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Sex differences in mortality among binational cohort of people with chronic kidney disease: population based data linkage study

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ABSTRACT

OBJECTIVE

To evaluate sex differences in mortality among people with kidney failure compared with the general population.

DESIGN

Population based cohort study using data linkage.

SETTING

The Australian and New Zealand Dialysis and Transplant Registry (ANZDATA), which includes all patients receiving kidney replacement therapy in Australia (1980-2019) and New Zealand (1988-2019). Data were linked to national death registers to determine deaths and their causes, with additional details obtained from ANZDATA.

PARTICIPANTS

Of 82 844 people with kidney failure, 33 329 were female (40%) and 49 555 were male (60%); 49 376 deaths (20 099 in female patients; 29 277 in male patients) were recorded over a total of 536 602 person years of follow-up.

MAIN OUTCOME MEASURES

Relative measures of survival, including standardised mortality ratios, relative survival, and years of life lost, using general population data to account for background mortality (adjusting for country, age, sex, and year). Estimates were stratified by dialysis modality (haemodialysis or peritoneal dialysis) and for the subpopulation of kidney transplant recipients.

RESULTS

Few differences in outcomes were found between male and female patients with kidney failure. However,

compared with the general population, female patients with kidney failure had greater excess all cause deaths than male patients (female patients: standardised mortality ratio 11.3, 95% confidence interval 11.2 to 11.5, expected deaths 1781, observed deaths 20 099; male patients: 6.9, 6.8 to 6.9, expected deaths 4272, observed deaths 29 277). The greatest difference was observed among younger patients and those who died from cardiovascular disease. Relative survival was also consistently lower in female patients, with adjusted excess mortality 11% higher (95% confidence interval 8% to 13%). Average years of life lost was 3.6 years (95% confidence interval 3.6 to 3.7) greater in female patients with kidney failure compared with male patients across all ages. No major differences were found in mortality by sex for haemodialysis or peritoneal dialysis. Kidney transplantation reduced but did not entirely remove the sex difference in excess mortality, with similar relative survival ($P=0.83$) and years of life lost difference reduced to 2.3 years (95% confidence interval 2.2 to 2.3) between female and male patients.

CONCLUSIONS

Compared with the general population, female patients had greater excess deaths, worse relative survival, and more years of life lost than male patients, however kidney transplantation reduced these differences. Future research should investigate whether systematic differences exist in access to care and possible strategies to mitigate excess mortality among female patients.

Introduction

Chronic kidney disease is defined as decreased kidney function, with an estimated glomerular filtration rate less than 60 mL/min/1.73 m², or markers of kidney damage for at least three months. In 2017, the global prevalence of chronic kidney disease was estimated at 9.1% (95% confidence interval 8.5% to 9.8%) and was ranked the 12th leading cause of death, directly resulting in 1.2 million deaths and indirectly contributing to an additional 1.4 million deaths.¹ When people have advanced chronic kidney disease, kidney failure is defined by an estimated glomerular filtration rate of less than 15 mL/min/1.73 m². Treatment options for kidney failure are dialysis, kidney transplantation, or palliative care. Provision of care for kidney failure accounts for around 2% of healthcare expenditure in developed countries.² Kidney failure continues to result in premature deaths and is responsible for most of the 28.5 million years of life lost. In 2017, 35.8 million disability adjusted life years could be attributed to chronic kidney disease globally.¹

WHAT IS ALREADY KNOWN ON THIS TOPIC?

Many chronic diseases have sex specific mechanisms whereby women might not develop the same symptoms as men, therefore diseases could go unrecognised leading to systematic differences in care

Chronic kidney disease is more prevalent in women, but men have a faster progression to kidney failure and represent most of the population with kidney failure

Few studies have explored sex differences in survival among the population with kidney failure, with most focusing on comparisons within the population rather than expected survival seen in the general population

WHAT THIS STUDY ADDS?

The life limiting impact of kidney failure is greater for women than men; the female survival advantage in the general population is lost in the presence of kidney failure

Female patients with kidney failure had more excess deaths, worse relative survival, and greater life years lost compared with male patients with kidney failure; the greatest disparity was seen in younger ages and from certain causes of death (such as cardiovascular disease)

Kidney transplantation improved survival in both sexes and reduced sex differences in excess mortality, although female patients still had more life years lost

In the general population, the life expectancy of women consistently exceeds that of men in many developed countries. This difference has been attributed to biology, such as the effect of oestrogen,³ and increased healthcare seeking behaviour and greater engagement with healthcare in women.⁴ However, sex inequalities in health service delivery might mean the survival advantage in women does not always persist. Growing evidence supports sex specific mechanisms whereby women might not develop the same symptoms of disease as men, leading to systematic differences in care including misdiagnosis and delays in receiving treatment.⁵ Women are also underrepresented in randomised clinical trials and animal models,⁶ which can lead to the development of drugs and treatments that are more harmful or less effective in women.

Chronic kidney disease manifests differently in men and women. Women have a higher prevalence of chronic kidney disease, but men have a faster progression to kidney failure and so represent a greater proportion of the population with kidney failure.⁷ Current evidence suggests there are differences in care received by men and women with chronic kidney disease. Women are more likely to start dialysis late at lower levels of kidney function, and have higher rates of dialysis withdrawal.⁹⁻¹² After a cardiovascular event, women receiving dialysis have lower rates of cardiac catheterisation and cardiac rehabilitation.¹⁰ Serum creatinine is a commonly used indicator of kidney function, but is not directly comparable between sexes. At the same level of serum creatinine, men have better kidney function than women because of higher muscle mass on average and increased endogenous creatinine production.¹³ To some extent this disparity is mitigated by the use of estimated glomerular filtration rate to monitor changes in kidney function, which accounts for sex, but women might still be referred for specialist care later than men with comparable kidney function.¹⁴ These factors could contribute to the poorer long term outcomes in women with kidney failure. Recommended dialysis dosage calculations were also found to favour male body compositions in a cohort study,¹⁵ but these effects were reduced in a subsequent clinical trial.¹⁶

Systematic differences in care for kidney failure might mean that women with kidney failure have comparatively poorer survival rates compared with men. Limited studies that have explored differences in survival between men and women have mainly focused on comparisons within the population with kidney failure. These studies provide little insight into the differences in relative measures of survival that account for background mortality or expected survival outcomes in the wider population.^{17 18} These studies also presented only one relative measure of survival in countries without universal healthcare or were carried out in earlier eras when any health inequalities in men and women were probably amplified by other social determinants, such as socioeconomic status or ethnicity.

Our study aimed to evaluate sex differences in mortality in the Australian and New Zealand population with kidney failure by using relative measures of survival to account for expected background mortality in the general population. We hypothesised that people with kidney failure would have greater mortality than the general population, and sought to explore whether the impact of kidney failure on excess mortality was comparable between sexes.

Method

Study design and setting

We undertook a population based cohort study of all people receiving kidney replacement therapy (dialysis or kidney transplantation) in Australia (from 1 January 1980 to 31 December 2019) and New Zealand (from 1 January 1988 to 31 December 2019). Both countries have a universal healthcare system and similar population demographics. Under mandate in both countries, all deaths are captured by the Births, Deaths and Marriages Registry. Primary and secondary causes of death are reported by a medical doctor and recorded on the medical certificate. A clinician then classifies causes of death according to ICD-10 codes (international classification of diseases, 10th revision). ICD-10 is an internationally agreed and standardised coding system that is used worldwide, which enables comparisons with other populations. The primary cause of death is defined as the disease or condition that started the sequence of events that resulted in death. The secondary causes of death are defined as any other disease or condition that contributed to death.

Participants, data linkage, and death outcomes

Population with kidney failure—the main study population consisted of all patients who received kidney replacement therapy as recorded on the Australian and New Zealand Dialysis and Transplant Registry (ANZDATA); a subpopulation included patients who received kidney transplantation. ANZDATA has been previously described.¹⁹ Briefly, prospective data are collected from all dialysis and transplant centres in Australia and New Zealand as they occur in real time and annually for each patient, including demographics, comorbidities, and clinical data. These data do not include people with kidney failure before they receive dialysis, those who are not receiving kidney replacement therapy, or people with kidney failure who are receiving palliative care. No data cleaning was necessary because ANZDATA conforms to an existing data dictionary.

Data linkage—all patients from ANZDATA in Australia (1980-2013) and New Zealand (1988-2017) were linked to respective national death registers to determine the date and cause of death. In Australia, probabilistic linkage to the National Death Index was undertaken by the Australia Institute of Health and Welfare, matching on personal identifiers such as date of birth, sex, and full name. In New Zealand, deterministic linkage to the Mortality Collection

(MORT) database was undertaken by the New Zealand Ministry of Health, matching on the National Health Index number. We were restricted by the years of death data available on the national death registers at the time of linkage in 2015, which commonly have some lag time. Therefore, our analysis included cause and fact of death information for our study cohort in Australia during 1980-2013 and in New Zealand during 1988-2017. Fact of death for the remaining study cohort and follow-up (Australia during 2014-2019 and New Zealand during 2017-2019) was obtained from ANZDATA, which has previously been shown to have strong agreement with national death registers for fact of death, but less strongly for cause of death.²⁰ Only deidentified patient data were made available to researchers for this study once data linkage was complete.

Death ascertainment and cause of death—ICD-10 diagnosis codes provided as the primary cause of death were used to define causes of deaths in Australia (1980-2013) and New Zealand (1980-2017). Deaths were categorised into broad causes of death, largely based on ICD chapters, and leading causes of death,²¹ as commonly reported in national death register reports. Appendix table 1 outlines categories for causes of death.

Time at risk was measured from the date of starting kidney replacement therapy for the kidney failure population and the earliest transplant date for the subpopulation who received kidney transplantation, until the date of death recorded on the national death register (Australia 1980-2013; New Zealand 1988-2017) or ANZDATA (Australia 2014-19; New Zealand: 2017-19), or 31 December 2019 (censor date), whichever occurred first. We also evaluated the effect of switching treatment modality on sex differences in mortality, considering four types of treatment: haemodialysis, peritoneal dialysis, deceased donor transplant, and living donor transplant. Patients who received haemodialysis or peritoneal dialysis were censored at first transplant date, date of death, or last known follow-up. Those who received a deceased or living donor transplant were censored at date of death or last follow-up.

As probabilistic linkage could result in a small proportion of incorrect links,²² Australian patients were censored at the date of death recorded in ANZDATA if they had died but the national death register did not capture any death. Furthermore, Australian patients with additional records after the registered date of death were considered to be alive and censored.

Statistical analyses

Patient characteristics were summarised using absolute counts and proportions, overall and stratified by sex. Causes of death during 1988-2017 were compared between sexes using logistic regression to make comparisons across age groups, trends over calendar year, and by treatment modality at death. Because of a lag in availability of Australian cause of death data, causes of death during 2013-17 were

predicted with five iterations based on patient and clinical characteristics including sex, age, ethnicity, cause of kidney failure, treatment modality, ever transplanted, follow-up time, ANZDATA cause of death, and comorbidities.

We calculated crude mortality rates and estimated standardised mortality ratios by using indirect standardisation, adjusting for five year age band, sex, calendar year, and country. General population mortality rates for each country were estimated using nationwide summary level data, which provided the number of deaths given in ICD-10 codes and by five year age band, sex, and calendar year. These data are publicly available from the Australian Bureau of Statistics²³ and the New Zealand Ministry of Health.²⁴ Linear regression was used to compare rates and log transformed standardised mortality ratios between sexes, across age, and over time.

We estimated the cumulative relative survival using the life table approach and Ederer II methods, matching to the general population by country, five year age band, sex, and calendar year.²⁴⁻²⁶ The cumulative relative survival can be interpreted as the proportion of patients alive compared with the expected proportion in the general population at x years of follow-up. A cumulative relative survival <1.0 indicates a lower proportion of the study population survived than would be expected in the matched general population. Additionally, we modelled excess mortality by using Poisson regression to estimate the excess mortality ratio. Covariates included age (categorised), sex, country, calendar year, year of follow-up, cause of kidney failure, and comorbidities (chronic lung disease, peripheral vascular disease, and coronary artery disease). An excess mortality ratio equal to 1 indicates the excess mortality (or difference in the hazard of mortality) in the study population is similar to that observed in the general population.

The life expectancy was estimated, and thereafter the expected years of life lost, as the area under the survival curve from a parametric survival model with a Gompertz distribution, stratified by sex.²⁷ The time at risk was altered to be relative to the patient's date of birth so that the hazard of death was a function of a patient's age. Covariates, selected a priori, included year when dialysis was started or when first transplant was received, cause of kidney failure, comorbidities (chronic lung disease, coronary heart disease, peripheral heart disease, cerebrovascular disease), smoking history, ethnicity, dialysis modality (haemodialysis or peritoneal dialysis), previous dialysis months (categorised; transplant only), and country. Smoking history was not routinely collected until after 1991, and so for a small proportion of patients this information is not available. Therefore, we used multiple imputation chained equations to impute smoking history with multinomial logistic regression of five iterations. Covariates in the imputation included patient and clinical characteristics, death outcome, and follow-up time (log transformed). An additional time varying binary covariate to indicate

the first six months of follow-up was included when modelling the life expectancy to increase the precision of survival predictions, and to adjust for differences in mortality after start of dialysis or transplantation. Life expectancies were determined by the area under the survival curve for six months in the first year and annually thereafter, from trapezoidal integration until age 110. Confidence intervals for life expectancy were determined using bootstrapping with 1000 iterations by randomly sampling the study population with replacement and refitting the Gompertz model. Average years of life lost were calculated as the difference between the estimated life expectancy in our study population and life expectancy in the general population, matching on five year age band at start of kidney replacement therapy, sex, calendar year, and country.^{24 26} We were unable to match on ethnicity or indigenous status because general population data are not available stratified by ethnicity and so we had no comparator.

We also performed subanalyses by considering treatment modality switching for the four kidney replacement therapies (haemodialysis, peritoneal dialysis, deceased donor transplant, and living donor transplant) and the subpopulation of kidney transplant recipients overall. We used the same statistical methods as described in the main analysis to estimate mortality rates, standardised mortality ratios, and expected years of life lost, except for the inclusion of a time varying covariate to take an as-treated approach. Among patients who received dialysis, a time varying covariate for dialysis modality was included to allow patient follow-up to be split between different periods of haemodialysis or peritoneal dialysis. Similarly, in transplant recipients, a time varying covariate was included to adjust for intermittent periods of dialysis after graft failure. We stratified estimates of cumulative relative survival by initial modality because methods to include time varying covariates have not been developed yet. Data were analysed using Stata version 15 (Stata Corporation, College Station, TX, USA).

Patient and public involvement

Our study was supported by a leading national patient advocacy group, Kidney Health Australia, through a competitive funding process. We have produced an impact report including a lay person summary of our study outputs. This report has been disseminated to Kidney Health Australia for sharing among their wider patient community and audience, and is freely available on our Collaborative Centre Organ Donation Evidence website (<https://organdonationevidence.org.au/celestial-study/>).

Results

Sex differences within population with kidney failure

A total of 82 844 patients started kidney replacement therapy in Australia (1980-2019) and New Zealand (1988-2019) and 49 376 (59.6%) died during the 536 602 person years of follow-up (table 1). Seventeen

patients (<0.1%) were censored at the registered date of death because ANZDATA considered them to be alive. While over half of the patients were male (59%), the proportions of female and male patients who died during follow-up were similar (20 099 female patients (60%); 29 277 male patients (59%)). A higher proportion of female patients were receiving peritoneal dialysis at death (5223 female patients (26%) v 6687 male patients (23%)), a higher proportion of male patients were undergoing haemodialysis (12 968 female patients (64%) v 19 432 male patients (66%)), however similar proportions had a functioning transplant (1908 female patients (10%) v 3158 male patients (11%)). A higher proportion of female patients identified as Aboriginal or Torres Strait Islander (11% v 6%), had never smoked (61% v 40%), and were underweight (7% v 3%). Additionally, a lower proportion of female patients were of European ethnicity (58% v 63%), were former smokers (28% v 46%), overweight (26% v 35%), and had glomerulonephritis or immunoglobulin A nephropathy as cause of kidney failure (22% v 27%). Coronary heart disease (29% v 37%) and peripheral vascular disease (19% v 23%) also affected a lower proportion of female patients than male patients.

Haemodialysis was the most common initial kidney replacement therapy, a slightly lower proportion among female patients (65% v 70%), followed by peritoneal dialysis (32% v 27%). Overall, about a third (22 328 of 80 400, 28%) switched their dialysis modality at least once; this was not substantially different between sexes (9733 of 32 336 female patients (30%) v 12 595 of 48 064 male patients (26%)). Only 20% overall (15 997 of 80 400) had a different dialysis modality at the end of the study compared with at the start of the study, and the proportion was similar for female and male patients (7027 of 32 336 (21%) v 8970 of 48 064 (19%), respectively). Switching the mode of delivery (eg, from home to dialysis centre) was more common in the 12 months before death when 31% overall (15 161 of 49 376) changed dialysis modality or mode of delivery.

The subpopulation of patients who received a kidney transplant included 9269 female patients and 14 847 male patients; 7668 deaths occurred (32% in female patients and 32% in male patients) over 255 233 person years. A slightly smaller proportion of female patients received a kidney transplant compared with male patients during the study (25% v 27%, respectively). Deceased donor transplants (n=16 898; 70%) were more common than living donor transplants (n=7218; 30%), overall and in both sexes.

Cause of death across age groups was similar between sexes (fig 1). Across all ages, the proportion of cancer deaths was 3.3% (95% confidence interval 2.7% to 3.9%, P<0.001) higher in male patients; the proportion of cardiovascular deaths was also higher in male patients (4.7% higher, 3.9% to 5.6%, P<0.001). However, the proportion of deaths caused by chronic kidney disease was 6.0% (4.9% to 7.1%, P<0.001) higher in female patients than in male patients and gastrointestinal deaths were also higher (0.8%, 0.3% to 1.3%, P=0.002) across all ages. We found no difference

Table 1 | Characteristics of all incident patients who started kidney replacement therapy in Australia and New Zealand during 1980-2019 by sex. Data are numbers (%) unless stated otherwise

Characteristics	Female patients	Male patients	Total
Total patients	33 329 (40)	49 555 (60)	82 884 (100)
Deaths during follow-up	20 099 (60)	29 277 (59)	49 376 (60)
Country			
Australia	27 822 (83)	41 525 (84)	69 347 (84)
New Zealand	5 507 (17)	8 030 (16)	13 537 (16)
Age at kidney failure, years			
≤17	759 (2)	1 037 (2)	1 796 (2)
18-34	3 162 (9)	4 221 (9)	7 383 (9)
35-49	6 214 (19)	8 877 (18)	15 091 (18)
50-59	7 220 (22)	9 989 (20)	17 209 (21)
60-79	14 461 (43)	22 296 (45)	36 757 (44)
≥80	1 513 (5)	3 135 (6)	4 648 (6)
Median age, years (IQR)	59 (46-69)	60 (47-70)	59 (47-70)
Year of kidney failure			
≤1995	10 018 (30)	12 978 (26)	22 996 (28)
1996-2005	10 593 (32)	15 739 (32)	26 332 (32)
2006-2013	12 718 (38)	20 838 (42)	33 556 (40)
Ethnicity*			
European	19 419 (58)	31 082 (63)	50 501 (61)
Australian and New Zealander	2 720 (8)	4 900 (10)	7 620 (9)
Aboriginal and Torres Strait Islander	3 498 (11)	2 756 (6)	6 254 (8)
Pasifika and Maori	3 743 (11)	4 736 (10)	8 479 (10)
Asian†	2 818 (8)	3 940 (8)	6 758 (8)
Other‡	1 131 (3)	2 141 (4)	3 272 (4)
Cause of kidney failure			
Diabetes	10 361 (31)	15 434 (31)	25 795 (31)
Hypertension or renal artery disease	3 262 (10)	6 737 (14)	9 999 (12)
Glomerulonephritis or IgA nephropathy	7 280 (22)	13 321 (27)	20 601 (25)
Polycystic kidney disease	2 548 (8)	3 077 (6)	5 625 (7)
Uncertain diagnosis	1 962 (6)	3 038 (6)	5 000 (6)
Other§	7 916 (24)	7 948 (16)	15 864 (19)
Smoking status			
Current	3 459 (11)	6 250 (14)	9 709 (13)
Former	8 351 (28)	21 195 (46)	29 546 (39)
Never	18 379 (61)	18 180 (40)	36 559 (48)
Not collected¶	3 140 (—)	3 930 (—)	7 070 (—)
Body mass index			
Underweight (≤18.4)	1 965 (7)	1 406 (3)	3 371 (5)
Normal (18.5-24.9)	10 432 (35)	15 239 (34)	25 671 (35)
Overweight (25.0-29.9)	7 684 (26)	15 523 (35)	23 207 (31)
Obese (≥30.0)	9 406 (32)	12 620 (28)	22 026 (30)
Not collected¶	3 842 (—)	4 767 (—)	8 609 (—)
Comorbidity at kidney failure			
Lung disease	4 535 (14)	7 299 (15)	11 834 (14)
Coronary heart disease	9 619 (29)	18 430 (37)	28 049 (34)
Peripheral vascular disease	6 270 (19)	11 343 (23)	17 613 (21)
Cerebrovascular disease	3 847 (12)	6 282 (13)	10 129 (12)
Diabetes	13 267 (40)	19 979 (40)	33 246 (40)
Initial kidney replacement therapy			
Haemodialysis	21 660 (65)	34 673 (70)	56 333 (68)
Peritoneal dialysis	10 676 (32)	13 391 (27)	24 067 (29)
Pre-emptive transplant	993 (3)	1 491 (3)	2 484 (3)
Transplant status			
Transplanted during follow-up	8 276 (25)	13 356 (27)	21 632 (26)
No transplant	24 060 (72)	34 708 (70)	58 768 (71)
Previous dialysis duration before first transplant			
0 to <6 months	1 976 (21)	3 115 (21)	5 091 (21)
≥6 months to <1 year	1 278 (14)	2 100 (14)	3 378 (14)
≥1 to <2 years	2 001 (22)	3 314 (22)	5 315 (22)
≥2 to <3 years	1 278 (14)	2 181 (15)	3 459 (14)
≥3 years	2 736 (30)	4 137 (28)	6 873 (29)
Median in months (IQR)	20 (8-41)	19 (8-39)	19 (8-40)

Ig=immunoglobulin G; IQR=interquartile range.

*Categorised based on the Australian Standard Classification of Cultural and Ethnic Groups 2016.

†Includes North-East Asian (eg, Chinese, Japanese, Korean, Taiwanese, and Mongolian), South-East Asian (eg, Burmese, Cambodian, Filipino, Indonesian, Lao, Malay, Singaporean, Thailander, Timorese, and Vietnamese), and Southern Asian (eg, Indian, Nepalese, Sri Lankan, and Pakistani).

‡Includes African, Middle East, North American and South American.

§Most common other causes of kidney failure included congenital abnormalities of the kidney and urinary tract (25%); drug and heavy metal toxicity (28%); obstructions (10%); and cancer (4%).

¶Data not routinely collected until after 1991.

between sexes across age for respiratory ($P=0.62$) and diabetes deaths ($P=0.11$). Additionally, there was no interaction between age and sex ($P>0.001$), indicating a consistent difference in the proportion attributed to each cause of death depending on sex and age (age did not modify the association). The leading causes of death were also similar between sexes overall (appendix table 3) and by age (appendix table 4).

We found some variations in causes of death for different treatment modalities at death; however, differences between sexes were consistent with the overall findings by age group (appendix fig 1; appendix table 2). The proportion of cancer deaths was 11.3% (95% confidence interval 10.2% to 12.4%) lower for patients undergoing haemodialysis and 14.6% (13.4% to 15.7%) lower for those receiving peritoneal dialysis compared with those who had transplantation in both sexes and across ages ($P<0.001$). The proportion of cancer deaths in patients who received living donor transplants was 6.1% (3.1% to 9.0%) higher compared with those who received deceased donor transplants. The proportion of deaths from chronic kidney disease in patients who received haemodialysis and peritoneal dialysis was 3.1% (1.5% to 4.7%) higher and 7.3% (5.5% to 9.0%) higher, respectively, compared with those who had transplantation, in both sexes and across ages. The proportion of deaths from diabetes in patients who received haemodialysis and peritoneal dialysis was 8.1% (7.4% to 8.7%) higher and 10.7%

(9.9% to 11.6%) higher compared with transplant recipients, respectively, in both sexes and across ages ($P<0.001$). The proportion of cardiovascular deaths was 5.1% (2.3% to 7.9%) lower for patients who received living donor transplants compared with those who received deceased donor transplants. No other significant differences were found for causes of death in patients who received deceased donor and living donor transplants.

Over time, male patients had a 3.1% (95% confidence interval 2.5% to 3.7%) higher proportion of cancer deaths and 5.2% (4.3% to 6.0%) higher proportion of cardiovascular deaths compared with female patients ($P<0.001$; fig 2). Female patients had a 5.4% (4.4% to 6.6%) higher proportion of deaths from chronic kidney disease and a 0.9% (0.4% to 1.4%) higher proportion of deaths from gastrointestinal disease compared with male patients ($P\leq 0.001$). No difference between sexes was found over time for respiratory deaths ($P=0.93$) and diabetes deaths ($P=0.36$). Additionally, no significant interactions were found in causes of death over time between sexes ($P>0.1$). In both sexes, cardiovascular disease deaths reduced the most over calendar time by 7.0% (5.4% to 8.7%; $P<0.001$) and cancer deaths increased the most by 2.6% (1.6% to 3.6%; $P<0.001$) in 2012-17 compared with 1994-99.

Sex differences compared with general population

Overall, mortality rates were similar between sexes in patients with kidney failure across age (fig 3 upper panel; $P>0.80$) and by treatment modality at death (appendix fig 2; $P>0.80$). However, compared with the general population, the number of excess deaths in female patients with kidney failure was much greater than that in male patients with kidney failure (fig 3 lower panel; sex interaction $P<0.001$). This finding was most evident in younger patients; in female patients aged 18-34 years with kidney failure, the standardised mortality ratio was 53.6 (95% confidence interval 49.2 to 58.4) and in male patients it was 16.7 (15.4 to 18.2). The excess death rate in female patients with kidney failure was also greater across calendar years (fig 4 upper panel). However, this figure has decreased over time at a greater rate in female patients than in male patients (sex interaction $P<0.001$), but has stagnated in recent years. In female patients, the standardised mortality ratio reduced from 17.0 (14.5 to 19.9) in 1988 to 9.6 (9.0 to 10.2) in 2019; in male patients the ratio reduced from 8.1 (7.0 to 9.4) in 1988 to 6.4 (6.1 to 6.7) in 2019. The greater excess deaths in younger female patients and trends in sex disparity over time were consistent for different dialysis modalities and transplant types (appendix fig 3).

Overall, female patients with kidney failure had greater excess all cause deaths compared with male patients (standardised mortality ratio 11.3, 11.2 to 11.5, and 6.9, 6.8 to 6.9, respectively), but excess deaths did vary by cause (fig 4 lower panel). The greatest sex disparity was for deaths from cardiovascular disease (standardised mortality ratio 8.7, 8.4 to 9.0, and 5.7, 5.6 to 5.9, for female and male

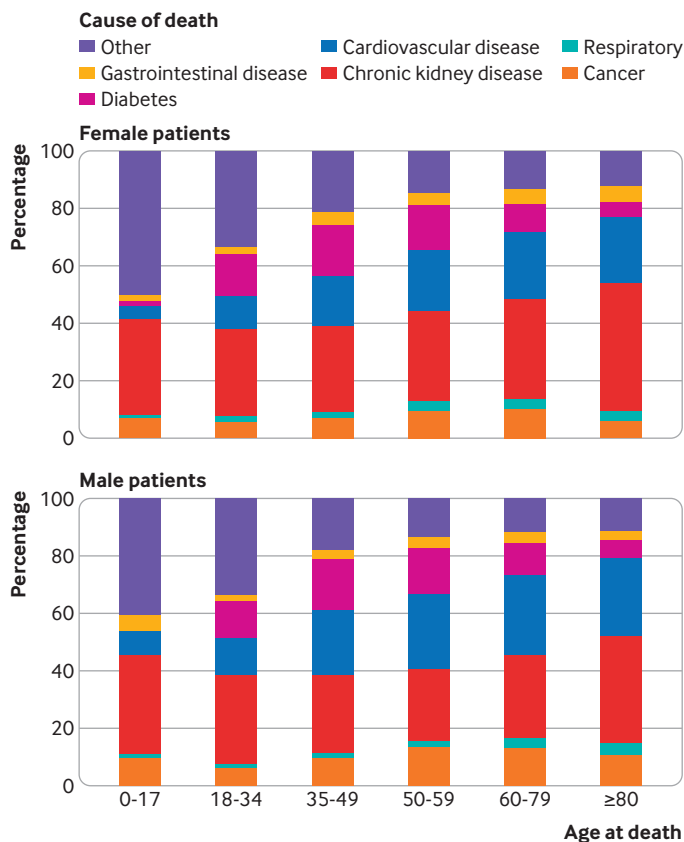


Fig 1 | Leading causes of death in patients receiving kidney replacement therapy in Australia and New Zealand by sex and age at death. See appendix table 1 for other causes of death by sex and appendix table 2 for absolute counts by sex

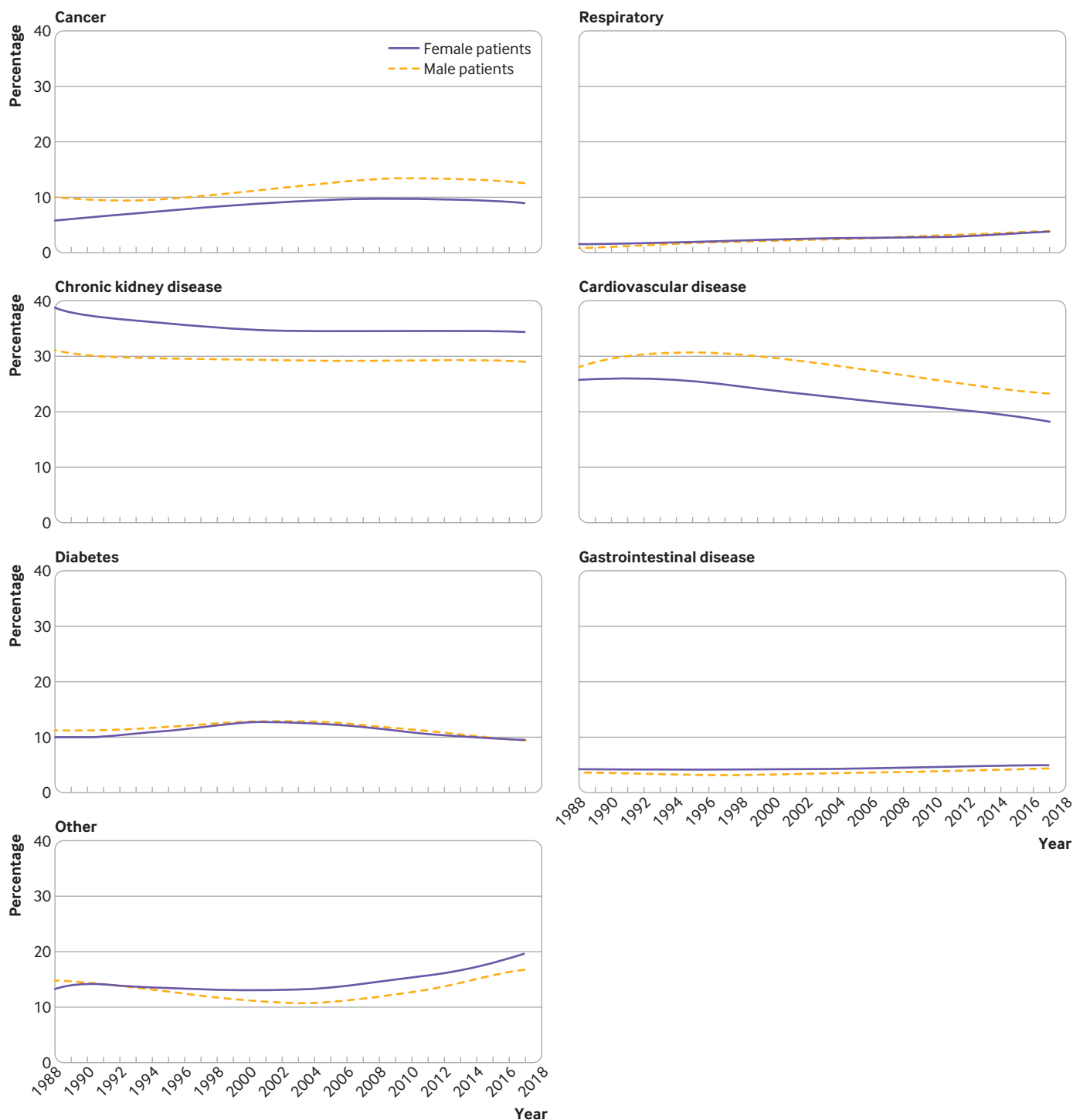


Fig 2 | Percentage of deaths by cause in patients receiving kidney replacement therapy in Australia and New Zealand over time, 1988-2017 (Lowess lines are used). See appendix table 1 for other causes of death by sex and appendix table 2 for absolute counts by sex

patients, respectively) and gastrointestinal disease (15.1, 13.9 to 16.3, and 7.3, 6.8 to 7.9, for female and male patients, respectively).

Survival rates among male patients with kidney failure compared with the general population were consistently better than the corresponding figures for female patients (fig 5 upper panel). At one year, the relative survival rate in female patients was 0.82 (95% confidence interval 0.81 to 0.83) and in male patients it

was 0.83 (0.83 to 0.84). These rates decreased to 0.39 (0.38 to 0.39) and 0.41 (0.40 to 0.42), respectively, at 10 years. At any given time, the adjusted excess mortality was 11% higher among female patients with kidney failure compared with male patients with kidney failure (adjusted excess mortality ratio 1.11, 95% confidence interval 1.08 to 1.13, $P < 0.001$); however, this ratio differed depending on treatment modality. Among those initially receiving haemodialysis, female

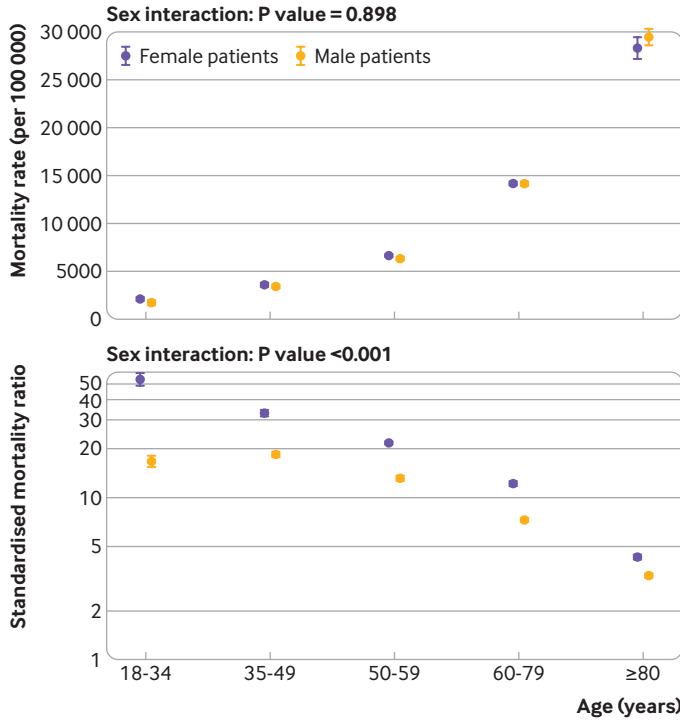


Fig 3 | Estimates of mortality rates by age and sex (upper panel) and standardised mortality ratios by age and sex (lower panel) for patients receiving kidney replacement therapy in Australia and New Zealand

patients had an excess mortality 7% higher than male patients (adjusted excess mortality ratio 1.07, 1.04 to 1.10, $P < 0.001$). In patients initially receiving peritoneal

dialysis, the sex difference in excess mortality varied significantly by age: female patients aged 30-49 years had 15% lower excess mortality compared with male patients (0.85, 0.76 to 0.95, $P = 0.004$). Female patients aged ≤ 29 years ($P = 0.48$) and 50-64 years ($P = 0.42$) had no excess mortality compared with male patients. However, female patients aged 65-74 years had 8% excess mortality (1.08, 1.01 to 1.15, $P = 0.034$) and those aged ≥ 75 years had 24% excess mortality (1.24, 1.11 to 1.38, $P < 0.001$) compared with male patients. This sex difference in relative survival was not seen in those who received a kidney transplant (fig 5 lower panel; 1.01, 0.95 to 1.06, $P = 0.83$), regardless of whether they received a deceased donor transplant (0.98, 0.92 to 1.03, $P = 0.41$) or living donor transplant (1.10, 0.95 to 1.27, $P = 0.20$).

The average years of life lost in female patients with kidney failure was 3.6 years (95% confidence interval 3.6 to 3.7) greater than in male patients with kidney failure ($P < 0.001$; fig 6 upper panel), adjusting for age. In those aged 15 years at the start of kidney replacement therapy, female patients had 33.2 years of life lost (95% confidence interval 32.4.5 to 34.0) while male patients had 27.7 years of life lost (27.0 to 28.5). The average years of life lost decreased to 17.2 years (17.1 to 17.4) in female patients and 14.3 years (14.1 to 14.4) in male patients aged 60 years at the start of kidney replacement therapy. The average years of life lost for each dialysis modality was also higher among female patients. The sex difference was consistent between dialysis modalities (haemodialysis

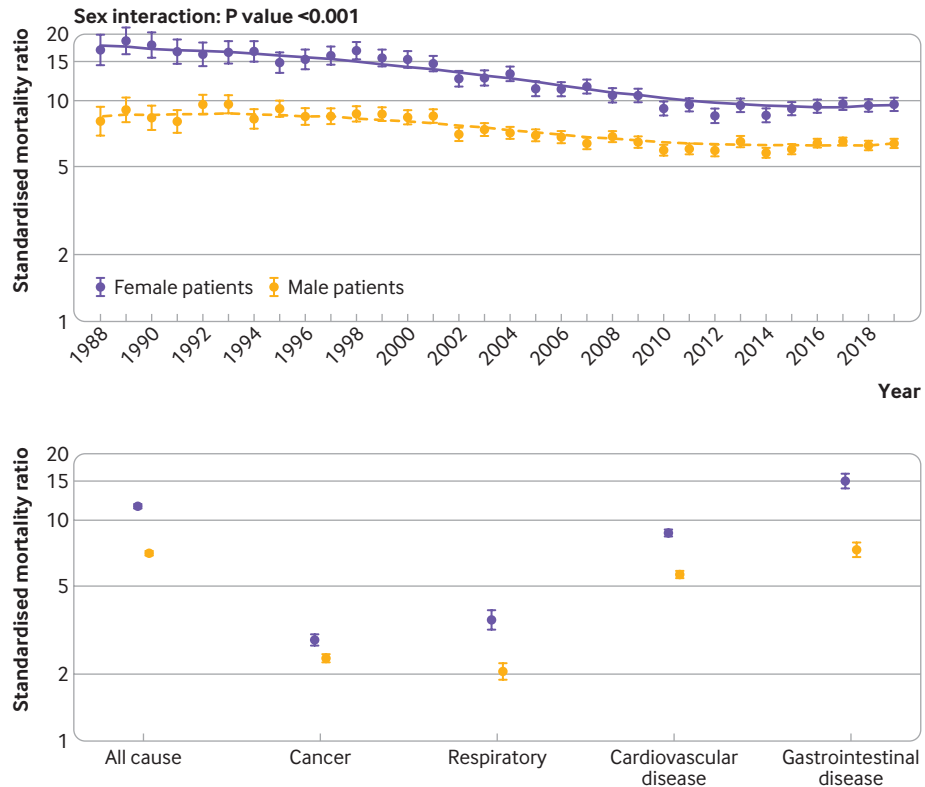


Fig 4 | Standardised mortality ratios by calendar year (with Lowess fitted line; upper panel) and by cause of death (lower panel) for patients receiving kidney replacement therapy in Australia and New Zealand

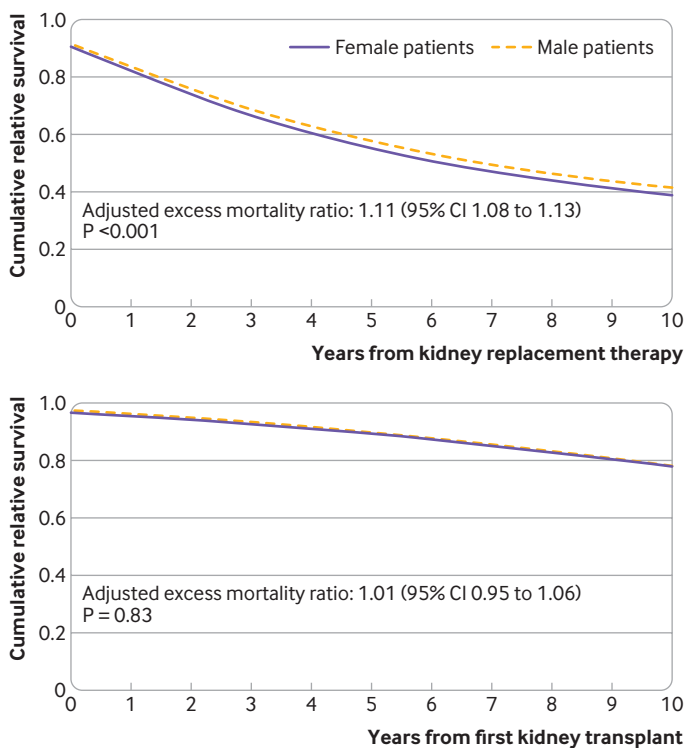


Fig 5 | Survival in population receiving kidney replacement therapy relative to matched general population (relative survival) in Australia and New Zealand by sex and time since start of kidney replacement therapy (upper panel) and first kidney transplant (lower panel)

or peritoneal dialysis); on average, female patients lost 3.4 years of life (3.3 to 3.5) more than their male counterparts (appendix fig 4). This sex difference was

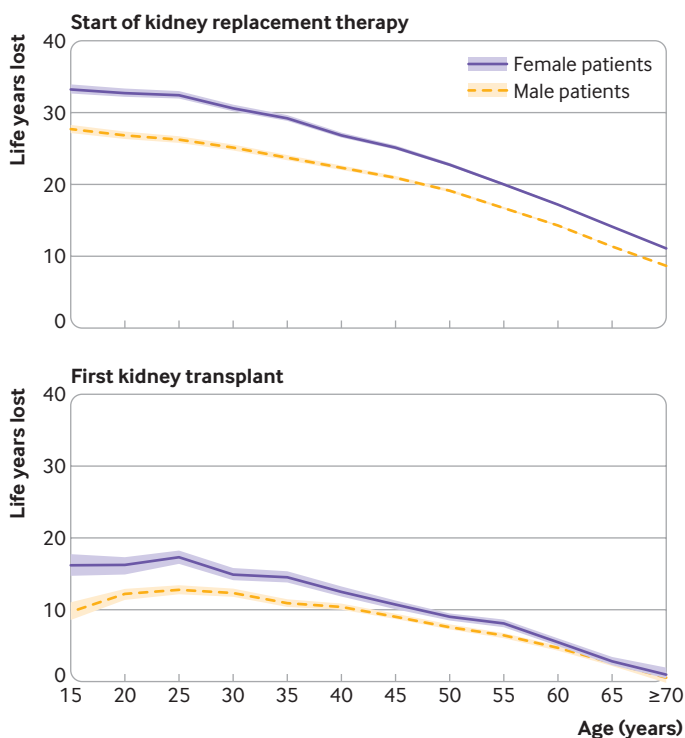


Fig 6 | Expected life years lost by sex and age at start of kidney replacement therapy (upper panel) and first kidney transplant (lower panel). Age represents five year age band except where indicated otherwise

reduced in those who received a kidney transplant, in whom the average years of life lost was 2.3 years (2.2 to 2.4) greater in female patients compared with male patients (fig 6 lower panel), adjusting for age ($P < 0.001$). The sex difference in average years of life lost was consistent regardless of type of donor transplant (deceased donor: average years of life lost in female v male patients 2.2, confidence interval 2.1 to 2.3; living donor transplant 2.8, 2.7 to 2.9). However, the average years of life lost in deceased donor transplants was 8.4 years (8.3 to 8.5) more than living donor transplants. Appendix tables 5 and 6 present life expectancy and years of life lost estimates.

Discussion

Principal findings

In this binational population based study, we found that the life limiting impact of kidney failure is greater for women than men, with the female survival advantage in the general population entirely lost in the presence of kidney failure. Sex differences in mortality were only apparent when compared with the general population. Female patients with kidney failure experienced more excess deaths, worse relative survival, and greater life years lost compared with male patients with kidney failure. The greatest sex disparity in excess deaths was seen in younger ages and from certain causes of death. We observed some differences between sexes in causes of death: more cancer and cardiovascular deaths were found for male patients, while female patients had more excess deaths from cardiovascular disease and gastrointestinal disease. Improvements were found over calendar time, with a substantial reduction in female excess mortality; however, the rate has stabilised in recent years and not approached male estimates. Kidney transplantation also improved survival and lessened sex differences in excess mortality, although female patients still had more years of life lost. We found no major differences in female excess mortality between those on haemodialysis or peritoneal dialysis, or between those who received deceased or living donor transplant.

Comparison with other studies

Our findings show that female patients with kidney failure had comparably poorer survival than male patients with kidney failure. Overall we found that female patients with kidney failure had 11% higher excess mortality at any given time, and on average had four more years of life lost than their male counterparts. As such, life expectancies in female patients with kidney failure were consistently lower than in male patients with kidney failure. The higher excess mortality among female patients was also observed for those receiving haemodialysis (7% excess mortality), but among those receiving peritoneal dialysis the higher rate was only present in those aged ≥ 65 years ($>8\%$ excess mortality). Few studies have explored sex differences after kidney failure by comparing outcomes with expected outcomes in the general population^{17 18}; none of these studies was based in countries with universal healthcare

coverage. The sex disparity in excess mortality seen in our study was greater than previous reports in the general population for cardiovascular disease^{28,29} and cancer.³⁰ After an acute myocardial infarction, women experienced a 7% higher excess mortality²⁸ and had an average 1.9 years of life lost more than men.²⁹ However, in patients with cancer, the average years of life lost was 2.2 years greater in women than men (14.9 v 12.7 years, respectively).³⁰ Findings from a cohort with kidney failure in the United States showed a higher excess mortality than our study at 18%, but a similar average years of life lost (3.2 years greater in female patients than in male patients).¹⁷ Our life expectancy estimates are slightly higher than those reported in the US Renal Data System annual data report 2020, but depict similar trends with female patients receiving dialysis having lower life years remaining and higher years of life lost compared with male patients.³¹ Reasons for comparably worse survival outcomes in female patients with kidney failure might be attributed to early onset of menopause which reduces the protective effect of oestrogen,^{32,33} and possible differences in the delivery and quality of healthcare overall and for kidney failure.⁷ While receiving dialysis, women report higher symptom burden and severity, and lower quality of life compared with men. In our study cohort, there was also a higher proportion of female patients who identified as Aboriginal or Torres Strait Islander, with disadvantages that are well recognised—greater risk of death and poorer access to healthcare.^{34,35} Aboriginal and Torres Strait Islanders represented <10% of the kidney failure population overall, but might contribute to some of the excess mortality among female patients with kidney failure. Other reasons for poorer survival among female patients with kidney failure might include poorer access to cardiovascular health services,¹⁰ non-adherence to drugs, and lower likelihood of receiving care according to recommended guidelines.⁷

Sex differences in excess mortality were amplified in those who were younger and who died from certain causes, including cardiovascular disease and gastrointestinal disease. Young female patients with kidney failure had the greatest excess mortality compared with expected deaths in the general population with 54 times the excess deaths, while young male patients with kidney failure had only 17 times the excess deaths. These data could reflect a systematic difference in symptom recognition of disease based on sex, with symptoms perceived as typical of disease actually being experienced more often by male patients, but not necessarily by female patients. There is probably an under recognition by providers of disease severity and mortality risk in younger female patients with kidney failure, particularly from cardiovascular disease³⁶ and stroke.³⁷ Women in the general population have worse outcomes than men after a cardiovascular event because of differences in their symptoms, presentation, and pathophysiology.³⁸ ³⁹ An Australian study found that general practitioners are more likely to perceive cardiovascular risk as lower and are less likely to prescribe combination prevention

therapy in women compared with men of the same age with established cardiovascular disease.⁴⁰ In the presence of kidney disease, cardiovascular disease manifests more rapidly, leading to underestimation of cardiovascular risk and lack of adherence to prevention guidelines.⁴¹ These factors could compound in young female patients with kidney failure, resulting in greater excess mortality risk.

Studies evaluating excess deaths from gastrointestinal causes in the population with kidney failure are lacking. Previous studies have not found female patients with kidney failure are at increased risk of gastrointestinal disorders compared with male patients with kidney failure, suggesting there might be sex differences in response to treatment and long term outcomes.^{42,43} However, the gap in excess mortality between female and male patients with kidney failure has reduced over time. A combination of factors has resulted in reduced excess mortality among female patients, such as more kidney transplants and higher graft survival.⁷ Excess mortality rates from cardiovascular disease and stroke have reflected similar trends,^{36,37} attributed to greater use of and access to cardiovascular prevention that has probably benefited the population with kidney failure.⁴⁴ This observation is supported by our findings, with the proportion of deaths from cardiovascular disease reducing over time in both sexes. In recent years, the reduction in excess deaths among the population with kidney failure has stabilised, with female patients continuing to have a greater burden of excess mortality. Further research needs to explore whether improvements in patient care for kidney failure or better access to healthcare and services can help to reduce this sex disparity.

Transplantation reduced the sex differences in excess mortality among the population with kidney failure, but still resulted in more years of life lost in female patients with kidney failure compared with the general population. Equitable access to waitlists and kidney transplantation are an ongoing issue, particularly for certain ethnicities, geographical regions, and sexes.⁴⁵ Sex inequalities in access to waiting lists and kidney transplantation have only been evaluated in Canada⁴⁶ and the US,⁴⁷ and to a lesser degree in Australia.⁴⁸ In these countries, sex disparities in transplantation were evident, particularly in earlier eras when waiting list rates were 16% higher for male patients than female patients.⁴⁷ This difference has reduced over time in the US, with greater access for women.⁷ A systematic review in 2014 found 17 studies evaluating nephrologists' preferences and attitudes towards referral, screening, and eligibility for kidney transplantation.⁴⁵ Only two studies evaluated the impact of participant sex, in which women were more likely to be considered unsuitable for transplantation compared with men of the same age and with similar comorbid conditions. Therefore, it is possible that access to transplantation is biased towards the selection of healthier women, which corresponds to our study findings of no excess mortality and comparable survival in women with kidney transplants and women in the general population.

However, further studies evaluating access to waiting lists, remaining on waiting lists, and receiving a transplant in Australia, New Zealand, and other countries are still needed given healthcare systems are vastly different. Our study found that in patients who had received a transplantation, survival was similar between sexes and sex was not associated with excess mortality in kidney transplant recipients. Female and male patients who received kidney transplants had comparable life expectancies after transplant, resulting in more life years lost in female patients who had received a transplant because women in the general population have higher life expectancies than men.

Strengths and limitations of this study

The strength of our study is the large patient cohort that included the entire population receiving kidney replacement therapy in two countries, Australia and New Zealand, and findings were stratified by dialysis modality. We used the general population as the reference group in our estimates of excess mortality, matching on sex, age at kidney failure, calendar year, and country. The general population is the least biased and most representative comparison group because it encompasses the entire population and is not prone to selection bias or use of administrative data not intended to address our research question. Our findings are therefore highly generalisable to Australia and New Zealand, and other developed countries that offer universal healthcare. Furthermore, we used data linkage to determine death information until 2013 in Australia and 2017 in New Zealand, including causes of death classified to an international standard (ICD-10). We relied on the primary cause of death reported in national death registers to define causes of death, although differences exist when using primary and secondary causes of death. For example, cardiovascular deaths represented less than 40% of causes of death overall in both sexes. However, when also including secondary causes of death the proportion of cardiovascular deaths increases to 40%. We believe primary cause of death is the most representative cause of death because it is difficult to distinguish the degree to which a disease or condition contributed to the death when relying on the primary and secondary causes of death. We used probabilistic data linkage for Australia, which might have led to incorrect links; however, this has been estimated to be relatively small at <5 per 1000 records⁴⁹ and there was high agreement for fact of death between the ANZDATA register and death registry.²⁰ While additional deaths up to 2019 were determined from ANZDATA, this is unlikely to introduce any bias because of the strong agreement with national death registers.²⁰ We were also limited to patient data collected on ANZDATA, which did not include use of preventative drugs that might lower mortality risks.

Conclusions

While the sex disparity has reduced over time, female patients with kidney failure continue to experience

greater losses in survival compared with their male counterparts in recent years. Life expectancies in those with kidney failure contrast with trends in the general population, where female patients with kidney failure have lower life expectancies than male patients with kidney failure. However, kidney transplantation reduces these sex differences. Our findings will inform clinicians and patients with kidney failure about expected survival outcomes when starting dialysis and additional life gains once transplanted, helping in shared clinical decision making. Future research should explore possible reasons for and strategies to mitigate excess mortality among female patients with kidney failure, such as more access to preventative drugs, healthcare, and services. Additionally, evaluating sex differences in other chronic diseases and countries is needed to ensure access to healthcare and health outcomes are equitable between sexes.

The data reported here have been supplied by the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA), the Australian Institute of Health and Welfare (AIHW), and the New Zealand Ministry of Health. The authors acknowledge the assistance provided by the AIHW in the data linkage process, and Kidney Health Australia for their financial support. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy of interpretation of ANZDATA, AIHW, or the New Zealand Ministry of Health.

Contributors: ACW, PJK, and PM attracted funding for the data linkage. NLDLM, ACW, PJK, RLM, and KW contributed to the concept development. NLDLM and PJK contributed to the statistical design. GM and NLDLM performed the statistical analysis and interpretation of results. NLDLM prepared the draft manuscript. All authors commented on the draft manuscript and approved the final manuscript for submission. NLDLM and ACW are guarantors of this study. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: support from Kidney Health Australia for the linked data used in the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This study received ethical approval from the University of Sydney (project No 2014/917) and AIHW (reference No EO2015/3/181). The New Zealand Ministry of Health did not require ethical approval (reference No 14/NTB/171).

Data sharing: No additional data available.

The lead author (NLDLM) confirms that the manuscript is an honest, accurate and transparent account of the study being reported and there are no important aspects of the study that have been omitted or any discrepancies from the study as planned have been reported and explained.

Dissemination to participants and related patient and public communities: The study was supported by a leading national patient advocacy group, Kidney Health Australia, through a competitive funding process. We have produced an impact report including a lay person summary of our study outputs. This has been disseminated to Kidney Health Australia for sharing among their wider patient community and audience, and is freely available on our Collaborative Centre Organ Donation Evidence website (<https://organdonationevidence.org.au/celestial-study/>). This work has been presented at national and international conferences (Australian and New Zealand Society of Nephrology Annual Scientific Meeting 2020; European Renal Association and European Dialysis and Transplant Association Congress 2020; International Population Data Linkage Network 2020 Conference), and at the NSW Health Scientific Talent Competition 2020.

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Web appendix: Appendix figures

Web appendix: Appendix tables