

Renal failure deaths and their risk factors in India 2001–13: nationally representative estimates from the Million Death Study



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Summary

Background Renal failure represents a growing but mostly undocumented cause of premature mortality in low-income and middle-income countries. We investigated changes in adult renal failure mortality and its key risk factors in India using the nationally representative Million Death Study.

Methods In this cross-sectional analysis of population-based data, two trained physicians independently assigned underlying causes to 150 018 deaths at ages 15–69 years from a nationally-representative mortality survey in India for 2001–03 and 2010–13, using the International Classification of Diseases, 10th version (ICD-10). We applied the age-specific proportion of renal failure deaths for the 2010–13 period to the 2015 UN estimates of total deaths in India and calculated age-standardised death rates for renal failure by rural or urban residence, state, and age group. We used proportional mortality of renal deaths (cases) to injuries (controls) to calculate the odds of renal death in the presence of different comorbidities and stratified risks by decade of birth.

Findings In 2001–03, 2.1% of total deaths among 15–69 year olds were from renal failure (1266 [2.2%] of 58 871; unweighted). By 2010–13, the proportion of deaths from renal failure had risen to 2.9% (2943 [3.2%] of 91 147; unweighted) of total deaths and corresponding to 136 000 renal failure deaths (range 108 000–150 000) of 4 688 000 total deaths nationally in 2015. Age-standardised renal death rates were highest in the southern and eastern states, particularly among adults aged 45–69 years in 2010–13. Diabetes, hypertension, and cardiovascular disease were all significantly associated with increased renal failure deaths, with diabetes the strongest predictor—odds ratio (OR) *vs* control 9.2 (95% CI 6.7–12.7) in 2001–03, rising to 15.1 (12.6–18.1) in 2010–13. In the 2010–13 study population, the diabetes to non-diabetes OR was twice as large in adults born in the 1970s (25.5, 95% CI 17.6–37.1) as in those individuals born during or before the 1950s (11.7, 9.1–14.9).

Interpretation Renal failure is a growing cause of premature death in India. Poorly treated diabetes is the most probable reason for this increase. Strategies aimed at diabetes prevention, and early detection and treatment are urgently needed in India, as well as greater access to renal replacement therapy.

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Introduction

In many high-income countries the prevalence of chronic kidney disease approaches 15% of the adult population,¹ predominantly due to diabetic and hypertensive nephropathy, and poses a large medical and economic burden.² Kidney disease and death from renal failure is also a major, but poorly documented burden for low-income and middle-income countries. In low-income countries, infectious causes, environmental pollutants, and toxins are thought to be the primary causes of both acute kidney injury and chronic kidney disease.³ Middle-income countries, such as India, which are undergoing rapid economic and epidemiological transitions appear to be facing a double burden, with continued high prevalence of infectious causes of kidney disease as well as rising rates of hypertension and particularly of untreated diabetes.^{3–5}

In India, nationally representative, population-based data for renal failure incidence, prevalence, and deaths are absent at both a national and a subnational level. However, several factors suggest morbidity and mortality from renal failure is likely to be a growing public health concern for India. The prevalence of diabetes is estimated at 9% among adults in urban India, and is greater among those who are overweight or wealthy.⁶ Hypertension prevalence is also rising in both urban and rural India.⁷ Because the development of chronic kidney disease is insidious, and aetiologies such as diabetes and hypertension are often underdiagnosed at the population level, presentation with kidney disease is typically late;⁸ for example, in one study,⁹ end-stage renal failure accounted for about half of all chronic kidney disease presentations in India.

In this Article, we aimed to estimate renal failure mortality in the nationally representative Million Death

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See [Comment](#) page e14

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Research in context

Evidence before this study

We systematically searched PubMed and Embase databases with no specified start date up to Aug 1, 2016 for English language sources. We used the following PubMed search terms and translated appropriately for Embase: ("kidney disease" [MeSH], OR "renal failure"[MeSH]) AND ("mortality estimates" [tw], OR "burden of disease" [tw], OR "disease burden" OR "household" [tw] AND "survey" [tw]). We further delineated by low-income or middle-income countries, and specifically screened for representative, population-based studies of mortality due to renal failure. We found no nationally representative, population-based studies of renal failure mortality for any middle-income country. Population-based studies at the state and community level of renal failure incidence and prevalence exist for India, but any estimations of national mortality drawn from these are likely to be weak because these are typically not representatively sampled, and because as our study findings show, subnational age-standardised rates of renal failure mortality vary widely within India.

Added value of this study

To our knowledge, our study results provide the first nationally representative population-based estimate of deaths from renal failure in any low-income and middle-income country, and show that renal failure is a growing public health concern for India. We establish that much of the high burden and rising death rates are due to diabetes. Our estimates also show very low coverage of renal replacement therapy (dialysis and transplantation).

Implications of all the available evidence

Renal failure is an important and growing cause of premature adult mortality in India, driven by the rising prevalence of poorly treated diabetes, especially in urban areas. Access to dialysis and transplantation is poor and not commensurate with the large and rising burden of renal disease. Greater priority should be given to addressing renal failure as well as access to preventive and treatment services, including for diabetes, in India and other comparable middle-income countries.

Study (MDS) conducted in India, comparing data for 2001–03 and 2010–13. We estimate the number of adults deaths from renal failure, the contribution of diabetes, hypertension and cardiovascular disease, and changes over time in each period.

Methods

Study design

Details of the MDS, including study design, physician assignment of the underlying cause of death, and statistical methods have been published elsewhere.^{10–12} Briefly, the study uses an enhanced type of verbal autopsy method (a structured survey administered to a household member or close relative of the deceased by a trained non-medical field worker to record the signs and symptoms that occurred before death—this information is used to assign the most probable cause of death¹³). From 2001 onwards, the MDS has monitored annual deaths in 1.3 million representative households within the Registrar General of India (RGI)'s Sample Registration System (SRS). The SRS partitions India into 1 million small areas after each census, from which 6671 small areas from the 2001 census and 7597 small areas from the 2011 census are randomly selected for continuous monitoring of household births and deaths. One of 800 non-medical RGI surveyors visits each house every 6 months and for any household with a death, interviews a family member or associate of the deceased and completes a two-page form¹⁴ with structured questions and a half-page local language narrative that probes the presence or absence of key symptoms before death. For all deaths in people over 15 years of age, the surveyors ask the living respondent about the deceased's use of smoked or chewed tobacco and alcohol, and

whether a doctor had ever diagnosed heart disease, stroke, hypertension, or diabetes. The field records are converted to electronic records and emailed independently to two of 400 specially trained physicians able to read the local language. Physician coding follows guidelines for the major underlying causes of deaths, coded using the International Classification of Diseases and Related Health Problems, 10th version (ICD-10).¹⁵ ICD-10 coding differences undergo anonymous reconciliation by each of the two physicians, and persisting differences are adjudicated by a third physician. Random independent resampling of about 3% of deaths has shown cause-of-death results to be consistent with the RGI fieldwork.^{10,16}

We focused on renal failure deaths (ICD-10 codes N00–N19) in adults aged 15–69 years because deaths at these ages are more likely to be avoidable and have lower unclassifiable causes than deaths at older ages.^{10–12} Biochemical or pathological confirmation of renal failure or kidney disease, while desirable, was not available in most cases.

Statistical analysis

We calculated age-specific and age-standardised death rates (directly, using the WHO standard population¹⁷) using the 2008 SRS total death rates by state for the 2001–03 study period and the 2013 SRS total death rates by state for the 2010–13 study period. We applied the sample-weighted MDS proportion from 2010–13 to the 2015 United Nations¹⁸ estimates of total deaths in India to estimate total renal failure deaths, as described previously.¹⁹ We compared prevalence of diabetes, hypertension, cardiovascular disease, and tuberculosis, as well as smoking and drinking (among males, because

	Study deaths, 2001–03			Study deaths, 2010–13			All India, 2015			
	Renal failure deaths/all coded deaths	Proportion renal failure (%) [*]	Urban deaths	Renal failure deaths/all coded deaths	Proportion renal failure (%) [*]	Urban deaths [†]	All deaths/population (thousands) [†]	Estimated deaths (thousands) [*]	Estimated deaths per 100 000 [‡]	Period risk (%) [§]
0–14 years	82/27 170	0.3%	9	72/25 885	0.2%	14	1444/377 427	3	2.3	0.03%
15–29 years	137/9041	1.5%	33	229/11 978	1.7%	73	535/354 355	9	7.2	0.11%
30–44 years	249/10 780	2.2%	55	524/16 587	2.7%	152	813/276 524	22	17.3	0.26%
45–59 years	449/18 028	2.5%	129	1146/29 435	3.6%	388	1544/186 192	56	43.9	0.66%
60–69 years	431/21 022	1.9%	109	1044/33 147	2.8%	317	1796/71 961	50	39.7	0.40%
>70 years	564/35 835	1.5%	146	1202/65 116	1.5%	385	3449/44 592	52	40.8	0.82%
Overall										
15–69 years	1266/58 871	2.1%	326	2943/91 147	2.9%	930	4688/889 032	136	15.3	1.42%
Bounds [¶]	838–1531	1.3–2.5	221–393	2304–3290	2.3–3.2	726–1020	..	108–150	12–17	..

^{*}Weighted for sampling probability. [†]For each age range sample-weighted percentages are multiplied by the UN estimated number of all deaths in 2015 to estimate national renal failure mortality. [‡]Age-specific rates, per 100 000. [§]Annual rate multiplied by the duration of age range, except for the period risk for 15–69 years which was calculated by summation of the age-specific period risks (giving the probability of death from renal failure at ages 15–69 years in the absence of other causes of death). [¶]Lower and upper bound estimates are based on both physicians immediately agreeing that the underlying cause of death was renal failure or if only one physician chose this diagnosis.

Table 1: Renal failure deaths among Indians in the Million Death Study, and estimated national totals 2001–03 and 2010–13

few women smoke or drink alcohol in India),²⁰ and rural versus urban residence among renal failure deaths (cases) with prevalence among deaths of a control group (people who died from injuries; ICD V00–Y99).¹² Proportional mortality assumes that the comorbid prevalence among the deceased in the control group is broadly similar to that observed in the general population, and that any biases in reporting are similar between case and control deaths.²¹ Because control deaths were generally younger than renal failure deaths, we standardised percentages for comorbidities to the age distribution of all cases in 2010–13. We used logistic regression to calculate odds ratios (OR) for deaths from renal failure versus control deaths in the presence of different comorbidities,²² adjusting for age (linear), nighttime light exposure as a proxy for socioeconomic status,^{23,24} urban residence, smoking, and alcohol use. We stratified risks by birth cohort, comparing adults born on or before 1955 (1950s birth cohort), 1956–65 (1960s), and 1966–75 (1970s). We also did subgroup analysis by sex for the proportional mortality analysis. We excluded missing data (<5% for exposures and <1% for deaths or birth cohorts) from the logistic regression. The main source of uncertainty in the MDS estimates arises from assignment to the ICD-10 codes for renal failure deaths and not from random variation, given the large sample size of the MDS.¹⁰ Thus, we provide lower bounds for the national totals if the death had been immediately attributed to renal failure by both physicians (hence, no subsequent reconciliation or adjudication was needed). Upper bounds were the cases in which only one physician attributed the underlying cause to renal failure (these cases were assigned to other conditions during subsequent reconciliation or adjudication). Standard 95% CIs are provided for the regression model for the proportional mortality analyses. Statistical analysis used Stata version 14 and ArcMap 10.3 and PostGIS 2.0.

As a supplementary analysis, using data from a national survey of dialysis units in India in 2009,^{25,26} we geocoded dialysis units using postal codes and computed spatial buffers at distance bands: 0–19.9 km, 20–49.9 km, and 50–99.9 km around each unit. We used the buffers and a population grid²⁷ to extract the number of people living within each buffer. We calculated coverage per million population of renal transplantation as reported by the WHO Global Observatory on Organ Transplantation.²⁸ Because India does not have a formal national transplant registry, renal transplantation rates represent best estimates only.

Role of the funding source

The funding sources had no role in the study design, conduct, data collection, analysis, or interpretation. PJ had full access to all data and final responsibility for the decision to submit for publication on behalf of all authors.

Results

In 2001–03, 2.1% of total deaths among 15–69 year olds were from renal failure (1266 [2.2%] of 58 871; unweighted). By 2010–13, the proportion of deaths from renal failure had risen to 2.9% (2943 [3.2%] of 91 147; unweighted) of total deaths (table 1). The age-standardised rate (all reported as per 100 000 population) for renal failure death at ages 15–69 years was 13 in 2001–03 and 17 in 2010–13. Among 45–69 year olds, the age-standardised death rate rose from 30 in 2001–03 to 40 in 2010–13. By comparison, the national age-standardised death rate for renal failure in 15–44 year olds remained relatively static across the study periods at about 5. The age-standardised death rates at ages 45–69 years were significantly higher overall in urban areas than in rural areas, and rose from 37 in 2001–03 to 45 in 2010–13 in urban areas and 27 in 2001–03 to 37 in 2010–13 in rural areas. The overall risk of death from renal failure at ages 15–69 years was 1.42%, in the hypothetical absence of other causes.

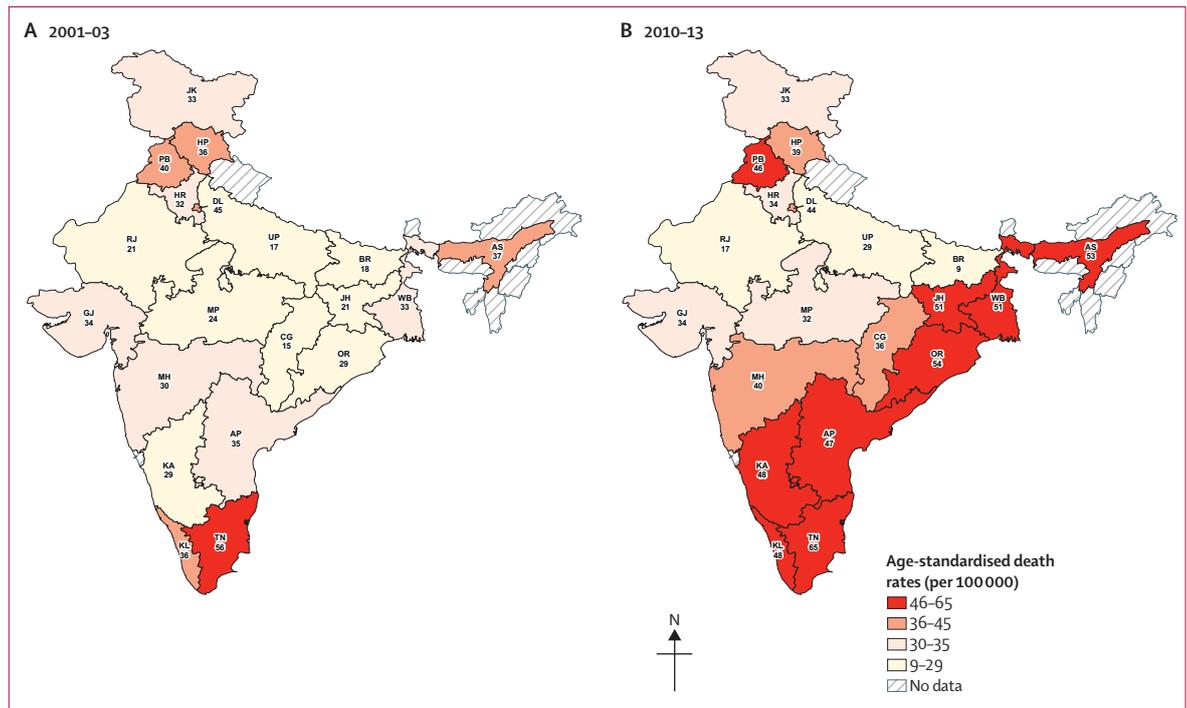


Figure 1: Age-standardised renal failure death rates among Indian adults aged 45–69 years in (A) 2001–03 and (B) 2010–13

Age-standardised death rates for renal failure deaths were calculated directly, per 100 000 population, using the WHO standard population¹⁸ and the population of the 2008 SRS death rates by state for 2001–03 and 2013 SRS death rates by state for 2010–13. AP=Andhra Pradesh. AS=Assam. BR=Bihar. CG=Chhattisgarh. DL=Delhi. GJ=Gujarat. HP=Himachal Pradesh. HR=Haryana. JH=Jharkhand. JK=Jammu and Kashmir. KA=Karnataka. KL=Kerala. MH=Maharashtra. MP=Madhya Pradesh. OR=Odisha. PB=Punjab. RJ=Rajasthan. TN=Tamil Nadu. UP=Uttar Pradesh. WB=West Bengal. SRS=sample registration system.

Results for subgroup analysis by sex are not presented because we identified no significant differences in death patterns or risk factors between men and women. At ages 15–69 years the proportion of renal failure deaths in the study (2·9%) corresponds to an estimated 136 000 renal failure deaths (range 108 000–150 000, based on the two physicians immediately agreeing if the death was from renal failure or not) of 4 688 000 total deaths in 2015 (UN death estimates,¹⁸ India 2015). The median age of renal failure death was 55 years (IQR 42–63) for patients aged 15–69 years during the two study periods. Deaths from renal failure were more common in male individuals in 2010–13 (64%, 1888 of 2943 total deaths) with similar proportions in 2001–03 (63·5%, 804 of 1266). Although the age-standardised rate of death was higher in urban areas than in rural areas, the total number of deaths was greatest in rural India, in keeping with population distribution. However, the percentage of total urban deaths rose from 26% (326 deaths) in 2001–03 to 32% (930 deaths) in 2010–13. With far less certainty than for ages 15–69 years, 52 000 renal failure deaths occurred nationally at ages 70 years or older.

Renal failure deaths varied substantially, geographically and temporally, at the state level within India. The age-standardised death rate from renal failure rose notably in the eastern and southern states, particularly among 45–69 year olds (figure 1). The death

rate from renal failure per 100 000 population at ages 15–69 years was highest in the southern state of Tamil Nadu and increased over the study period (17 in 2001–03 and 20 in 2010–13 for 0–69 years; 56 in 2001–03 and 65 in 2010–13 among 45–69 year olds). Modest increases also occurred in the southern states of Kerala, Andhra Pradesh, and Karnataka. The eastern states of Assam, West Bengal, Orissa, and Jharkhand also had high death rates and experienced the greatest increase throughout the two time periods, mostly as a result of the rapidly rising death rates in the 45–69 year age group. By 2010–13, these eastern states had renal failure death rates of more than 50 per 100 000 population, almost double that in 2001–03. Geographical disparity also increased during the study period because renal death rates in the northern and western states remained relatively static during the two study periods whereas rates in the southern and eastern states increased.

The prevalence of diabetes among renal failure deaths rose from 26% in 2001–03 to 34% in 2010–13 (table 2). By contrast, 16% of control deaths were patients known to be diabetic in 2001–03 and 23% were in 2010–13, after standardising to the age-distribution of renal failure deaths. The diabetes to non-diabetes OR was higher among renal failure deaths than among control deaths at both timepoints, after adjusting for hypertension, cardiovascular history, and smoking (table 2). In the

	Renal failure cases (%)		Renal failure controls (%)*		Odds ratio (95% CI)		Attributable fraction (%)†	
	2001-03	2010-13	2001-03	2010-13	2001-03	2010-13	2001-03	2010-13
Total‡	1151	2943	7478	14 501
Residence								
Urban	310 (27%)	930 (32%)	1300 (17%)	2977 (21%)	1.3 (1.1-1.4)	1.6 (1.4-1.8)
Rural	841 (73%)	2013 (68%)	6178 (73%)	11 524 (79%)	Ref	Ref
Comorbidities								
Diabetes	257 (26%)	937 (34%)	85 (16%)	205 (23%)	9.2 (6.7-12.7)	15.1 (12.6-18.1)	56.8%	76.3%
Hypertension	274 (28%)	637 (23%)	228 (18%)	445 (16%)	4.0 (3.0-5.1)	2.0 (1.7-2.4)	35.4%	13.8%
Cardiovascular disease	111 (12%)	230 (8%)	105 (9%)	130 (6%)	2.7 (1.8-4.0)	2.2 (1.6-2.9)	13.3%	7.1%
Tuberculosis	30 (3%)	63 (2%)	48 (2%)	65 (2%)	3.0 (1.6-5.6)	1.3 (0.8-2.1)	4.4%	0.7%
Male§								
Total	724	1892	45 660	61 328
Smoker	319 (45%)	679 (38%)	15 067 (34%)	10 735 (18%)	1.1 (0.9-1.3)	1.3 (1.2-1.5)	3.3%	5.6%
Alcohol drinker	211 (30%)	696 (38%)	7520 (17%)	6850 (12%)	1.9 (1.6-2.3)	4.0 (3.6-4.5)	13.4%	25.9%

The control group for comorbidities were MDS deaths from injuries (V00-Y99). The control group for lifestyle risk factors were living relatives of the cases, whose data were collected as part of the adult MDS survey. The comorbidity ORs adjust for age, gender, urban or rural residence, night-time light (as a proxy for socioeconomic status), each comorbidity, alcohol, and smoking. The selected risk factor ORs adjusted for age, urban or rural residence, and night-time light. Both OR calculations exclude cases with missing variables. *Percentages exclude missing records and are standardised to the age distribution of all cases in 2010-13. †Attributable fractions are of risk factors. ‡Total cases do not sum to the totals in Table 1 due to cases with missing variables for 2001-03. §Selected risk factors are presented for men. MDS=Million Death Study. ..=not applicable. Ref=reference group in the logistic regression model. OR=odds ratio.

Table 2: Comorbidity and risk of death from renal failure among Indian adults aged 15-69 years in 2001-03 and 2010-13: proportional mortality analysis

2010-13 study population, the diabetes to non-diabetes OR was twice as large in adults born in the 1970s (25.5, 95% CI 17.6-37.1) as in those born during or before the 1950s (11.7, 9.1-14.9; figure 2). The OR for hypertension and cardiovascular disease were less strongly associated with renal failure deaths, and smoking was modestly associated in 2010-13 (table 2). Because drinking alcohol is probably selectively under-reported among injury controls, the observed excess ORs in both time periods are probably artifacts (table 2).²⁹

Discussion

Our nationally representative mortality surveys show that renal failure contributes substantially to adult premature death before 70 years of age in India, and represents a growing cause of death. In 2015, we estimate that about 136 000 Indian adults died prematurely as a result of renal failure, representing about 3% of all premature adult mortality, 1.5 times the proportions observed a decade earlier. Renal failure deaths now exceed AIDS-related deaths in India.^{30,31} We also noted substantial geographical variation in renal failure mortality within India, with renal failure death rates highest in urban India and in the southern and eastern states. Diabetes was the most important risk factor associated with death from renal failure among adults at all ages; it was associated with the highest odds of renal failure death and by 2010-13 was also the most frequently occurring comorbid risk factor among renal failure cases. The risk associated with diabetes increased between study periods and was particularly high in cohorts of more recently born adults.

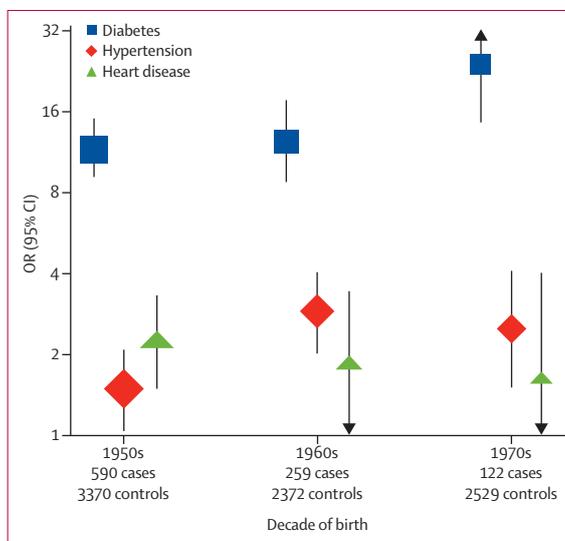


Figure 2: Birth cohort analysis of comorbidities among Indian adults and risk of renal failure death, 2010-13

The y-axis is on a doubling scale. Numbers on the x-axis represent case (renal failure) and control (injuries; V00-Y99) deaths at each decade. Cases and controls with missing information were excluded from these totals. The 1980s onwards cohort was excluded on the basis that most in the cohort were too young to have developed the major comorbidities studied. Weights of the estimates are relative to the inverse of square root of SE. Odds ratios are adjusted for sex, night-time light (as a proxy for socioeconomic status), urban or rural residence, alcohol, and smoking. OR=odds ratio.

These findings highlight a rapidly changing pattern of mortality in India¹² away from deaths from infectious diseases in rural areas, to chronic non-communicable

See Online for appendix

diseases in rural and especially urban areas.⁵ Diabetes is a leading cause of chronic kidney disease in high-income countries,³ and our study findings suggest it is now also the leading risk factor associated with renal failure death in India. Health facility registry data in India show diabetic nephropathy to be the most common cause of chronic kidney disease⁹ and representative community surveys find a substantial prevalence of undiagnosed or poorly treated diabetes.³² In high-income countries, around 20–30% of diabetics develop kidney disease. Renal failure is typically considered a late complication of diabetes.^{6,33,34} Our data support other studies showing that most people with diabetes in India have poor glycaemic control.^{35,36} Hyperglycaemia, along with hypertension, dyslipidaemia, and genetic factors, all of which are reported among the Indian diabetic population, accelerate the onset of diabetic complications, including kidney damage.^{6,34} As a result, onset of diabetic kidney disease among Indian adults appears to occur at a much younger age (20–40 years) compared with high-income countries.^{34,37} The rising prevalence of diabetes, the increased risks among more contemporary birth cohorts, and the earlier onset of diabetic complications suggest the age-standardised rates of renal failure deaths in India will continue to increase throughout the coming decades, posing substantial challenges to health services and budgets.^{26,38} Moreover, other large populations, such as in Mexico³⁹ and China,⁴⁰ have high rates of untreated diabetes leading to excess mortality from renal and vascular disease, suggesting a global pattern among middle-income countries.

We were unable to reliably differentiate acute from chronic renal failure in this study using the verbal autopsy methodology, and therefore analysed all renal failure deaths together. Chronic kidney disease is not clinically detectable until very late in the disease process when it presents similarly to acute renal failure. The MDS definitions of comorbidities relied on a history of a doctor previously diagnosing diabetes, hypertension, or cardiovascular disease. The true population prevalence of these conditions might be higher, including among the study cohorts, because these conditions remain underdiagnosed at the community level. We were also not able to capture in our study all comorbidities or environmental risks that might be causally associated with renal failure death, for example kidney stone disease. Chronic kidney disease also significantly increases the risk of premature cardiovascular death.³ Therefore, the total number of deaths associated with kidney disease in India might be substantially higher than deaths attributed to renal failure alone.

Once established, patients with end-stage kidney disease require renal replacement therapy in the form of dialysis or kidney transplantation to prevent death. Data from a national survey²⁵ of dialysis units in India report only 3.4 dialysis machines per million population in both the public and private sectors for those with

end-stage renal failure in 2009. Further geospatial analysis of these units suggests low population coverage of dialysis facilities: on the basis of these data, almost 60% of Indians live more than 50 km away from a health facility providing dialysis (appendix). 50 km or more are substantial distances given that patients in India mostly rely on haemodialysis and might require as many as five dialysis sessions per week. Kidney transplantation is the most effective and cost-effective treatment for kidney failure, particularly for diabetic nephropathy.^{41,42} Estimates of national kidney transplantation rates from the WHO Global Observatory on Organ Donation and Transplantation suggest that at only four transplantations per million population in India per year, transplantation is even less accessible than dialysis.²⁸ By comparison, middle-income countries in South America, which have developed regulated transplant networks and national transplant registries, perform 25–35 kidney transplantations per million population per year and most high-income countries perform more than 45 kidney transplantations per million population per year.²⁸ The Indian Chronic Kidney Disease Registry reported that of the patients with end-stage kidney disease followed by a nephrologist, most (61%) were not on any form of renal replacement therapy: 32% were on haemodialysis, 5% on peritoneal dialysis, and 2% were being considered for, or were listed, for transplantation.⁹ A 2015 global review³⁸ suggests that as many as 83% of renal failure patients in Asia are not receiving the treatment they need.

Renal failure is a growing cause of premature adult mortality in India. Reductions in renal failure mortality require, most urgently, improved glycaemic control of patients with diabetes, paired with earlier diagnosis and prevention of diabetes and other key risk factors. Those patients with end-stage renal failure require substantially improved access to renal replacement therapy, especially transplantation.

Contributors

AJD and PJ conceived the study. AJD, SHF, JP, and PSR analysed the data. AJD and PJ wrote the paper. All authors were involved with data interpretation, critical revisions of the paper, and approval of the final version. PJ is the guarantor.

Declaration of interests

We declare no competing interests.

Acknowledgments

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