollution (27) are said to be important but inconclusive. The existence of an unknown protective environmental factor is supported by the finding that the annual incidence of ESRD among patients with diabetes in Northwestern Europe (Denmark, Finland, Iceland, Norway, Sweden, U.K.) ranged from 212 to 510 pmp in 2015 compared with 1,143 pmp among people in the U.S. state of Maine (95% European ethnicity) in 2014 (13). Food choice such as high meat intake is another risk factor for the progression of diabetes complications (25). Interestingly, Fuller and Rowlands proposed a long-lasting difference in food selection and preparation between eastern and western Asia since 8000 BC: grinding, roasting, and bread baking in western Eurasia, including the Mediterranean region, versus whole grain boiling and steaming in China and the Far East (28). It is possible that food and its culinary techniques may have gradually shaped people's disease vulnerability.

Race/ethnicity is another factor to consider. In the U.S., diabetes as the primary cause of ESRD varied among different ethnic groups, from 69.8% in American Indian to 42.5% in African American (29). Asian people with diabetes have a greater risk of developing related complications than their counterparts in Western countries; consequently, the former population also faces higher risks of all-cause and cause-specific mortality (30,31). Data from the USRDS indicated that from 2000 to 2004, the age- and sex-adjusted incidence of ESRD due to diabetes was 3.8-, 3.5-, and 1.5-fold higher among African Americans, Native Americans, and Asian Americans, respectively, relative to Caucasian Americans (32). A longitudinal observational study of 62,432 patients with diabetes conducted at Kaiser Permanente of Northern California reported adjusted hazard ratios for ESRD of 2.03 for Black, 1.85 for Asian, and 1.46 for Hispanic participants relative to White participants. These racial/ethnic disparities in the risk of ESRD consequent to diabetes persist despite the provision of uniform medical care and control of other factors (33,34). In the U.K., a South Asian patient with diabetes may have as much as 13-fold higher risk of developing ESRD compared with the patient's counterpart of European descent (35). In a sample of patients with diabetes with advanced CKD (estimated glomerular filtration rate of 20.60 mL/min/1.73 m^2) from a multinational clinical trial, the incidence of ESRD was higher among Black (10.1/100 patient-years) and Hispanic patients (9.3/100 patient-years) than among White patients (6.1/100 patient-years) (36). Our and others' findings lead us to propose the existence of genetic factors in certain racial/ethnic groups that promote both survival and vulnerability to diabetic kidney failure.

We used two approaches to validate our model. First, we compared our data regarding the annual incidence of ESRD among patients with diabetes with data from a limited number of literature reports. The data in the latter sources were generally higher because the study populations had been carefully followed and all recruited case subjects reached ESRD. In contrast, our model had a larger denominator because it included the entire population at risk (i.e., all patients with prevalent diabetes) and a smaller

numerator because it was nearly impossible to count all ESRD patients. Second, we compared the ESRD prevalence in this study with the data provided by Fresenius Medical Care and determined a high level of similarity, with few exceptions. Accordingly, the Fresenius data set is validated as an accurate reference. Furthermore, the similarities between our estimates and the Fresenius data vindicate the model-building concept in our study in terms of estimating the global ESRD prevalence.

Only six countries, namely, India, Myanmar, Sri Lanka, China, Vietnam, and Bangladesh, showed a twofold difference between the reported or estimated ESRD prevalence and the Fresenius data. For the first three countries (and Yemen), we estimated the prevalence of ESRD patients requiring RRT, which was the prevalence of treated ESRD multiplied by a ratio between the ESRD patients who required RRT and those who received it. Apparently, this correction made the estimates remarkably high. Take India, for example. If only the "treated" ESRD patients were considered, the number (94.4 pmp) was very close to that for the Fresenius data in 2012 (70.2 pmp). The sample to report the prevalence in China was presumably overrepresenting because the subjects were urban residents and insured (37). The ESRD prevalence for Vietnam was derived from the total number of dialysis patients and, hence, supposed to be more accurate than the Fresenius data. The data of ESRD prevalence in Bangladesh were obtained from the USRDS and were considered authorized.

This study had a few limitations. First, even in a patient with diabetes, ESRD may or may not be caused by diabetic nephropathy; diabetes might simply be a comorbidity with ESRD (38). The annual incidence of diabetes-related ESRD may have been overestimated. Second, the incidence of ESRD mostly described treated ESRD patients instead of the entire population who had reached ESRD, regardless of the RRT status. Accordingly, the calculated annual incidence of ESRD among patients with diabetes would have been considerably underestimated. Third, our model equation was based on the number of patients with prevalent diabetes, who had diabetes for various periods of time. A patient with longstanding diabetes might progress to ESRD much sooner than a newly diagnosed, or incident, diabetes patient. Thus, the annual rate of ESRD from an incident, or inception, diabetes cohort might have been lower than our estimates (14,15). In addition, the proportion of those with undiagnosed diabetes to total population with diabetes varied among countries (69% in African countries vs. 38% in European and American countries) (39). The annual rate of ESRD among patients with diabetes might become deceptively low in those countries with high prevalence of undiagnosed diabetes because of missing those real cases of ESRD with diabetes. Fourth, our estimates on the percentages of national incident and prevalent ESRD patients with diabetes from studies that recruited only relatively small numbers of subjects, or that focused on not-yet-in-ESRD CKD patients, are possibly inaccurate. Fifth, there was no consensus in determining an acceptable margin of error in the comparison between our ESRD prevalence and the Fresenius data. It appears that 50% of difference was a reasonable range to cover a large majority of countries. Sixth, the methodology we used to estimate the ESRD incidence of "all new cases" among patients with diabetes in sub-Saharan Africa gave exceptionally high values. However, the estimates were very close to the actual conservative estimate of 1,000 pmp according to a local expert (40). One caveat was that the gap% value was reported only for year 2010, but it was used to model all years from 2000 to 2015.

In conclusion, our study has provided a global overview of diabetes-related kidney failure during 2000–2015. Notably, we observed substantial differences in both the extent of ESRD incidence in patients with diabetes and the trends over time among the geographic regions. These differences highlight the decisive role of distinct factors in the progression of diabetic kidney disease, and the importance of tailoring the efforts to prevent and treat the affected patients, with the aim of easing the ever-increasing burden of this disease.

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Author Contributions. H.-T.C. and K.-Y.H. initiated and developed the study. H.-T.C. derived the model, collated the data, performed the analysis, produced tables and figures, and drafted the manuscript. P.S.L. and X.X. processed and provided the relevant data. All authors interpreted the results and gave advice for revision. H.-T.C. and K.-Y.H. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. World Health Organization. Global Report on Diabetes. Geneva,World Health Org., 2016
2. International Diabetes Federation. *IDF Diabetes Atlas*. 9th ed. Brussels, Belgium, 2019
3. Webster AC, Nagler EV, Morton RL, Masson P. Chronic kidney disease. Lancet 2017;389:1238–1252
4. Meguid El Nahas A, Bello AK. Chronic kidney disease: the global challenge. Lancet 2005;365:331–340
5. Jager KJ, Fraser SDS. The ascending rank of chronic kidney disease in the global burden of disease study. Nephrol Dial Transplant 2017;32(Suppl. 2):ii121–ii128
6. Foster BJ, Mitsnefes MM, Dahhou M, Zhang X, Laskin BL. Changes in excess mortality from end stage renal disease in the United States from 1995 to 2013. Clin J Am Soc Nephrol 2018;13:91–99
7. Storey BC, Staplin N, Harper CH, et al. Declining comorbidity-adjusted mortality rates in English patients receiving maintenance renal replacement therapy. Kidney Int 2018;93:1165–1174
8. Thomas B, Wulf S, Bikbov B, et al. Maintenance dialysis throughout the world in years 1990 and 2010. J Am Soc Nephrol 2015;26:2621–2633
9. Wetmore JB, Collins AJ. Global challenges posed by the growth of end-stage renal disease. Ren Replace Ther 2016;2:15
10. Bello AK, Levin A, Tonelli M, et al. Assessment of global kidney Health care status. JAMA 2017;317:1864–1881
11. United States Renal Data System. *2018 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States.* Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2018
12. Glassock RJ, Warnock DG, Delanaye P. The global burden of chronic kidney disease: estimates, variability and pitfalls. Nat Rev Nephrol 2017;13:104–114
13. Burrows NR, Hora I, Geiss LS, Gregg EW, Albright A. Incidence of end-stage renal disease attributed to diabetes among persons with diagnosed diabetes - United States and Puerto Rico, 2000-2014. MMWR Morb Mortal Wkly Rep 2017;66:1165–1170
14. Finne P, Groop PH, Arffman M, et al. Cumulative risk of end-stage renal disease among patients with type 2 diabetes: a nationwide inception cohort study. Diabetes Care 2019;42:539–544

15. Narres M, Claessen H, Droste S, et al. The incidence of end-stage renal disease in the diabetic (compared to the non-diabetic) population: a systematic review. PLoS One 2016;11: e0147329
16. Koye DN, Shaw JE, Reid CM, Atkins RC, Reutens AT, Magliano DJ. Incidence of chronic kidney disease among people with diabetes: a systematic review of observational studies. Diabet Med 2017;34:887–901
17. ERA-EDTA Registry Annual Report 2016. Amsterdam, the Netherlands, Academic Medical Center, Department of Medical Informatics, 2018
18. International Diabetes Federation. *IDF Diabetes Atlas*. 7th ed. Brussels, Belgium, International Diabetes Federation, 2015
19. World Health Organization. Raised fasting blood glucose (≥ 7.0 mmol/L or on medication) (crude estimate). Accessed 27 July 2019. Available from https://apps.who.int/gho/data/view.main.2469?lang=en
20. Liyanage T, Ninomiya T, Jha V, et al. Worldwide access to treatment for end-stage kidney disease: a systematic review. Lancet 2015;385: 1975–1982
21. Baena-Díez JM, Peñafiel J, Subirana I, et al.; FRESCO Investigators. Risk of cause-specific death in individuals with diabetes: a competing risks analysis. Diabetes Care 2016;39:1987–1995
22. Bello AK, Levin A, Lunney M, et al. Status of care for end stage kidney disease in countries and regions worldwide: international cross sectional survey. BMJ 2019;367:l5873
23. McEwen LN, Kim C, Karter AJ, et al. Risk factors for mortality among patients with diabetes: the Translating Research Into Action for Diabetes (TRIAD) Study. Diabetes Care 2007;30: 1736–1741
24. McGurnaghan S, Blackbourn LAK, Mocevic E, et al. Cardiovascular disease prevalence and risk factor prevalence in type 2 diabetes: a contemporary analysis. Diabet Med 2019;36:718–725
25. Horikawa C, Kamada C, Tanaka S, et al.; Japan Diabetes Complications Study Group. Meat intake and incidence of cardiovascular disease in Japanese patients with type 2 diabetes: analysis of the Japan Diabetes Complications Study (JDCS). Eur J Nutr 2019;58:281–290
26. Seposo XT, Dang TN, Honda Y. How does ambient air temperature affect diabetes mortality in tropical cities? Int J Environ Res Public Health 2017;14:385
27. Raaschou-Nielsen O, Sørensen M, Ketzel M, et al. Long-term exposure to traffic-related air pollution and diabetes-associated mortality: a cohort study. Diabetologia 2013;56:36–46
28. Fuller DQ, Rowlands M. Ingestion and food technologies: maintaining differences over the long-term in West, South and East Asia. In *Interweaving Worlds: Systemic Interactions in Eurasia, 7th to 1st Millennia BC*Wilkinson TC, Sherratt S, Bennet J, Eds. Oxford, Oxbow Books, 2011
29. Xiang J, Morgenstern H, Li Y, et al. Incidence of ESKD among Native Hawaiians and Pacific Islanders living in the 50 US states and Pacific Island territories. Am J Kidney Dis 2020;76:340–349.e1
30. Ramachandran A, Ma RC, Snehalatha C. Diabetes in Asia. Lancet 2010;375:408–418
31. Yang JJ, Yu D, Wen W, et al. Association of diabetes with all-cause and cause-specific mortality in Asia: a pooled analysis of more than 1 million participants. JAMA Netw Open 2019;2:e192696
32. Lopes AA. End-stage renal disease due to diabetes in racial/ethnic minorities and disadvantaged populations. Ethn Dis 2009;19(Suppl. 1):S1-47-51
33. Karter AJ, Ferrara A, Liu JY, Moffet HH, Ackerson LM, Selby JV. Ethnic disparities in diabetic complications in an insured population. JAMA 2002;287:2519–2527
34. Nee R, Agodoa LY, Chapter 8, Racial differences in kidney disease and end-stage kidney disease in the USA. In *Chronic Kidney Disease in Disadvantaged Populations*García-García G, Agodoa LY, Norris KC, Eds. London, U.K., Academic Press, 2017, pp. 65–75
35. Feehally J. Ethnicity and renal disease: questions and challenges. Clin Med (Lond) 2003;3: 578–582
36. Lewis EF, Claggett B, Parfrey PS, et al. Race and ethnicity influences on cardiovascular and renal events in patients with diabetes mellitus. Am Heart J 2015;170:322–329
37. Han YC, Huang HM, Sun L, et al. Epidemiological study of RRT-treated ESRD in Nanjing - a ten-year experience in nearly three million insurance covered population. PLoS One 2016;11: e0149038
38. Yuan CM, Nee R, Ceckowski KA, Knight KR, Abbott KC. Diabetic nephropathy as the cause of end-stage kidney disease reported on the medical evidence form CMS2728 at a single center. Clin Kidney J 2017;10:257–262
39. Cho NH, Shaw JE, Karuranga S, et al. IDF Diabetes Atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract 2018;138:271–281
40. Koigi B. Nikhil Pereira, CEO, Africa Healthcare Network, East Africa. In *African Healthcare Network*. African Business Communities, 2019 (Interview). Accessed 3 October 2019. Available from https://africabusinesscommunities.com/features/interview-nikhil-pereira-ceo,-africa-healthcare-network-east-africa/