Worldwide access to treatment for end-stage kidney disease: a systematic review

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Summary

Background End-stage kidney disease is a leading cause of morbidity and mortality worldwide. Prevalence of the disease and worldwide use of renal replacement therapy (RRT) are expected to rise sharply in the next decade. We aimed to quantify estimates of this burden.

Methods We systematically searched Medline for observational studies and renal registries, and contacted national experts to obtain RRT prevalence data. We used Poisson regression to estimate the prevalence of RRT for countries without reported data. We estimated the gap between needed and actual RRT, and projected needs to 2030.

Findings In 2010, 2·618 million people received RRT worldwide. We estimated the number of patients needing RRT to be between 4·902 million (95% CI 4·438–5·431 million) in our conservative model and 9·701 million (8·544–11·021 million) in our high-estimate model, suggesting that at least 2·284 million people might have died prematurely because RRT could not be accessed. We noted the largest treatment gaps in low-income countries, particularly Asia (1·907 million people needing but not receiving RRT; conservative model) and Africa (432 000 people; conservative model). Worldwide use of RRT is projected to more than double to 5·439 million (3·899–7·640 million) people by 2030, with the most growth in Asia (0·968 million to a projected 2·162 million [1·571–3·014 million]).

Interpretation The large number of people receiving RRT and the substantial number without access to it show the need to both develop low-cost treatments and implement effective population-based prevention strategies.

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Introduction

Renal replacement therapy (RRT), through either dialysis or renal transplantation, is a lifesaving yet high-cost treatment for people with end-stage kidney disease. It has been available in high-income countries for more than 50 years, with rapid growth in the number of people treated during this period. The use of dialysis to treat end-stage kidney disease varies substantially between regions, probably because of differences in population demographics, prevalence of end-stage kidney disease, and factors affecting access to and provision of RRT.[1,2]

The prevalence of end-stage kidney disease could rise sharply over the next few decades, driven by population ageing and an increasing prevalence of diabetes and hypertension.[1,3,4] The demographic transition driving this rise is expected to occur predominantly in developing rather than developed countries, challenging the economic capacity of many countries to provide RRT to an increasing number of people with end-stage kidney disease.[5–7]

To develop service provision strategies for people with end-stage kidney disease, the burden of the disorder and availability of RRT need to be known, and projections of future demand for RRT made. In this systematic review, we quantified the worldwide burden of end-stage kidney disease and use of RRT, and estimated future trends.

Methods

Data sources

We systematically searched the literature describing the prevalence of end-stage kidney disease in countries around the world according to the Meta-analysis of Observational Studies in Epidemiology group consensus statement[8] for conduct of such studies. We defined end-stage kidney disease as kidney failure needing continuing maintenance dialysis or a kidney transplant for survival. We defined RRT as any form of maintenance dialysis (either haemodialysis or peritoneal dialysis, excluding short-term dialysis methods for acute kidney injury, such as continuous venovenous haemofiltration, haemodialysis, and haemodiafiltration, or acute peritoneal dialysis) or kidney transplantation. We obtained separate data on dialysis prevalence. All completed studies, reviews, and registries reporting the epidemiology of end-stage kidney disease or RRT, or both, after the year 2000 were eligible for inclusion. Two authors (TL and TN) independently did the literature search using a standardised approach. Because of the scarcity of data on incidence of end-stage kidney disease, we restricted this analysis to prevalence data.

We identified relevant studies by searching Medline via Ovid from Jan 1, 1950, to Aug 31, 2013, using relevant text words and medical subject headings that included all spellings of "renal replacement therapy", "renal dialysis", "kidney transplantation", "haemodialysis", "peritoneal dialysis", "renal transplant", "incidence", "prevalence", and "epidemiology", without any language restrictions (appendix). We manually scanned reference lists from identified reports and reviews to identify any other relevant studies. We also did Google and Google Scholar searches using individual country names for relevant information such as conference proceedings and individual country or regional registries. Additionally, we contacted experts for unpublished data from regions where reliable data were unavailable or available data were out of date. We assessed Taiwan, Hong Kong, and Macao separately from China because they use different renal registry systems from those used on the mainland.

See Online for appendix

We obtained life expectancy at birth, median age of the population, and population size by 5 year age groups for the year 2010 from the UN Department of Economic and Social Affairs website,[9] along with future projections for each country. We obtained information on gross national income (GNI) from the World Bank website[10] and the forecast annual change in gross domestic product (GDP) for each country (up to 2018) from the International Monetary Fund website.[11] Finally, we obtained relevant data for Taiwan from the Frederick S Pardee Center for International Futures website,[12] and data about prevalence of diabetes and hypertension from the Global Health Observatory Data website.[13]

Data extraction

We obtained published reports for each renal registry, review article, and individual study (appendix), and extracted standard information. For the prevalence of dialysis and renal transplantation, when available, we regarded end-stage kidney disease registries as the primary information source for data extraction, otherwise we used individual articles. We used the most recent available data. We classified data sources as high, good, or moderate quality. We deemed formalised national registries to be high quality, published national and regional surveys to be good quality, and all other sources to be moderate quality (appendix).

Statistical analysis

We obtained actual numbers of patients receiving RRT in each country where available, or estimated them by multiplying the prevalence of RRT by the total population in each country. For 71 countries and Hong Kong, we based the prevalence of RRT on combined data for renal transplantation and dialysis, and for 52 countries and Taiwan, we based it on dialysis only. For the 76 countries and Macao without reported prevalence data, we made a national estimate by use of a multivariable Poisson regression and generalised estimating equation (appendix). This model used the information available from the 123 countries (and Taiwan and Hong Kong) with prevalence data in conjunction with life expectancy at birth and GNI to derive a national estimate.[14] We made worldwide estimates by summing numbers across the countries.

Access to RRT is widely recognised to be restricted in many countries, and reported numbers using RRT are likely to underestimate needs. To estimate the total number of people needing RRT, we used age-specific prevalence data for RRT from 20 high-income countries (table 1). For four of these countries (Japan, Singapore, Taiwan, and the USA), RRT is known to be provided to

	High-estimated model (USA, Japan, Taiwan, and Singapore)	Conservatively estimated model (other 16 countries)*
0–19 years	309·5 (285·3–335·7)	214·1 (177·8–257·7)
20–24 years	561·3 (512·1–615·1)	352·8 (311·5–399·6)
25–29 years	705·7 (640·9–777·1)	427·6 (386·3–473·3)
30–34 years	887·2 (801·8–981·9)	518·2 (478·6–561·1)
35–39 years	1115·6 (1002·8–1241·2)	628·0 (592·1–666·1)
40–44 years	1402·6 (1253·8–1569·2)	761·1 (729·7–793·8)
45–49 years	1763·6 (1567·3–1984·5)	922·3 (890·3–955·5)
50–54 years	2217·4 (1958·8–2509·9)	1117·8 (1070·3–1167·3)
55–59 years	2788·1 (2448·0–3175·2)	1354·7 (1275·0–1439·3)
60–64 years	3505·2 (3058·6–4017·1)	1641·7 (1513·4–1780·8)
65–69 years	4407·3 (3821·5–5083·3)	1989·4 (1793·7–2206·8)
70–74 years	5541·4 (4773·9–6432·4)	2411·0 (2124·5–2736·4)
75–79 years	6967·5 (5962·9–8141·3)	2922·0 (2515·5–3394·2)
≥80 years	10 050·8 (8510·1–11 869·3)	3973·9 (3294·5–4793·5)

Data are prevalence per million people (95% CI). *Australia, Austria, Belgium, Canada, Denmark, Finland, France, Greece, Iceland, Netherlands, New Zealand, Norway, Saudi Arabia, Spain, Sweden, and the UK.

Table 1: **Estimated age-specific prevalence of patients with end-stage kidney disease based on data from 20 high-income countries**

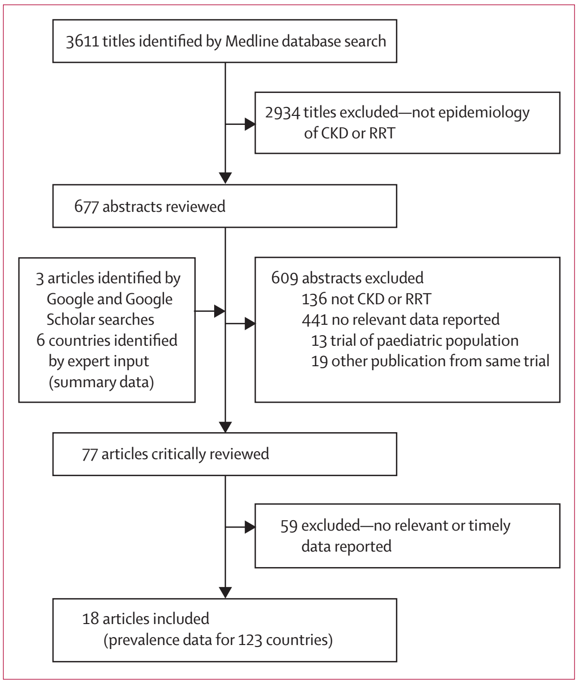

Figure 1: **Search strategy**
CKD=Chronic kidney disease. RRT=renal replacement therapy.

almost all individuals needing it. For at least some of the remaining 16 countries, about half of people needing RRT receive it.[15,16] We developed high and low estimates of the total national need for RRT in every country by applying estimated age-specific prevalence data for RRT to the population of every country in the world. We again made this estimation by use of Poisson regression models with generalised estimating equations (appendix). We used the model developed using the data drawn from the four countries where RRT uptake is high to provide an upper estimate of the likely need for RRT in each country, and the one for the other 16 countries where uptake is known to be incomplete to provide a lower estimate. Once again, we made worldwide estimates by summing numbers across the countries.

We calculated future projections of national prevalence of RRT for each country by applying an estimate of the annual percentage change in GNI—extrapolated from the annual percentage change of GDP from 2010 to each year—to the baseline figures obtained. Beyond 2018, the annual percentage change of GNI up to 2018 was projected to continue. We calibrated the national projections from the baseline prevalence of RRT in a similar way to that done for risk equations (appendix).[17] We calculated the number of patients receiving RRT for each year by multiplying the estimated prevalence of RRT for each year by the total population projected for that year on the basis of data obtained from the UN Department of Economic and Social Affairs website.[9] We made worldwide estimates by summing data across countries. We did all statistical analyses with SAS (version 9.3) and regarded two-sided values of $p<0 \cdot 05$ to be significant in all analyses.

Role of the funding source

The funding bodies had no role in study design, data collection, data analysis, data interpretation, or writing of the report. TL, TN, VJ, JK, and VP had full access to all the data in the study. VP had final responsibility for the decision to submit for publication.

Results

With our search strategy, we identified 3611 articles, of which 68 were selected for full text review. We also identified nine potential articles from other sources, such

	Total population (×1000)	Receiving dialysis		Receiving RRT*		Needing RRT (conservatively estimated model)			Needing RRT (high-estimated model)		
		Estimated number (×1000)	Prevalence (pmp)	Estimated number (×1000)	Prevalence (pmp)	Estimated number (×1000)	Prevalence (pmp)	Difference between needing and receiving RRT (%)	Estimated number (×1000)	Prevalence (pmp)	Difference between needing and receiving RRT (%)
Region											
World	6 915 149	2050	296	2618	379	4902 (4438–5431)	709 (642–785)	–47% (–52 to –41)	9701 (8544–11021)	1403 (1235–1594)	–73% (–76 to –69)
Africa	1 031 079	81	79	83	80	515 (463–574)	499 (449–556)	–84% (–86 to –82)	949 (845–1067)	920 (820–1035)	–91% (–92 to –90)
Asia	4 165 440	909	218	968	232	2875 (2610–3174)	690 (627–762)	–66% (–70 to –63)	5632 (4969–6387)	1352 (1193–1533)	–83% (–85 to –81)
Europe	739 963	327	442	532	719	759 (683–846)	1026 (923–1143)	–30% (–37 to –22)	1600 (1396–1836)	2162 (1886–2481)	–67% (–71 to –62)
Latin America and the Caribbean	595 872	276	463	373	626	401 (363–444)	673 (609–745)	–7% (–16 to 3)	785 (693–891)	1317 (1163–1496)	–52% (–58 to –46)
North America	346 373	441	1273	637	1839	323 (292–360)	933 (842–1038)	97%† (77–118)	673 (588–770)	1943 (1697–2223)	–5% (–17 to 8)
Oceania	36 420	15	412	25	686	30 (27–33)	824 (743–916)	–17% (–24 to –7)	61 (54–70)	1675 (1474–1920)	–59% (–64 to –54)
Income level‡											
Low income	793 525	16	20	16	20	408 (367–454)	514 (462–572)	–96% (–96 to –96)	757 (673–853)	954 (849–1074)	–98% (–98 to –98)
Lower-middle income	2 496 046	170	68	172	69	1486 (1347–1645)	595 (540–659)	–88% (–90 to –87)	2833 (2510–3200)	1135 (1006–1282)	–94% (–95 to –93)
Upper-middle income	2 520 598	688	273	803	319	1903 (1729–2099)	755 (686–833)	–58% (–62 to –54)	3783 (3330–4299)	1501 (1321–1706)	–79% (–81 to –76)
High income	1 104 980	1176	1064	1628	1473	1106 (995–1233)	1001 (900–1116)	47% (32–64)	2327 (2030–2669)	2106 (1837–2416)	–30% (–39 to –20)

Ranges in brackets are 95% CIs. pmp=per million people. RRT=renal replacement therapy. *In countries without available information about renal transplantation, the number of patients receiving RRT was estimated to be the same as the number receiving dialysis. †In the conservatively estimated model, the estimated prevalence of patients receiving RRT was lower than the actual prevalence in four countries with high prevalence—namely Japan, Singapore, Taiwan, and the USA. ‡Income levels were categorised according to the World Bank income groups in 2010: low-income GNI per capita ≤US $1005; lower-middle income $1006–3975; upper-middle income $3976–12 275; high income ≥$12 276.

Table 2: **Estimated number of patients receiving renal replacement therapy worldwide and by region or income level in 2010**

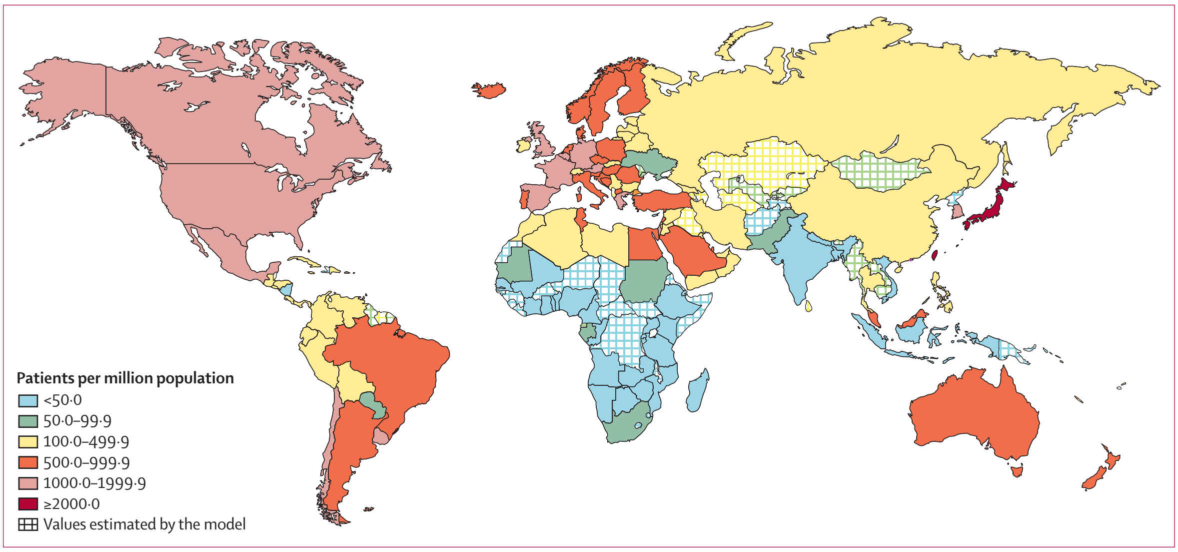

Figure 2: **Patients receiving renal replacement therapy in 2010**

as conference proceedings, input from the experts in the discipline, and Google and Google Scholar searches that used individual country names. We included 18 articles in this systematic review after full text review of these 77 reports (figure 1). These included 13 renal registries, of which four reported regional data for 42 countries and six reported individual country data (appendix). Additionally, experts in the region provided unpublished data of the number of people undergoing RRT for some countries—namely India, Pakistan, Bangladesh, and Thailand (JV), China (M-hZ and LJ), and African countries (HMP). In total, we obtained prevalence data on dialysis for 123 countries (and Taiwan and Hong Kong), representing 93% of the world population.

When classified geographically, data were available for countries in all six major regions, but covered a variable proportion of the included countries for each region. We obtained dialysis prevalence data for 31 African countries (81% of African population), 28 Asian countries (94%), 35 European countries (98%), 25 Latin American and Caribbean countries (98%), two North American countries (100%), and two countries in Oceania (74%). Additionally, we obtained age-specific dialysis prevalence rates from 20 high-income countries in Europe, North America, and Oceania, and from Japan, Taiwan, and Singapore (12% of global population; appendix).

The completeness and robustness of the data capture and reporting used for data extraction varied considerably. High-quality reports were available for 57 countries (including Hong Kong and Taiwan), good-quality reports for 62, and moderate-quality reports for six. Even within the high-quality reports, noticeable differences existed in catchment area (national *vs* regional), data collection and reporting methods (mandatory *vs* voluntary), and level of internal and external validation. We derived age-specific RRT prevalence data of 20 countries from high-quality reports.

In total, 2·618 million people received RRT in 2010 (table 2). 2·050 million (78%) received dialysis, and the remainder received a transplant. Actual data were available for 99% of these people across the countries with available data, whereas we estimated the prevalence in the countries without available data using a multivariable Poisson regression and generalised estimating equation (figure 2, appendix). To develop this model, predictors of RRT prevalence were found to be GNI and life expectancy (both $p<0·0001$), but not the prevalence of diabetes or hypertension (both $p>0·2$). The validity of this model, developed on the basis of data from 20 high-income countries, was assessed by establishing the consistency of actual and estimated number of patients receiving dialysis in the countries for which data were available ($R^2=0·80$, interclass correlation coefficient (1,1)=0·86; appendix).

The prevalence of RRT varied widely both within and across geographical regions, ranging from 80 per million people in Africa to 1840 per million people in North America (figures 2, 3). The absolute number of people receiving RRT was highest in Asia (0·968 million) and North America (0·637 million). With regard to income levels, the prevalence of RRT increased steeply with income levels (figure 4). Most RRT recipients (92·8%) were in high-income (1·628 million) and upper-middle-income (0·803 million) countries, with only 7·2% of RRT recipients living in lower-middle income (0·172 million) and low-income (0·016 million) countries.

We calculated the number of patients needing RRT using age-standardised data from the 20 high-income countries for which age-specific prevalence estimates were available. The prevalence of patients undergoing

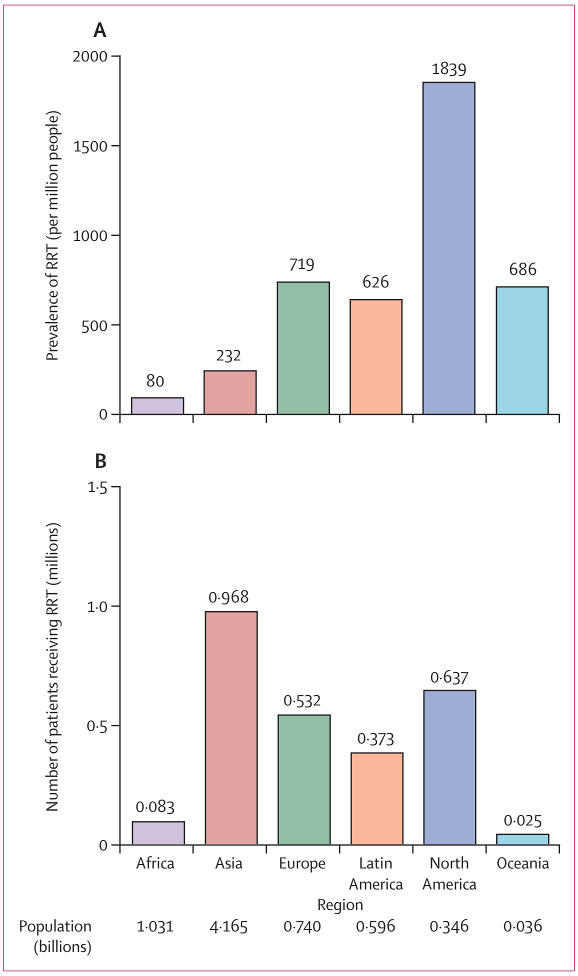

Figure 3: **Prevalence (A) and number of patients (B) receiving RRT according to region**
RRT=renal replacement therapy.

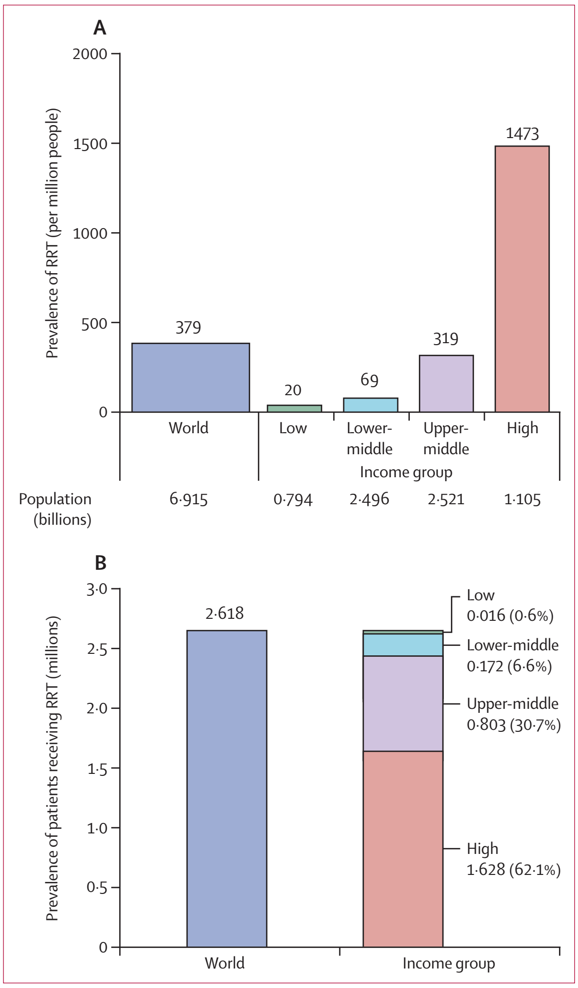

Figure 4: **Prevalence (A) and number of patients (B) receiving RRT according to income level**
Income levels were classified according to the World Bank income groups in 2010: low-income GNI per capita ≤US $1005; lower-middle income $1006–3975; upper-middle income $3976–12 275; high income ≥$12 276. GNI=gross national income. RRT=renal replacement therapy.

RRT steadily increased with age, but two groups of countries had manifestly different patterns in old ages: four countries (Japan, Taiwan, Singapore, and the USA) had a very high prevalence of RRT, particularly in old people, whereas the remaining 16 countries had a lower prevalence (appendix).

In total, the number of patients needing RRT in 2010 was estimated to be 4·902 million (95% CI 4·438–5·431 million) when using the model derived from the data in 16 countries (conservatively estimated model), in which RRT is likely to be only partly implemented (table 2). The estimate was 9·701 million (8·544–11·021 million) when we used the model derived from data in the four countries (high-estimate model), with near-complete levels of RRT use. This analysis suggests that between 2·284 million (47%) and 7·083 million (73%) individuals needing RRT worldwide did not receive it. By region, Asia was estimated to have the highest number of people needing RRT (2·875 million; conservative model), but the proportion actually receiving this treatment ranged from 17% to 34% across the two models. Africa had the lowest access to RRT, ranging from 9% to 16%. Middle and eastern Africa had remarkably lower access than the rest of the continent, with only 1–3% in need of treatment receiving RRT (appendix).

On the basis of data describing demographic projections and the forecast rate of economic growth, we estimated that the projected number of people receiving RRT will more than double from 2·618 million people worldwide in 2010 to 5·439 million (95% CI 3·899–7·640 million) in 2030 (figure 5). The largest absolute growth in the number of people receiving RRT is projected for Asia, rising from 0·968 million people in 2010 to 2·162 million (1·571–3·014 million) by 2030. The number of people receiving RRT is also forecast to increase rapidly in Africa, from 0·083 million in 2010 to

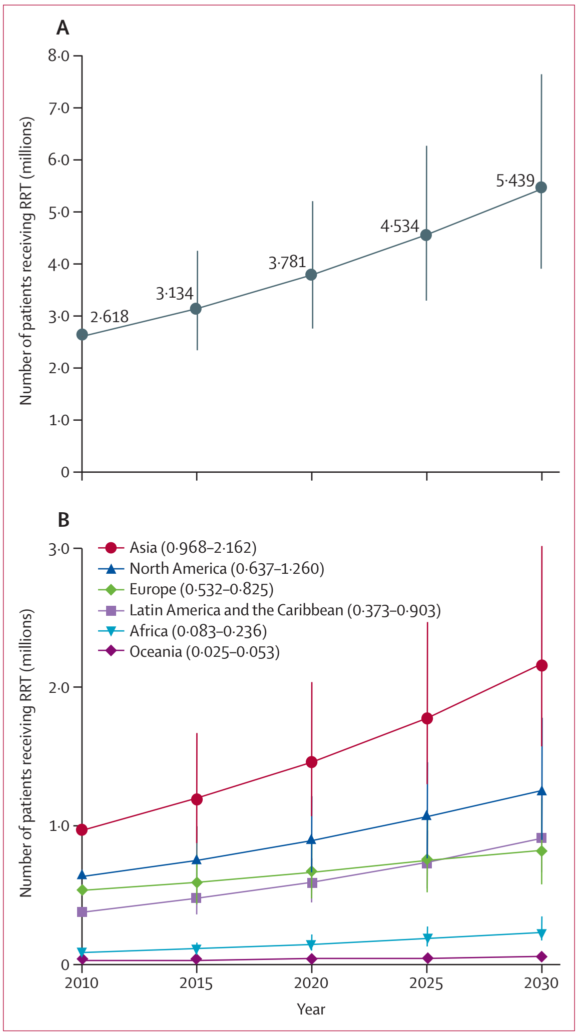

Figure 5: **Estimated number of patients undergoing RRT from 2010 to 2030 worldwide (A) and by region (B)**
95% CIs shown as error bars. RRT=renal replacement therapy.

0·236 million (0·167–0·347 million) by 2030, and Latin America and the Caribbean, increasing almost 2·5 times from 0·373 million in 2010 to 0·903 million (0·663–1·234 million) by 2030.

Discussion

In this systematic review, we used the best available data to calculate the number of people receiving RRT in 2010, noting that about 2·618 million people received this life-sustaining treatment worldwide. Additionally, our findings suggest that, at best, only half or less of all people needing RRT worldwide had access to it in 2010, meaning at least 2·284 million people might have died prematurely because they did not have access to the treatment in 2010. Most of this burden of preventable deaths fell on low-income and middle-income countries. Further modelling suggests that the number of people undergoing RRT will more than double to 5·439 million by 2030, mostly in developing regions such as Asia and Africa; however, the number of people without access to RRT will remain substantial. These data show a pressing need to develop low-cost RRT alternatives to reduce disparities in access to the treatment, and the importance of development, implementation, and assessment of cost effective end-stage kidney disease prevention strategies.

These estimates build on and extend previous estimates of worldwide end-stage kidney disease burden—the number of people estimated to be receiving RRT has increased steadily from 1·1 million people during the 1990s[18] to 1·8 million in 2004,[19] 1·9 million in 2005,[20] and now 2·618 million in 2010. Our data suggest that this trend is likely to continue, driven by demographic change—especially ageing of the global population—and improvements in access to dialysis in countries with growing economies. Importantly, these estimates do not take account of any future changes in prevalence of end-stage kidney disease potentially driven by projected increases in diabetes[5] or hypertension,[7] or by changes in urbanisation, diet, and physical activity,[6] as relations between these variables and RRT prevalence were not apparent in our analysis. Nonetheless, these variables are very likely to be captured in the model because of the high degree of collinearity with life expectancy and economic development. The fact that an association was not noted could also be the result of the aggregate nature of the data obtained, which could obscure relations that would be apparent if more granular data were available. Any increases in the prevalence of diabetes and hypertension could therefore be additional to those estimated in this analysis and probably bring with them further preventable deaths and additional health-care costs.

The most important finding of this analysis is that a large number of people in need of RRT worldwide do not presently receive it. One previous study[20] used national rates of diabetes and hypertension to estimate incidence of end-stage kidney disease and access to RRT, and suggested that more than 1·2 million premature deaths occurred as a result of untreated end-stage kidney disease related to diabetes and hypertension in 2010. However, we did not find a strong relation between these risk factors and the prevalence of RRT at a national level, but instead noted that age, life expectancy, and economic development were the strongest drivers. Although economic factors have been previously reported to be predictors of RRT prevalence,[3,21,22] the observation regarding the relation between average life expectancy and RRT prevalence is new. The strong predictive ability of our model for prevalence of RRT suggests that this approach is robust.

The large number of deaths occurring because of poor access to treatment sets a demanding task for the nephrology community and the health-care and research communities in general. Although documentation of the magnitude of the issue is a necessary first step, the size of the gap demands a combined advocacy, health-care delivery, and research approach.[2] First, governments should be made aware of the number of preventable deaths in their jurisdictions and lobbied to increase access to dialysis for affected individuals where it is affordable in the context of the broad health needs of their populations. Second, effective population-based approaches to prevention of end-stage kidney disease—such as blood pressure control,[23] renin–angiotensin system blockade, and management of key risk factors, including diabetes and obesity[24]—and acute kidney injury[25] should be refined and tested. Innovative models of preventive care should be piloted in low-income and middle-income countries, especially in areas where access to physicians is low.[26] Evidence exists from places such as Chile, Taiwan, the UK, and Uruguay to suggest that multifaceted preventive strategies might stabilise or even reduce the incidence of people needing RRT, and lead to cost savings.[1,27–30] These models should be implemented widely and rigorously assessed. Third, cost-effective dialysis techniques should be developed and made available. For the foreseeable future, present dialysis techniques costing tens of thousands of US dollars per patient per year will remain unaffordable for many of the countries where access to RRT is lowest. In view of the increase in the expected number of patients needing treatment, dialysis provision will represent a substantial financial burden for even the most affluent countries in the years ahead. Finally, barriers to patients receiving a kidney transplant should be identified and removed because these transplants are the most cost-effective form of RRT and produce the best outcomes.[3] Professional bodies such as the International Society of Nephrology have a key role to play in this effort.

Our study has several strengths. We obtained contemporary data from 123 countries plus Taiwan and Hong Kong (almost double that of the most recent report),[20] including 93% of the worldwide population, using a comprehensive and systematic approach, with conservative estimates used wherever possible. This study reports estimates of RRT use worldwide, and uses the most reliable methods available to develop estimates of premature deaths due to an absence of access to RRT. It also expands on previous studies by identifying a new association with life expectancy.

Some limitations should also be considered, mainly due to variability in the datasets used and their quality and reliability. The available data were not complete for some countries, and the two countries with the largest populations in the world, China and India, do not have comprehensive national registries. Nonetheless, we obtained data from the most reliable available sources and believe that any variability in reliability of estimates for these countries would have a small effect on the results at most. We were unable to obtain sufficient RRT incidence data to allow meaningful analysis of incidence. Because we deemed national dialysis prevalence equal to total RRT prevalence where renal transplantation data were unavailable, the number of patients receiving RRT is probably slightly underestimated in this study. We also recognise that a much larger number of patients have kidney failure as defined by the Kidney Disease: Improving Global Outcomes group[31] (estimated glomerular filtration rate <15 mL/min per 1·73 m²) than the number needing RRT because the indications for RRT are neither clear nor uniform. The models needed a series of assumptions, but each was well supported by the available data, and although strong predictive ability was achieved, substantial variation was still seen. We developed two different models of expected RRT need, and have focused on the more conservative one to minimise the risk of overestimation. Finally, our estimates do not take account of continuing changes such as urbanisation and westernisation and their association with rapidly increasing rates of diabetes and hypertension, so the estimates here might be conservative and underestimate the future burden of disease.

The number of people receiving RRT is projected to grow from 2·618 million in 2010 to 5·439 million by 2030. Between 2·284 and 7·083 million people who could have been kept alive with RRT in 2010 died prematurely because they did not have access to the treatment. Most of these deaths occurred in low-income and middle-income countries in Asia, Africa, and Latin America and the Caribbean. The predicted growth in the prevalence of end-stage kidney disease demands development of affordable RRT techniques and implementation of effective and affordable early detection and prevention programs.

Contributors

TL, TN, VJ, and VP were responsible for study concept design, data interpretation, and manuscript preparation. TL, TN, HMP, IO, JL, AXG, and JK were responsible for data collection, and TN was also responsible for data analysis. All authors were responsible for critical revision of the analyses, interpretation of the findings, and editing of the report.

Declaration of interests

VP has received funding support for a clinical trial and served on an extramural grant committee for Baxter. VJ has received research funding from Baxter. BN reports research support, honoraria, and travel reimbursement paid to his institution from several pharmaceutical companies of compounds prescribed for prevention of chronic kidney disease. AC reports grants from Baxter, Amgen, Merck, Novartis, and the Australian National Health and Medical Research Council outside of the submitted work. TL is supported by an Australian Postgraduate Award from the Government of Australia. VP was supported by an Australian National Health and Medical Research Council Senior Research Fellowship. BN is supported by an Australian Research Council Future Fellowship (DP100100295) and a National Health and Medical Research Council of Australia Senior Research Fellowship (APP100311). All other authors declare no competing interests.

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