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Health Care Costs in Chronic Kidney Disease & Renal Replacement Therapy: A Population-Based Cohort Study

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ABSTRACT

Objective: To compare health care costs in chronic kidney disease (CKD) stages 4 or 5 not on dialysis (estimated glomerular filtration rate <30 ml/min/1.73m^2), peritoneal dialysis, hemodialysis, and in transplanted patients with matched general population comparators.

Design: Population-based cohort study.

Setting: Swedish national health care system.

Participants: Prevalent adult patients with CKD 4 or 5 (n=1046, mean age 68y), on peritoneal dialysis (n=101; 64y), on hemodialysis (n=460; 65y), and with renal transplants (n=825; 52y) were identified in Stockholm County clinical quality registers for renal disease on January 1st, 2010. Five general population comparators from the same county were matched to each patient by age, sex, and index year.

Primary and Secondary Outcome Measures: Annual health care costs in 2009 incurred through inpatient and hospital-based outpatient care and dispensed prescription drugs ascertained from nationwide health care registers. Secondary outcomes were annual number of hospital days and outpatient care visits.

Results: Patients on hemodialysis had the highest mean annual cost (€87,600), which was 1.49 (95%CI 1.38-1.60) times that observed in peritoneal dialysis (€58,600). The mean annual cost was considerably lower in transplanted patients (€15,500) and in the CKD group (€9600). In hemodialysis patients, outpatient care costs made up more than two-thirds (€62,500) of the total, while costs related to fluids ($29,900) was the largest cost component in peritoneal dialysis patients (51%). Compared to their matched general population comparators, the mean annual cost (95%CI) in hemodialysis, peritoneal dialysis, transplanted, and CKD patients was 45 (39-51), 29 (22-37), 11 (10-13), and 4.0 (3.6-4.5) times higher, respectively.

Conclusion: Mean annual costs were approximately 50% higher in hemodialysis than peritoneal dialysis patients. Compared to the general population, costs were substantially elevated in all groups, from 4-fold in CKD patients to 11, 29 and 45 times higher in transplanted patients, patients on peritoneal dialysis and hemodialysis, respectively.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- In this population-based study data were collected from routine clinical care to which there is universal access in Sweden
- By linking nationwide health care registers using the personal identity number, follow-up on an individual level was virtually complete regarding hospital days, hospital-based outpatient care and dispensed prescription drugs
- Costs related to in-hospital use of erythropoietin stimulating agents (ESA) for patients on hemodialysis were assessed using records from a smaller patient sample
- Costs related to fluids for patients on peritoneal dialysis were assessed using aggregated data, since these costs were not collected on an individual level in registers
- Although the proportion of undiagnosed individuals with CKD stage 4 or 5 have decreased with time, this group is still underdiagnosed and an unknown number of these patients were missed

INTRODUCTION

Chronic kidney disease (CKD) and end-stage renal disease are associated with substantial health care resource use and considerably higher mortality.[1 2] Although some reports suggest a decline in the incidence of CKD,[3] demographic changes together with increasing type 2 diabetes are likely to result in a higher prevalence of CKD.[4] To evaluate the value of therapeutic interventions in this patient group, an assessment of the economic burden related to CKD and end-stage renal disease is necessary, as is an available benchmark in terms of the corresponding costs in the general population.

Several studies have investigated the burden or costs in patients with different stages of CKD and renal replacement therapy, using different methods and in different settings.[5-7] The majority of cost studies from Europe and North America of patients on dialysis have reported higher health care costs of hemodialysis ranging from 1.0-1.9 times the cost in peritoneal dialysis.[5] Similarly, previous studies have reported increasing health care use and costs with higher CKD stages,[8-11] and estimates in patients with CKD that are 2-3 times the cost as compared to controls without CKD.[9 11] Recent studies from Europe, North America and Australia on the burden of CKD and renal replacement therapy with reported annual per patient cost have typically been based on small study samples or by using a modeling approach collecting data from published aggregated estimates.[12-21] Only a few studies have used individual data from larger study samples.[8-10]

To the best of our knowledge no study has from the same study population and on an individual level described health care use and costs in CKD stages 4 or 5 not on dialysis, hemodialysis, peritoneal dialysis, and transplanted patients separately, and compared the result to costs in the general population.

The aim of this population-based cohort study was to examine annual costs assessed from nationwide health care registers related to hospital days, outpatient care visits, and prescription of drugs in prevalent CKD stages 4 or 5 not on dialysis, peritoneal dialysis, hemodialysis, and transplanted patients, and to put these costs in relation to matched general population comparators.

METHODS

In this population-based cohort study we identified patients on CKD stages 4 or 5 not on dialysis, patients on dialysis and transplanted patients from clinical quality of care registers in Stockholm County and added data from national health registers. By using the personal identity number, a unique number assigned to all Swedish residents,[22] we enriched these data with inpatient and hospital-based outpatient care from the National Patient Register as well as data on dispensed drugs from the Prescribed Drug Register kept by the National Board of Health and Welfare. We further sampled up to five general population comparators to each patient from the Register of the Total Population held by Statistics Sweden. Data on emigration and highest attained education were also retrieved from the Register of the Total Population. Finally, we retrieved information on health care use and prescription drugs from the same data sources also for the general population cohort.

Ethical approval was granted by the regional ethics committee at Karolinska Institutet, Stockholm, Sweden.

Chronic Kidney Disease and the Swedish National Health Service

Sweden had a population of 7.4 million ≥18 years on December 31, 2009 (www.scb.se), and comprised 21 counties. Stockholm County was the biggest with 1.6 million inhabitants ≥18 years, accounting for 22% of the population. The Swedish health care system was tax funded and offered universal access, while prescription drugs were provided free of charge above a threshold of around €200 annually.

Patients with renal replacement therapy were treated by nephrologists in inpatient and outpatient facilities,[23] rather than by general practitioners, while care for CKD patients was a mix of mainly hospital-based outpatient care, and to some extent primary care. The decision to initiate renal replacement therapy was made by nephrologists from clinical evaluations based on the Swedish guidelines[24] originating from the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) guidelines[25] and the corresponding European guidelines.[26]

Quality Register Sources

CKD Patients: From the Stockholm County CKD Register we identified adult CKD patients in stages 4 or 5 who were not on dialysis, on January 1st, 2010, registered at Karolinska and Danderyd University Hospital in the outpatient setting. This does not include all CKD stages 4 and 5 patients in the county, as some may get care elsewhere and some remain undetected. Stages 4 and 5 were defined as an eGFR of 15-29.9 and <15, respectively. GFR was estimated using the abbreviated Modification of Diet in Renal Disease equation (MDRD; ml/min/1.73m^2) using serum creatinine levels.[27] Data on albuminuria were incomplete and therefore no analyses by albuminuria status were performed.

Renal Replacement Therapy Patients: Patients on hospital-based dialysis or with a kidney transplant on January 1st, 2010, were identified in the Swedish Register of Renal Replacement Therapy, which includes all adult patients on renal replacement therapy in Stockholm County.[28 29]

The National Patient Register

Data on inpatient and hospital-based outpatient care were retrieved from the Swedish National Patient Register in 2009. This register contains the personal identity number, visit/admission date (and discharge date for the inpatient component), diagnostic related group (DRG) associated with the visit, and main as well as contributory diagnoses coded according to the International Classification of Diseases version 10 (ICD-10).[30]

Hospital days and outpatient visits were converted into costs using the DRG coding system, where clinically similar hospitalizations or outpatient visits are grouped together. The price per DRG is fixed for a specific year, and is a weighted average for all the health care delivered in that group and year. In 2009 the inpatient and outpatient component of the National Patient Register included around 580 and 400 DRG groups, respectively.

The Prescribed Drug Register

From the Prescribed Drug Register we collected data on dispensed prescriptions in ambulatory care in 2009. Data on in-hospital drug use are not recorded on a patient level in the Prescribed Drug Register. Among other variables the register includes the personal identity number, date of prescription and dispensation, costs (total cost, patient cost, reimbursed cost), dosage, route of administration, and name as well as the of Anatomic Therapeutic Chemical (ATC) code of the drug.

Outcome and follow-up

The main outcome was annual health care costs incurred through inpatient and outpatient care, as well as dispensed prescription drugs. Secondary outcomes were annual number of hospital days and outpatient visits. Costs were assessed during 2009 and converted to euros (€1=SEK9.54 in 2010). Patients were followed in the same health state as when they were identified in January 1st, 2010, with estimated annualized costs in those patients who did not have 1 year of follow-up.

Annualized Costs: Health care use and costs in patients who were not in CKD stages 4 or 5, on dialysis, or did not yet have a kidney transplant on January 1st, 2009, and hence were not followed the complete year of 2009, were annualized from the time of entry into the respective health states. To have enough data available for each patient, we restricted the study population to patients with at least 1 month of follow-up, i.e. patients who were exposed on or before December 1st, 2009. For example, if a patient started hemodialysis on July 1st, 2009, we doubled that patient's health care use and costs to achieve an annualized estimate. Costs related to the transplantation procedure were not annualized.

Costs Related to Hemodialysis Visits: As a data quality control, patients on hemodialysis that had less than 2 registered dialysis visits per week (n=135) in the National Patient Register were scrutinized using the patient registration database at the clinic. Data were imputed with 156 hemodialysis visits per year (3 visits/week) in patients having missing visit data over longer periods of time (n=14), while in patients with missing data over shorter periods (n=3), we extrapolated visits in time intervals with missing data. In total of 88 (65%) of the scrutinized patients on hemodialysis we added information from the registration database at the clinic.

Costs Related to Erythropoietin stimulating agents (ESA) in Hemodialysis and Fluids in Peritoneal Dialysis: As the Prescribed Drug Register does not include in-hospital use of drugs, the cost for ESA is underestimated in hemodialysis patients when using this data source. We retrieved data on ESA use in a sub-sample of hemodialysis patients (n=85) and calculated the cost using 2009 drug prices in Sweden (http//:www.tlv.se). In this sub-sample the annual cost per patient related to ESA was estimated to €3911, which we applied to all hemodialysis patients. Further, the cost of fluids for peritoneal dialysis is also not covered by the Prescribed Drug Register. This cost has previously been estimated to SEK 200,000-370,000 (€21,000-€38,800) per patient and year.[31] We used the mid-value (€29,900) in this range and applied it on all patients on peritoneal dialysis.

Statistical Analysis

Cost distributions were non-normal in patients with CKD stages 4 or 5, patients on peritoneal dialysis, and transplanted patients, but approached a normal distribution in patients on hemodialysis (**Figure 1**). As the arithmetic mean has been described to be the most informative measure for cost and resource use data,[32] we report the mean annual cost (complemented by the median for descriptive purposes). Mean annual cost ratios, when comparing costs in CKD stages 4 or 5, peritoneal dialysis, hemodialysis and transplanted patients, or when comparing patients vs their matched general population comparators, were adjusted for age, sex, and diabetes status using a generalized linear regression model with negative binomial distribution, and 95% confidence intervals were estimated using robust standard errors.

Data were complete on age, sex, and register-determined comorbidity status (**eTable 1**). If baseline eGFR was missing in patients with CKD stages 4 or 5, this resulted in exclusion from CKD analyses.

Statistical analyses were performed using SAS (version 9.3).

RESULTS

A total of 2432 prevalent patients who were alive on January 1st, 2010, were included (**Table 1**). CKD stages 4 or 5 patients (n=1046) were on average 68 years old, while dialysis patients (n=101 on peritoneal dialysis; n=460 on hemodialysis) were younger (64y and 65y, respectively), and transplanted patients (n=825) much younger (52 years). All groups were predominantly male, and the education level was broadly similar to that in the general population (Table 1, **eTable 2**). The vast majority of transplanted patients had complete follow-up through 2009 (93%), while one quarter of the CKD stage 4 or 5 and hemodialysis patients did not have the full year of follow-up, and 40% of the patients in the peritoneal dialysis group were also followed for less than one year (Table 1).

Regarding selected register-identified comorbidities, approximately 90% of the patients had circulatory disease history, with about 15% having had a myocardial infarction and 10% a stroke (except transplanted patients; **Figure 2**). The CKD stages 4 or 5 and dialysis patients were similar, with the exception of a higher prevalence of cardiovascular disease in the hemodialysis patient group. The younger transplanted patients displayed lower prevalence, as compared to the CKD and dialysis patients, for most of the selected comorbidities, but a higher occurrence of malignancies. All groups had similar prevalence of chronic obstructive pulmonary disease as the general population comparators, but displayed higher or much higher prevalence in the other selected comorbidities, including diabetes where more than 30% of patients (except the transplanted group) had diabetes, compared to 6-9% in the matched general population (eTable 2).

Health Care Use

Annual Hospital Days: Mean annual hospital days in patients on hemodialysis was 21.4, with the majority of hospital days listing a main or contributory diagnosis for cardiovascular disease (8.2 days) or infection (6.7 days; **Table 2**). Patients on peritoneal dialysis displayed lower overall mean hospital days (16.0), with 5.4 days and 2.6 days related to cardiovascular disease and infection, respectively. Transplanted patients and patients in CKD stages 4 or 5 had similar level of inpatient care use with 4.6 and 6.2 annual hospital days, respectively.

Outpatient Care: In hemodialysis patients, 152 out of a mean 159 annual visits were due to dialysis. The corresponding number in peritoneal dialysis patients was 29 visits per year with 15 visits listing dialysis. Again, transplanted patients and patients in CKD stages 4 or 5 had similar numbers with 10 and 8 visits, respectively.

Prescription Drug Costs: The mean annual cost of dispensed prescription drugs was €7400 in the peritoneal dialysis group, €6800 in transplanted patients, €8400 (of which €3911 on ESA) in hemodialysis patients, and €2900 in the CKD 4 or 5 group (Table 2, **Figure 3**).

Costs related to Fluids in Peritoneal Dialysis: Based on a regional report of dialysis care in southern Sweden, the annual cost of fluids in patients on peritoneal dialysis were estimated to €29,900.[31]

Total Costs

The highest mean annual cost was observed in the hemodialysis group with €87,600, out of which 71% were accounted for by outpatient care costs (€62,500; Figure 3; **eTable 3**). Of the total outpatient care cost, 97% (€60,400) were costs for visits listing dialysis.

Patients on peritoneal dialysis incurred a mean annual cost of €58,600 which was about two thirds of the cost compared to hemodialysis patients (adjusted ratio [hemodialysis vs peritoneal dialysis] 1.49,

95% CI 1.38-1.60; **Table 3**). The largest cost component in the peritoneal dialysis group was costs related to fluids (€29,900; 51% of total cost), while costs related to inpatient and outpatient care were similar (€11,400 and €10,000, respectively).

In contrast, transplanted patients was the only group where dispensed prescription drugs made up the largest cost component (€6800; 44% of total cost), while the mean annual cost in this group of €15,500 was a fourth of the estimated cost in peritoneal dialysis patients (adjusted ratio [peritoneal dialysis vs transplanted] 4.04, 95% CI 3.58-4.56; Table 3).

Patients in CKD stages 4 or 5 displayed the lowest mean annual costs at €9600, where 45% (€4300) was accounted for by inpatient care. The adjusted mean annual cost ratio for transplanted vs CKD stages 4 or 5 was 1.70 (95% CI 1.51-1.92; Table 3). This difference was primarily explained by greater use of immunosuppressive drugs but also partly due to more expensive inpatient care among transplanted patients (Table 2, Figure 3).

Health Care Use and Costs Compared to the General Population

Mean annual health care use in the matched general population comparators to CKD stages 4 or 5, peritoneal dialysis, and hemodialysis patients were 0.2-0.3 hospital days, 1.8-2.2 outpatient visits, and €500-€600 in prescription drug costs, which resulted in a mean annual total cost of €2000-€2400 (Figure 3).

The corresponding health care use in general population comparators matched to the younger transplanted patients were 0.1 hospital days, 1.4 outpatient visits, and $400 in drug costs, resulting in a mean annual total cost of €1300.

Compared to their matched general population comparators, the mean annual cost in the hemodialysis group was 45 (95% CI 39-51) times higher, 29 (95% CI 22-37) times higher in the peritoneal dialysis group, 11 (95% CI 10-13) times higher in transplanted patients, and 4.0 (95% CI 3.6-4.5) times higher in patients with CKD stages 4 or 5 (Figure 3; Table 3).

DISCUSSION

Principal Findings

In this population-based cohort study we found that CKD stages 4 or 5 and renal replacement therapy are associated with substantial health care costs ranging from 4 to 45 times that expected in the general population. With 3.1 visits per week in outpatient care, patients on hemodialysis had the highest health care costs (€87,600) with dialysis care making up more than two thirds of the total cost. The total health care cost in hemodialysis was about 50% higher than in peritoneal dialysis patients, where similar costs of inpatient and outpatient care were observed, while cost of fluids was a major cost driver in peritoneal dialysis (€29,900). The mean annual costs in transplanted patients was €15,500, where prescription drugs constituted almost 50%, and in CKD stages 4 or 5 €9600, with inpatient care making up almost half of the total cost.

Strengths and limitations

Strengths of this study include the population-based data collected from routine clinical care in the Swedish health care system where registered individuals in Sweden have universal access. No comorbidity-based inclusion restrictions were used. Instead, we reported comorbidity status among included patients, as well as prescription drug costs in drug groups, and costs of hospital admissions and outpatient visits for specific diagnoses (e.g. cardiovascular disease). Furthermore, using individual level data from several nationwide registers, linked together by using the personal identity number, follow-up was virtually complete regarding outcome data for hospital days, hospital-based outpatient visits and prescription drug cost, as well as data on comorbidities, death and migration. Available registers enabled analysis of health care use in CKD stages 4 or 5, as well as in hemodialysis, peritoneal dialysis, and transplanted patients during the same year and at the same hospitals using the same data sources. Finally, we had the possibility to match comparators from the general population to each patient as a benchmark for health care resource utilization.

One limitation was that not all health care cost components were included in the available register sources. Fluids used for patients on peritoneal dialysis were not included in the Prescribed Drug Register, and these costs were therefore assessed using aggregated data.[31] Similarly, costs related to ESA for patients on hemodialysis is usually administered in the hospital, resulting in individual level data for ESA not being recorded in the Prescribed Drug Register. Using a smaller sample of patients on hemodialysis we could assess the costs related to ESA and apply this estimate to all hemodialysis patients in the study. Other costs not included were costs related to primary care and certain laboratory services, probably leading to an underestimation of the actual cost. Furthermore, patients on hemodialysis with few registered dialysis visits were scrutinized using the patient registration databases at the clinics. While a few patients for some reason had apparent missing data on dialysis visits also in this system, we imputed data with the mean. However, we cannot know whether hemodialysis visits were missing in the patients who were not scrutinized, which may result in an underestimation of the true hemodialysis cost.

Although all renal replacement therapy patients in Stockholm County were included, and the proportion of individuals with undiagnosed CKD stages 4 or 5 may have decreased with time, some patients are identified at start of dialysis, or die before identification. An unknown number of these individuals were missed, and our results should only be generalized to CKD stages 4 or 5 patients in nephrology care.

Previous Research

A recent study from the UK (£UK2011) recruited 7246 patients with CKD or patients who were receiving dialysis in Europe, North America and Australasia, and hospital admissions were recorded every 6 month at clinic visits.[8] They reported a mean hospital cost (drug cost not included) in patients with CKD 4 to £3700, £12,952 in CKD 5, and £20,511 in patients on dialysis. Excluding drug costs, our estimates of €6700 in CKD stages 4 or 5 and €21,400 in patients on peritoneal dialysis are in line with the UK study. Although the majority of patients in their dialysis group were patients on hemodialysis (83%) our cost estimates are higher when combining the hemodialysis and peritoneal dialysis groups (€68,800), mainly due to different methodologies for collecting costs related to dialysis sessions in outpatient care. In our study, we used prospectively recorded visit data from outpatient care, or annualized estimates for those who did not have a full year of follow-up, while they assumed thrice weekly hemodialysis sessions using £25,000 as a per patient annual cost. Our estimated 2.9 dialysis outpatient visits per week (and additional dialysis sessions in inpatient care for some patients), resulted in substantially higher annual cost of dialysis delivered in the outpatient setting (€60,400), indicating challenges when comparing study results between different health care settings.

Cost ratios of hemodialysis and peritoneal dialysis have recently been reported in a comprehensive review including 78 publications from 46 countries.[5] Based on 37 studies between 1998 to 2011 from Europe, the authors conclude that hemodialysis is 30-60% more expensive than peritoneal dialysis, while the cost ratio based on 5 studies from the US from 2005-2012 was estimated to 1.29, results that are less than our estimated ratio (adjusted cost ratio 1.49 [95% CI 1.38-1.60]).

Recent estimates (2010) from the US have reported a mean annual health care cost of US$12,386 in patients in CKD 4 (n=413) and US$23,445 in patients in CKD 5 (n=138) using health insurance claims data.[10] These estimates are higher than our result in the CKD 4 or 5 group (€9600). Although both studies used the same eGFR intervals when defining CKD stage 4 and CKD stage 5, our result was more similar to their estimated mean annual cost in patients in CKD 3 (US$10,100). The differences appeared to be driven by 2-3 times higher cost of outpatient care in CKD stages 4 and 5 and 3 times higher cost of inpatient care in patients in CKD 5 in their study, while our drug cost estimates were higher.

Another study from the US from 2004 reported a mean annual cost in patients in CKD stage 4 (n=777) to US$7600, which was 2.6 times the cost as compared to age and sex matched controls without CKD, results that are in line with our estimates when restricting the CKD 4 or 5 group to CKD stage 4 only (€8500 and 3.5 times the cost in comparators).

With respect to previous cost estimates from Sweden, a regional study from 2002, based on questionnaires in 136 patients, estimated the per patient mean annual cost related to peritoneal dialysis to US$34,600 and in hemodialysis to US$36,220 during the first 5 years after initiating treatment.[18] When taking inflation into account, our estimates are substantially higher, which may partly be explained by increased costs due to technology development of medical equipment (their estimates were based on data from 1990-1993), and by more complete follow-up when using register data. However, when comparing our adjusted mean annual cost ratio of hemodialysis and peritoneal dialysis the results are similar.

Implications

While the cost in CKD and renal replacement therapy are substantially elevated as compared to the general population, in particular in patients on dialysis, the annual mean and median costs among

patients on dialysis were similar (Figure 3), indicating a rather homogeneous use of health care resources. In contrast, the cost distributions of patients in CKD stages 4 or 5 and transplanted patients were skewed (Figure 1), as is commonly seen in other chronic diseases.[33] In this study we aimed to estimate the burden and health care costs for CKD and renal replacement therapy, but results may also be used to find potential cost components where it is possible to achieve savings. With the observed cost distributions, substantial savings could be achieved either by reducing smaller costs among many patients on dialysis, or by reducing costs among few patients in CKD or transplanted patients that are in the higher cost segments of the distribution. A possible next step would therefore be to determine predictors of costs among CKD patients in order to identify those that are in the higher end of the distribution as early as possible in the disease course, or to further study and validate predictors of failure in patients that are considered for kidney transplantation.[34] Furthermore, with the lower cost in CKD stages 4 or 5 as compared to dialysis, our result highlight the importance of good secondary prevention of patients in CKD stages 4 or 5 to postpone or even prevent the progression to end stage renal disease, a strategy that may generate significant savings, while also reducing the risk of mortality among these patients.[2]

Conclusion

The annual health care costs in patients in CKD stages 4 or 5, dialysis or transplanted patients are substantial. Patients on hemodialysis incurred the highest cost, 45 times as compared to general population, and 50% higher than patients on peritoneal dialysis. Transplanted patients and patients in CKD stages 4 or 5 incurred lower but considerable costs with 11 and 4 times the cost in the general population, respectively. More attention to secondary prevention in CKD stages 4 or 5 may generate savings by reducing time and number of patients on dialysis.

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Competing interest statement

JE declares that the answer to the questions on your competing interest form (http://resources.bmj.com/bmj/authors/checklists-forms/competing-interests) are all No and therefore has nothing to declare. MN has received payment for a lecture from Baxter. CGE and BH have received a grant to their academic institution from Baxter to support the work with this publication. SHJ has acted on an advisory board for Baxter, and received lecture payments at scientific meetings.

Details of contributors

BH, CGE, JE and MN conceived the study hypothesis. JE conducted the statistical analyses. JE wrote the first draft of the manuscript. BH, CGE, JE, MN and SHJ critically reviewed and contributed to the final draft. All authors are guarantors.

Additional Contributions

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Ethical approval

Ethical approval was granted by the regional ethics committee at Karolinska Institutet, Stockholm, Sweden (DNR: 2009/1225-31/5).

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Statement of independence of researchers from funders

BH, SHJ and CGE are employed by Stockholm County Council. No person representing Baxter read or commented on any version of the manuscript.

Data sharing statement

Data sharing: No additional data available

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Table 1 Participant characteristics[a]

	CKD Stages 4 or 5 (not on dialysis)	Peritoneal dialysis	Hemo-dialysis	Trans-planted
N	1046	101	460	825
Sex (% men)	683 (65%)	53 (52%)	271 (59%)	513 (62%)
eGFR[b], Mean (SD)	18 (6)	-	-	-
- <15	338 (32%)	-	-	-
- 15-29.9	708 (68%)	-	-	-
Time since transplantation (years)				
- Mean (SD)	-	-	-	9.1 (7.5)
- Median (25th-75th)	-	-	-	7.1 (3.3-12.8)
Age (years)				
- Mean (SD)	68 (14)	64 (16)	65 (15)	52 (14)
- Median (25^{th}-75^{th})	71 (60-79)	68 (54-78)	68 (55-75)	54 (43-63)
n (%)				
- 18-49y	130 (12%)	19 (19%)	76 (17%)	336 (41%)
- 50-59y	126 (12%)	16 (16%)	71 (15%)	212 (26%)
- 60-69y	232 (22%)	22 (22%)	125 (27%)	224 (27%)
- ≥70y	558 (53%)	44 (44%)	188 (41%)	53 (6%)
Education level[c]				
- Patients <75y	636 (61%)	66 (65%)	343 (75%)	808 (98%)
- ≤9y	172 (27%)	14 (21%)	115 (34%)	173 (21%)
- 10-12y	260 (41%)	31 (47%)	137 (40%)	347 (43%)
- >12y	193 (30%)	19 (29%)	69 (20%)	278 (34%)
- Missing	11 (2%)	2 (3%)	22 (6%)	10 (1%)
- Patients ≥75y (no information)	410 (39%)	35 (35%)	117 (25%)	17 (2%)
First registration in 2009	260 (25%)	40 (40%)	120 (26%)	57 (7%)
Follow-up days in 2009				
- Mean (SD)	323 (89)	288 (113)	320 (90)	353 (52)
- Median (25th-75^{th} percentile)	365 (365-365)	365 (217-365)	365 (352-365)	365 (365-365)

[a] SD=standard deviation; 25^{th}-75^{th} = 25^{th} to 75^{th} percentile

[b] Most recent recorded eGFR in relation to January 1, 2010. Full distribution shown in **eFigure 1**.

[c] Education level only available in patients <75 years

Table 2 Mean (SD) annualized hospital admission, outpatient visits, and dispensed prescription drug costs (ICD and ATC codes are specified in eTable 1)

	CKD Stages 4 or 5 (not on dialysis)	Peritoneal dialysis	Hemo-dialysis	Trans-planted
Annual admissions	1.0 (1.9)	2.6 (3.3)	3.6 (3.8)	0.9 (1.7)
Annual hospital days	6.2 (16.4)	16.0 (25.1)	21.4 (40.6)	4.6 (11.5)
- Cardiovascular disease	2.3 (8.3)	5.4 (15.1)	8.2 (29.1)	0.7 (3.7)
- Malignancy	0.5 (3.8)	0.3 (2.2)	0.7 (7.1)	0.2 (2.9)
- Infection	1.1 (5.2)	2.6 (7.5)	6.7 (21.6)	1.5 (6.6)
Annual outpatient visits	7.8 (6.8)	28.6 (19.4)	159.4 (28.8)	9.6 (10.5)
- Dialysis	0	15.2 (18.5)	152.2 (27.4)	0.1 (0.7)
- Cardiovascular disease	0.3 (1.1)	0.3 (1.2)	0.3 (0.7)	0.2 (0.7)
- Malignancy	0.4 (2.0)	0.3 (1.2)	0.5 (3.3)	0.4 (2.6)
Prescription drug costs, €	2917 (3690)	7353 (6870)	8395 (4286)	6794 (5134)
- Erythropoietin stimulating agents (ESA)	957 (1805)	2913 (2510)	3911 (938)	268 (952)
- Antineoplastic and immunomodulating agents	189 (1105)	97 (449)	249 (973)	5137 (4115)
- Various	297 (1675)	1086 (1357)	1420 (1460)	23 (161)
- Cardiovascular system	434 (410)	399 (459)	285 (329)	371 (327)
- Antidepressant drugs	54 (330)	42 (179)	68 (171)	30 (177)
Fluids for peritoneal dialysis, €**	-	29,900	-	-

*For hemodialysis, costs related to Erythropoietin stimulating agents (ESA) were estimated from a smaller sample (n=85) of hemodialysis patients as ESA use in this patient group does not enter the Prescribed Drug Register as it is administrated in the hospital in conjunction with dialysis

**Based on a regional report of dialysis care in southern Sweden[31]

Table 3 Adjusted cost ratios* (95% CI) of annualized total costs between patients with chronic kidney disease (CKD) stages 4 or 5 not on dialysis, peritoneal dialysis, hemodialysis and transplanted patients, and their matched general population comparators

	CKD stages 4 or 5 (not on dialysis)	Peritoneal dialysis	Hemodialysis	Transplanted	General population
CKD 4 or 5	-	0.15 (0.14-0.17)	0.11 (0.10-0.11)	0.59 (0.52-0.66)	4.0 (3.6-4.5)
Peritoneal Dialysis	6.45 (5.81-7.17)	-	0.67 (0.62-0.73)	4.04 (3.58-4.56)	28.5 (21.8-37.4)
Hemodialysis	9.41 (8.74-10.1)	1.49 (1.38-1.60)	-	5.97 (5.49-6.50)	44.5 (38.5-51.4)
Transplanted	1.70 (1.51-1.92)	0.25 (0.22-0.28)	0.17 (0.15-0.18)	-	11.1 (9.7-12.7)

*Adjusted for age, sex and diabetes status

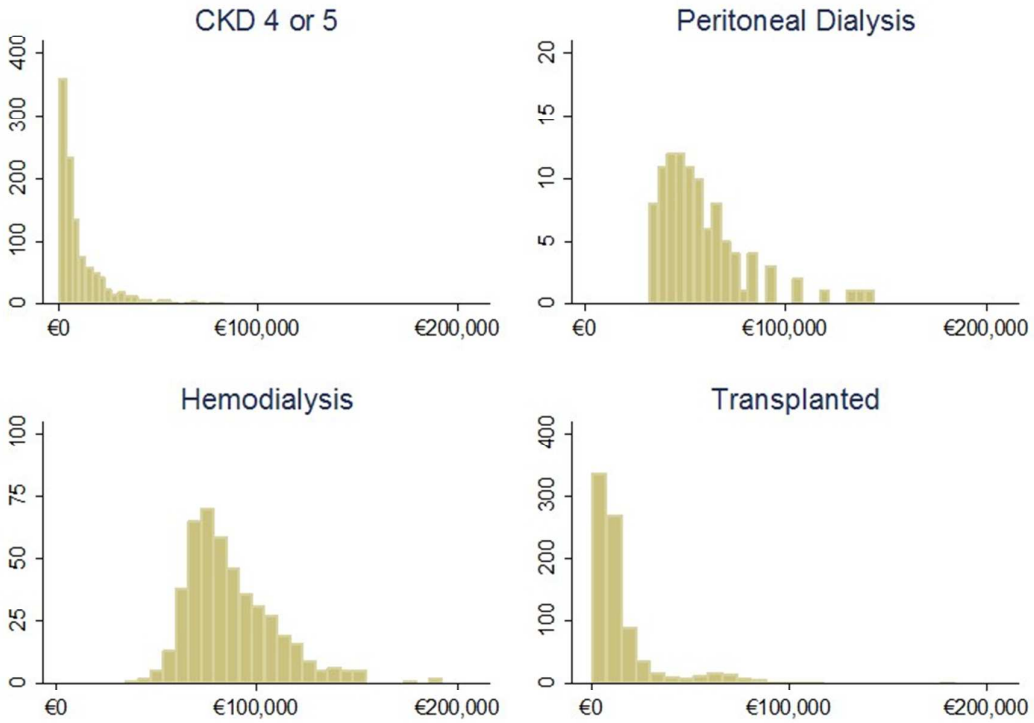


Figure 1 Distribution of annualized total costs in patients with chronic kidney disease (CKD) stages 4 or 5 (not on dialysis), peritoneal dialysis, hemodialysis and transplanted patients (y-axis indicates number of patients)

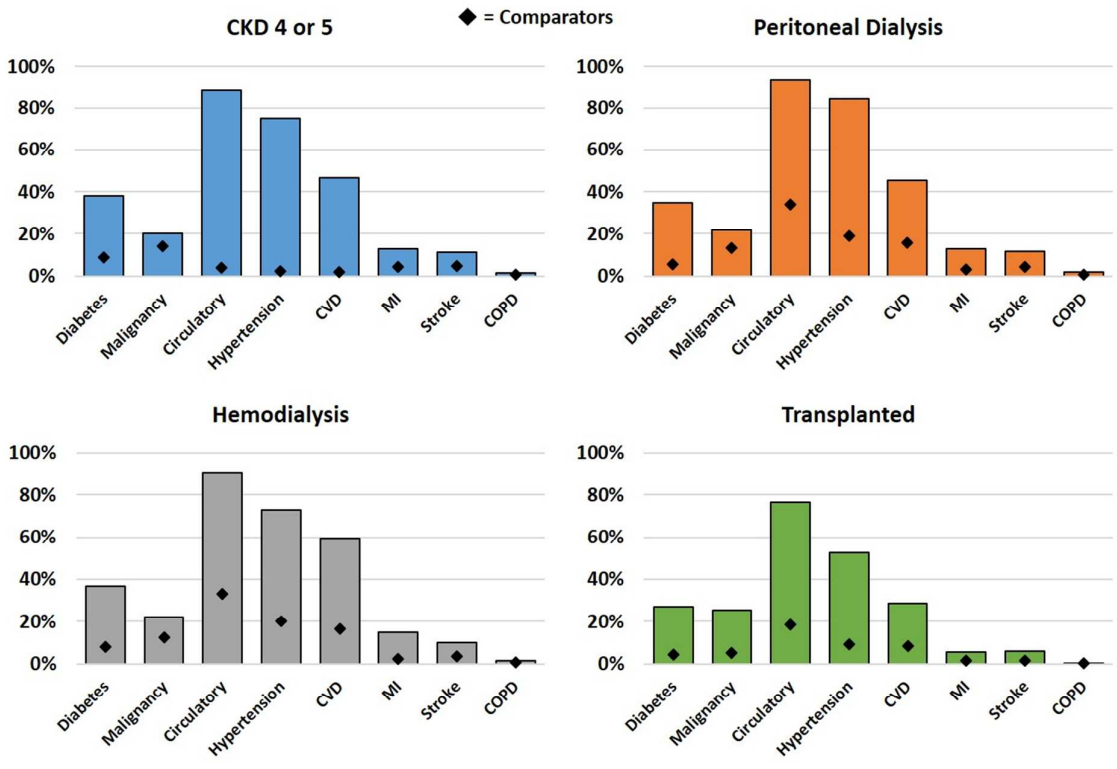


Figure 2 Comorbidity status in patients with chronic kidney disease (CKD) stages 4 or 5 not on dialysis, peritoneal dialysis, hemodialysis and transplanted patients (bars), as well as in their matched general population comparators (black diamonds)

Comorbid conditions defined as having a visit in inpatient or outpatient care during the last 10 years with a main or contributory diagnosis of the respective ICD-codes used (specified in **eTable 1**);
CVD: Cardiovascular disease; MI: Myocardial infarction; COPD: Chronic obstructive pulmonary disease

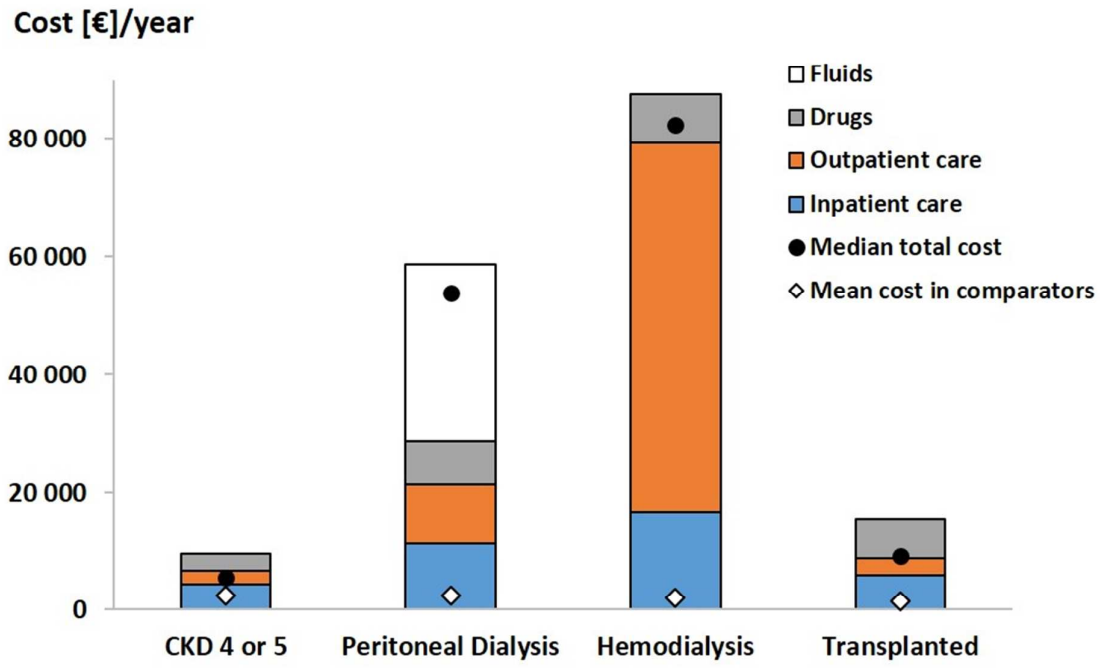


Figure 3 Annualized mean and median costs in patients with chronic kidney disease (CKD) stages 4 or 5 not on dialysis, peritoneal dialysis, hemodialysis and transplanted patients, as well as mean total cost in matched general population comparators
(matched 5:1 by age, sex and index year)

Supplementary Web Appendix

Health Care Costs in Chronic Kidney Disease & Renal Replacement Therapy: A Population-Based Cohort Study

Jonas K Eriksson (PhD), Martin Neovius (senior researcher), Stefan H Jacobson (senior nephrologist, professor), Carl-Gustaf Elinder (senior nephrologist, professor) & Britta Hylander (senior nephrologist, associate professor)

eTable 1 International Classification of Diseases (ICD) codes for comorbidities[a] and Anatomic Therapeutic Chemical (ATC) codes for drug prescriptions

Group	Code
Comorbidities	**ICD-10 codes**
Diabetes	E10-E11
Malignancies	C00-C99
Circulatory	I00-I99
- Hypertension	I10-I15
- Cardiovascular Disease	I20-I51
- Myocardial Infarction	I21
- Stroke	I60-I64
Chronic Obstructive Pulmonary Disease	J41-J44
Uremia	N00-N19
Infection	A00-B99, G00-G02, G04.2, G05-G07, H66-H67, H70, J00-J22, J32, J34.0, J36, J38.3, J39.0-J39.1, K10.2, L00-L08, M00-M01, M46.2-M46.5, M86, N10, N30.0
Prescription drugs	**ATC codes**
Erythropoietin stimulating agents	B03XA
Antineoplastic and immunomodulating agents	Chapter L
Various	Chapter V
Cardiovascular system	Chapter C
Antidepressant drugs	N05A, N05B, N05C, N06A, N06B

[a] Comorbidities assessed from 10 years prior to January 1st, 2010, i.e. only ICD 10 codes used

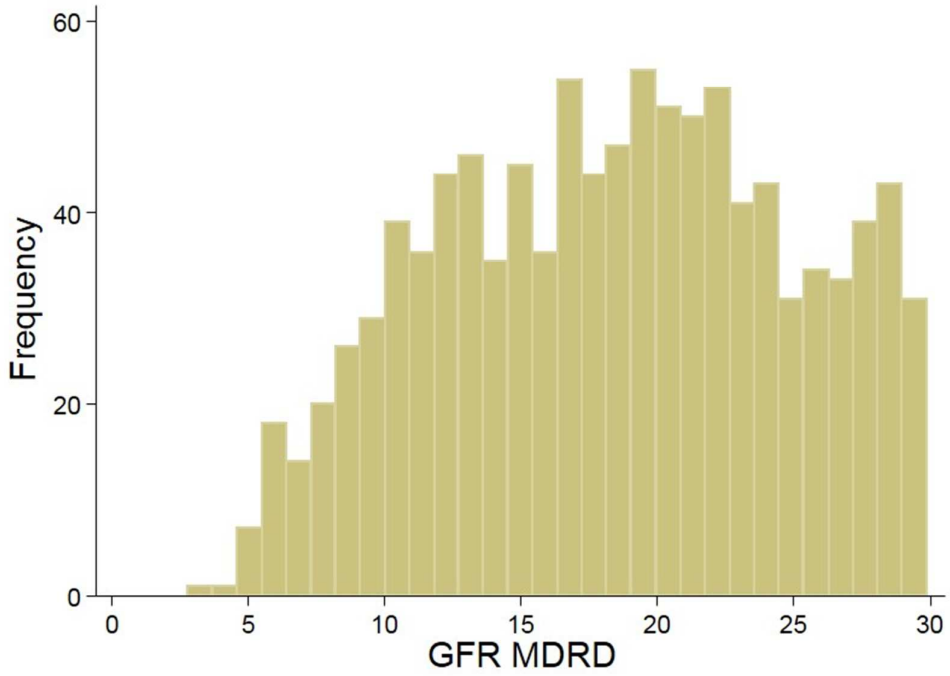
eTable 2 Characteristics of matched general population comparators (matched by age, sex, and index year)[a]

	CKD Stages 4 or 5 (not on dialysis)	Peritoneal Dialysis	Hemodialysis	Transplanted
N	4 949	484	2153	3 872
Sex (% men)	3212 (65%)	251 (52%)	1265 (59%)	2391 (62%)
Age (Years)				
- Mean (SD)	68 (14)	64 (16)	64 (15)	52 (13)
- Median (25^{th}-75^{th})	71 (60-79)	67 (54-78)	67 (55-75)	53 (43-63)
n (%)				
- 18-49y	634 (13%)	95 (20%)	358 (17%)	1619 (42%)
- 50-59y	609 (12%)	78 (16%)	344 (16%)	1008 (26%)
- 60-69y	1165 (24%)	106 (22%)	611 (28%)	1026 (26%)
- ≥70y	2541 (51%)	205 (42%)	840 (39%)	219 (6%)
Education level[b]				
- Patients <75y	3121 (63%)	328 (68%)	1628 (76%)	3812 (98%)
- ≤9y	699 (22%)	54 (16%)	357 (22%)	713 (19%)
- 10-12y	1277 (41%)	150 (46%)	676 (42%)	1589 (42%)
- >12y	1094 (35%)	110 (34%)	562 (35%)	1455 (38%)
- Missing	51 (2%)	14 (4%)	33 (2%)	55 (1%)
- Patients ≥75y (no information)	1828 (37%)	156 (32%)	525 (24%)	60 (2%)
Start follow-up in 2009	1294 (26%)	200 (41%)	589 (27%)	279 (7%)
Follow-up days in 2009				
- Mean (SD)	321 (91)	285 (114)	318 (91)	352 (53)
- Median (25th-75th)	365 (351-365)	365 (203-365)	365 (336-365)	365 (365-365)
Comorbidity[c]				
- Diabetes	438 (9%)	27 (6%)	175 (8%)	164 (4%)
- Malignancies	698 (14%)	65 (13%)	270 (13%)	193 (5%)
- Circulatory disease	1898 (38%)	165 (34%)	723 (34%)	719 (19%)
- Hypertension	1089 (22%)	91 (19%)	438 (20%)	348 (9%)
- Cardiovascular disease	1063 (21%)	77 (16%)	365 (17%)	318 (8%)
- Myocardial Infarction[d]	211 (4%)	15 (3%)	53 (2%)	49 (1%)
- Stroke	237 (5%)	22 (5%)	76 (4%)	51 (1%)
- COPD[e]	34 (1%)	3 (1%)	11 (1%)	16 (0%)

[a] SD=standard deviation; 25^{th}-75^{th} = 25^{th} to 75^{th} percentile
[b] Education level only available in patients <75 years
[c] Comorbid conditions defined as having a visit in inpatient or outpatient care during the last 10 years with a main or contributory diagnosis of the respective ICD-codes used (specified in eTable 1)
[d] Myocardial infarction also included as a subgroup of cardiovascular disease
[e] Chronic obstructive pulmonary disease

eTable 3 Annualized mean (SD) costs in patients with chronic kidney disease (CKD) stages 4 or 5 not on dialysis, peritoneal dialysis, hemodialysis and transplanted

Costs	CKD Stages 4 or 5 not on dialysis	Peritoneal Dialysis	Hemodialysis	Transplanted
Inpatient care	4338 (8404)	11 408 (15 079)	16 730 (18 674)	5889 (12 756)
- Cardiovascular disease	1770 (5422)	3702 (9990)	5508 (13 270)	879 (5191)
- Malignancy	403 (2641)	227 (1340)	396 (3145)	172 (1566)
- Infection	740 (3259)	1455 (4054)	3966 (9800)	1551 (8478)
Outpatient care	2326 (2093)	9987 (7304)	62 475 (11 542)	2834 (3180)
- Dialysis	10 (100)	5867 (7193)	60 357 (11 207)	25 (286)
- Cardiovascular disease	108 (526)	97 (363)	110 (475)	59 (285)
- Malignancy	120 (712)	98 (416)	119 (779)	100 (610)
Drugs	2917 (3690)	7353 (6870)	8395 (4286)	6794 (5134)
Fluids	0	29 900	0	0
Total	**9581 (10 828)**	**58 648 (22 027)**	**87 600 (22 339)**	**15 518 (18 608)**



eFigure 1 Distribution of estimated glomerular filtration rate (GFR; ml/min/1.73m^2) in patients with chronic kidney disease stages 4 or 5 (n=1046)[a]

[a] Estimated using the MDRD formula

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5, 6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6, 7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	6, 7
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) Summarise follow-up time (eg, average and total amount)	8, Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	8, 9, Table 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8, 9
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10, 11, 12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Health Care Costs in Chronic Kidney Disease & Renal Replacement Therapy: A Population-Based Cohort Study in Sweden

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Health Care Costs in Chronic Kidney Disease & Renal Replacement Therapy: A Population-Based Cohort Study in Sweden

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Abstract Word Count:	300 words (max 300)
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Figures:	3
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eFigures:	1

Key words: chronic kidney disease, cost, dialysis, renal replacement therapy, transplantation

ABSTRACT

Objective: To compare health care costs in chronic kidney disease (CKD) stages 4 or 5 not on dialysis (estimated glomerular filtration rate <30 ml/min/1.73m^2), peritoneal dialysis, hemodialysis, and in transplanted patients with matched general population comparators.

Design: Population-based cohort study.

Setting: Swedish national health care system.

Participants: Prevalent adult patients with CKD 4 or 5 (n=1046, mean age 68y), on peritoneal dialysis (n=101; 64y), on hemodialysis (n=460; 65y), and with renal transplants (n=825; 52y) were identified in Stockholm County clinical quality registers for renal disease on January 1st, 2010. Five general population comparators from the same county were matched to each patient by age, sex, and index year.

Primary and Secondary Outcome Measures: Annual health care costs in 2009 incurred through inpatient and hospital-based outpatient care and dispensed prescription drugs ascertained from nationwide health care registers. Secondary outcomes were annual number of hospital days and outpatient care visits.

Results: Patients on hemodialysis had the highest mean annual cost (€87,600), which was 1.49 (95%CI 1.38-1.60) times that observed in peritoneal dialysis (€58,600). The mean annual cost was considerably lower in transplanted patients (€15,500) and in the CKD group (€9600). In hemodialysis patients, outpatient care costs made up more than two-thirds (€62,500) of the total, while costs related to fluids ($29,900) was the largest cost component in peritoneal dialysis patients (51%). Compared to their matched general population comparators, the mean annual cost (95%CI) in hemodialysis, peritoneal dialysis, transplanted, and CKD patients was 45 (39-51), 29 (22-37), 11 (10-13), and 4.0 (3.6-4.5) times higher, respectively.

Conclusion: Mean annual costs were approximately 50% higher in hemodialysis than peritoneal dialysis patients. Compared to the general population, costs were substantially elevated in all groups, from 4-fold in CKD patients to 11, 29 and 45 times higher in transplanted patients, patients on peritoneal dialysis and hemodialysis, respectively.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- In this population-based study data were collected from routine clinical care to which there is universal access in Sweden
- By linking nationwide health care registers using the personal identity number, follow-up on an individual level was virtually complete regarding hospital days, hospital-based outpatient care and dispensed prescription drugs
- Costs related to in-hospital use of erythropoietin stimulating agents (ESA) for patients on hemodialysis were assessed using records from a smaller patient sample
- Costs related to fluids for patients on peritoneal dialysis were assessed using aggregated data, since these costs were not collected on an individual level in registers
- Although the proportion of undiagnosed individuals with CKD stage 4 or 5 have decreased with time, this group is still underdiagnosed and an unknown number of these patients were missed

INTRODUCTION

Chronic kidney disease (CKD) and end-stage renal disease are associated with substantial health care resource use and considerably higher mortality.[1 2] Although some reports suggest a decline in the incidence of CKD,[3] demographic changes together with increasing type 2 diabetes are likely to result in a higher prevalence of CKD.[4] To evaluate the value of therapeutic interventions in this patient group, an assessment of the economic burden related to CKD and end-stage renal disease is necessary, as is an available benchmark in terms of the corresponding costs in the general population.

Several studies have investigated the burden or costs in patients with different stages of CKD and renal replacement therapy, using different methods and in different settings.[5-7] The majority of cost studies from Europe and North America of patients on dialysis have reported higher health care costs of hemodialysis ranging from 1.0-1.9 times the cost in peritoneal dialysis.[5] Similarly, previous studies have reported increasing health care use and costs with higher CKD stages,[8-11] and estimates in patients with CKD that are 2-3 times the cost as compared to controls without CKD.[9 11] Recent studies from Europe, North America and Australia on the burden of CKD and renal replacement therapy with reported annual per patient cost have typically been based on small study samples or by using a modeling approach collecting data from published aggregated estimates.[12-21] Only a few studies have used individual data from larger study samples.[8-10]

To the best of our knowledge no study has from the same study population and on an individual level described health care use and costs in CKD stages 4 or 5 not on dialysis, hemodialysis, peritoneal dialysis, and transplanted patients separately, and compared the result to costs in the general population.

The aim of this population-based cohort study was to examine annual costs assessed from Swedish nationwide health care registers related to hospital days, outpatient care visits, and prescription of drugs in prevalent CKD stages 4 or 5 not on dialysis, peritoneal dialysis, hemodialysis, and transplanted patients, and to put these costs in relation to matched general population comparators.

METHODS

In this population-based cohort study we identified patients on CKD stages 4 or 5 not on dialysis, patients on dialysis and transplanted patients from clinical quality of care registers in Stockholm County and added data from national health registers. By using the personal identity number, a unique number assigned to all Swedish residents,[22] we enriched these data with inpatient and hospital-based outpatient care from the National Patient Register as well as data on dispensed drugs from the Prescribed Drug Register kept by the National Board of Health and Welfare.

Ethical approval was granted by the regional ethics committee at Karolinska Institutet, Stockholm, Sweden.

Chronic Kidney Disease and the Swedish National Health Service

Sweden had a population of 7.4 million ≥18 years on December 31, 2009 (www.scb.se), and comprised 21 counties. Stockholm County was the biggest with 1.6 million inhabitants ≥18 years, accounting for 22% of the population. The Swedish health care system was tax funded and offered universal access, while prescription drugs were provided free of charge above a threshold of around €200 annually.

Patients with renal replacement therapy were treated by nephrologists in inpatient and outpatient facilities,[23] rather than by general practitioners, while care for CKD patients was a mix of mainly hospital-based outpatient care, and to some extent primary care. The decision to initiate renal replacement therapy was made by nephrologists from clinical evaluations based on the Swedish guidelines[24] originating from the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) guidelines[25] and the corresponding European guidelines.[26]

Identification of Patients in Quality Register Sources

CKD Patients: From the Stockholm County CKD Register we identified adult prevalent CKD patients in stages 4 or 5 who were not on dialysis, on January 1st, 2010, registered at Karolinska and Danderyd University Hospital in the outpatient setting. This does not include all CKD stages 4 and 5 patients in the county, as some may get care elsewhere and some remain undetected. Furthermore, patients in CKD stages 1-3B were generally not registered and were for this reason not included in the study. Stages 4 and 5 were defined as an eGFR of 15-29.9 and <15, respectively. GFR was estimated using the abbreviated Modification of Diet in Renal Disease equation (MDRD; ml/min/1.73m^2) using serum creatinine levels.[27] If baseline eGFR was missing in patients with CKD stages 4 or 5, this resulted in exclusion from CKD analyses (n=5). Data on albuminuria were incomplete and therefore no analyses by albuminuria status were performed.

Renal Replacement Therapy Patients: Prevalent patients on hospital-based dialysis or with a kidney transplant on January 1st, 2010, were identified in the Swedish Register of Renal Replacement Therapy, which includes all adult patients on renal replacement therapy in Stockholm County.[28 29]

General Population Comparators from the Register of the Total Population

From the Register of the Total Population held by Statistics Sweden, up to five general population comparators from the Stockholm County were sampled and matched on age, sex and index year to each patient (exact matching). The matched comparators received the same index date as their corresponding patient. Data on emigration and highest attained education were also retrieved from the Register of the Total Population.

The National Patient Register

Data on inpatient and hospital-based outpatient care were retrieved from the Swedish National Patient Register in 2009. This register contains the personal identity number, visit/admission date (and discharge date for the inpatient component), diagnostic related group (DRG) associated with the visit, and main as well as contributory diagnoses coded according to the International Classification of Diseases version 10 (ICD-10).[30] Comorbid conditions were defined as having a visit in inpatient or outpatient care during the last 10 years with a main or contributory diagnosis of the respective ICD-codes used (**eTable 1)**.

Hospital days and outpatient visits were converted into costs using the DRG coding system, where clinically similar hospitalizations or outpatient visits are grouped together. The price per DRG is fixed for a specific year, and is a weighted average for all the health care delivered in that group and year. In 2009 the inpatient and outpatient component of the National Patient Register included around 580 and 400 DRG groups, respectively.

The Prescribed Drug Register

From the Prescribed Drug Register we collected data on dispensed prescriptions in ambulatory care in 2009. Data on in-hospital drug use are not recorded on a patient level in the Prescribed Drug Register. Among other variables the register includes the personal identity number, date of prescription and dispensation, costs (total cost, patient cost, reimbursed cost), dosage, route of administration, and name as well as the of Anatomic Therapeutic Chemical (ATC) code of the drug.

Outcome and follow-up

The main outcome was annual health care costs incurred through inpatient and outpatient care, as well as dispensed prescription drugs. Secondary outcomes were annual number of hospital days and outpatient visits. Costs were assessed during 2009 and converted to euros (€1=SEK9.54 Swedish kronor in 2010). Patients were followed in the same health state as when they were identified in January 1st, 2010, with estimated annualized costs in those patients who did not have 1 year of follow-up.

Annualized Costs: Health care use and costs in patients who were not in CKD stages 4 or 5, on dialysis, or did not yet have a kidney transplant on January 1st, 2009, and hence were not followed the complete year of 2009 (all patients were identified on January 1st, 2010), were annualized from the time of entry into the respective health states. To have enough data available for each patient, we restricted the study population to patients with at least 1 month of follow-up, i.e. patients who were exposed on or before December 1st, 2009. For example, if a patient started hemodialysis on July 1st, 2009, we doubled that patient's health care use and costs to achieve an annualized estimate. For transplanted patients who received a kidney transplant in 2009, the cost for the kidney transplant procedure were included. However, costs related to the transplantation procedure were not annualized.

Costs Related to Hemodialysis Visits: As a data quality control, patients on hemodialysis that had less than 2 registered dialysis visits per week (n=135) in the National Patient Register were scrutinized using the patient registration database at the clinic. Data were imputed with 156 hemodialysis visits per year (3 visits/week) in patients having missing visit data over longer periods of time (≥3 months) and where extrapolation was not adequate (n=14), while in patients with missing data over shorter periods (<3 months, n=3), we extrapolated visits in time intervals with missing data. In total of 88

(65%) of the scrutinized patients on hemodialysis we added information from the registration database at the clinic.

Costs Related to Erythropoietin stimulating agents (ESA) in Hemodialysis and Fluids in Peritoneal Dialysis: As the Prescribed Drug Register does not include in-hospital use of drugs, the cost for ESA is underestimated in hemodialysis patients when using this data source. We retrieved data on ESA use in a sub-sample of hemodialysis patients (n=85) and calculated the cost using 2009 drug prices in Sweden (http//:www.tlv.se). In this sub-sample the annual cost per patient related to ESA was estimated to €3911, which we applied to all hemodialysis patients. Further, the cost of fluids for peritoneal dialysis is also not covered by the Prescribed Drug Register. This cost has previously been estimated to SEK 200,000-370,000 (€21,000-€38,800) per patient and year.[31] We used the mid-value (€29,900) in this range and applied it on all patients on peritoneal dialysis.

Statistical Analysis

Cost distributions were non-normal in patients with CKD stages 4 or 5, patients on peritoneal dialysis, and transplanted patients, but approached a normal distribution in patients on hemodialysis (**Figure 1**). As the arithmetic mean has been described to be the most informative measure for cost and resource use data,[32] we report the mean annual cost (complemented by the median for descriptive purposes). Mean annual cost ratios, when comparing costs in CKD stages 4 or 5, peritoneal dialysis, hemodialysis and transplanted patients, or when comparing patients vs their matched general population comparators, were adjusted for age, sex, and diabetes status using a generalized linear regression model with negative binomial distribution, and 95% confidence intervals were estimated using robust standard errors.

Statistical analyses were performed using SAS (version 9.3).

RESULTS

A total of 2432 prevalent patients who were alive on January 1st, 2010, were included (**Table 1**). CKD stages 4 or 5 patients (n=1046) were on average 68 years old, while dialysis patients (n=101 on peritoneal dialysis; n=460 on hemodialysis) were younger (64y and 65y, respectively), and transplanted patients (n=825) much younger (52 years). All groups were predominantly male, and the education level was broadly similar to that in the general population (Table 1, **eTable 2**). The vast majority of transplanted patients had complete follow-up through 2009 (93%), while one quarter of the CKD stage 4 or 5 and hemodialysis patients did not have the full year of follow-up, and 40% of the patients in the peritoneal dialysis group were also followed for less than one year (Table 1).

Regarding selected register-identified comorbidities, approximately 90% of the patients had circulatory disease history, with about 15% having had a myocardial infarction and 10% a stroke (except transplanted patients; **Figure 2**). The CKD stages 4 or 5 and dialysis patients were similar, with the exception of a higher prevalence of cardiovascular disease in the hemodialysis patient group. The younger transplanted patients displayed lower prevalence, as compared to the CKD and dialysis patients, for most of the selected comorbidities, but a higher occurrence of malignancies. All groups had similar prevalence of chronic obstructive pulmonary disease as the general population comparators, but displayed higher or much higher prevalence in the other selected comorbidities, including diabetes where more than 30% of patients (except the transplanted group) had diabetes, compared to 6-9% in the matched general population (eTable 2).

Total Costs

The highest mean annual cost was observed in the hemodialysis group with €87,600, out of which 71% were accounted for by outpatient care costs (€62,500; **Figure 3**; **eTable 3**). Of the total outpatient care cost, 97% (€60,400) were costs for visits listing dialysis.

Patients on peritoneal dialysis incurred a mean annual cost of €58,600 which was about two thirds of the cost compared to hemodialysis patients (adjusted ratio [hemodialysis vs peritoneal dialysis] 1.49, 95% CI 1.38-1.60; **Table 3**). The largest cost component in the peritoneal dialysis group was costs related to fluids (€29,900; 51% of total cost), while costs related to inpatient and outpatient care were similar (€11,400 and €10,000, respectively).

In contrast, transplanted patients was the only group where dispensed prescription drugs made up the largest cost component (€6800; 44% of total cost), while the mean annual cost in this group of €15,500 was a fourth of the estimated cost in peritoneal dialysis patients (adjusted ratio [peritoneal dialysis vs transplanted] 4.04, 95% CI 3.58-4.56; Table 3).

Patients in CKD stages 4 or 5 displayed the lowest mean annual costs at €9600, where 45% (€4300) was accounted for by inpatient care. The adjusted mean annual cost ratio for transplanted vs CKD stages 4 or 5 was 1.70 (95% CI 1.51-1.92; Table 3). This difference was primarily explained by greater use of immunosuppressive drugs but also partly due to more expensive inpatient care among transplanted patients (**Table 2**, Figure 3).

In a stratified analysis on treatment start before or during 2009, similar total cost estimates, as compared to the overall patient group, were observed in patients in CKD stages 4 or 5, hemodialysis and peritoneal dialysis, while transplanted patients who received a kidney transplant in 2009 had considerably higher costs (**eTable 4 & 5**).

Drug Costs

Prescription Drug Costs: The mean annual cost of dispensed prescription drugs was €7400 in the peritoneal dialysis group, €6800 in transplanted patients, €8400 (of which €3911 on ESA) in hemodialysis patients, and €2900 in the CKD 4 or 5 group (Table 2, Figure 3).

Costs related to Fluids in Peritoneal Dialysis: Based on a regional report of dialysis care in southern Sweden, the annual cost of fluids in patients on peritoneal dialysis were estimated to €29,900.[31]

Health Care Use

Annual Hospital Days: Mean annual hospital days in patients on hemodialysis was 21.4, with the majority of hospital days listing a main or contributory diagnosis for cardiovascular disease (8.2 days) or infection (6.7 days; Table 2). Patients on peritoneal dialysis displayed lower overall mean hospital days (16.0), with 5.4 days and 2.6 days related to cardiovascular disease and infection, respectively. Transplanted patients and patients in CKD stages 4 or 5 had similar level of inpatient care use with 4.6 and 6.2 annual hospital days, respectively.

Outpatient Care: In hemodialysis patients, 152 out of a mean 159 annual visits were due to dialysis. The corresponding number in peritoneal dialysis patients was 29 visits per year with 15 visits listing dialysis. Again, transplanted patients and patients in CKD stages 4 or 5 had similar numbers with 10 and 8 visits, respectively.

Health Care Use and Costs Compared to the General Population

Mean annual health care use in the matched general population comparators to CKD stages 4 or 5, peritoneal dialysis, and hemodialysis patients were 0.2-0.3 hospital days, 1.8-2.2 outpatient visits, and €500-€600 in prescription drug costs, which resulted in a mean annual total cost of €2000-€2400 (Figure 3).

The corresponding health care use in general population comparators matched to the younger transplanted patients were 0.1 hospital days, 1.4 outpatient visits, and $400 in drug costs, resulting in a mean annual total cost of €1300.

Compared to their matched general population comparators, the mean annual cost in the hemodialysis group was 45 (95% CI 39-51) times higher, 29 (95% CI 22-37) times higher in the peritoneal dialysis group, 11 (95% CI 10-13) times higher in transplanted patients, and 4.0 (95% CI 3.6-4.5) times higher in patients with CKD stages 4 or 5 (Figure 3; Table 3).

DISCUSSION

Principal Findings

In this population-based cohort study we found that CKD stages 4 or 5 and renal replacement therapy are associated with substantial health care costs ranging from 4 to 45 times that expected in the general population. With 3.1 visits per week in outpatient care, patients on hemodialysis had the highest health care costs (€87,600) with dialysis care making up more than two thirds of the total cost. The total health care cost in hemodialysis was about 50% higher than in peritoneal dialysis patients, where similar costs of inpatient and outpatient care were observed, while cost of fluids was a major cost driver in peritoneal dialysis (€29,900). The mean annual costs in transplanted patients was €15,500, where prescription drugs constituted almost 50%, and in CKD stages 4 or 5 €9600, with inpatient care making up almost half of the total cost.

Strengths and limitations

Strengths of this study include the population-based data collected from routine clinical care in the Swedish health care system where registered individuals in Sweden have universal access. No comorbidity-based inclusion restrictions were used. Instead, we reported comorbidity status among included patients, as well as prescription drug costs in drug groups, and costs of hospital admissions and outpatient visits for specific diagnoses (e.g. cardiovascular disease). Furthermore, using individual level data from several nationwide registers, linked together by using the personal identity number, follow-up was virtually complete regarding outcome data for hospital days, hospital-based outpatient visits and prescription drug cost, as well as data on comorbidities, death and migration. Available registers enabled analysis of health care use in CKD stages 4 or 5, as well as in hemodialysis, peritoneal dialysis, and transplanted patients during the same year and at the same hospitals using the same data sources. Finally, we had the possibility to match comparators from the general population to each patient as a benchmark for health care resource utilization.

One limitation was that not all health care cost components were included in the available register sources. Fluids used for patients on peritoneal dialysis were not included in the Prescribed Drug Register, and these costs were therefore assessed using aggregated data.[31] Similarly, costs related to ESA for patients on hemodialysis is usually administered in the hospital, resulting in individual level data for ESA not being recorded in the Prescribed Drug Register. Using a smaller sample of patients on hemodialysis we could assess the costs related to ESA and apply this estimate to all hemodialysis patients in the study. Applying these aggregated costs to all patients on peritoneal dialysis (fluids) and hemodialysis (ESA) will most likely result in smaller variation and overestimated precision of the cost estimates than would have been observed in data including these cost components. Other costs not included were costs related to primary care and certain laboratory services, probably leading to an underestimation of the actual cost. Furthermore, patients on hemodialysis with few registered dialysis visits were scrutinized using the patient registration databases at the clinics. While a few patients for some reason had apparent missing data on dialysis visits also in this system, we imputed data with the mean. However, we cannot know whether hemodialysis visits were missing in the patients who were not scrutinized, which may result in an underestimation of the true hemodialysis cost.

Although all renal replacement therapy patients in Stockholm County were included, and the proportion of individuals with undiagnosed CKD stages 4 or 5 may have decreased with time, some patients are identified at start of dialysis, or die before identification. An unknown number of these

individuals were missed, and our results should only be generalized to CKD stages 4 or 5 patients in nephrology care. Finally, an important underlying assumption with the methodology used in this study, where a mix of patients with short and long treatment duration were included, the proportion of patients starting their treatment have to be constant over time, in this case by calendar year. This assumption is particularly important in transplanted patients who have a high initial cost with the kidney transplant procedure.

Previous Research

A recent study from the UK (costs in £UK2011) recruited 7246 patients with CKD or patients who were receiving dialysis in Europe, North America and Australasia, and hospital admissions were recorded every 6 month at clinic visits.[8] They reported a mean hospital cost (drug cost not included) in patients with CKD 4 to £3700, £12,952 in CKD 5, and £20,511 in patients on dialysis. Excluding drug costs, our estimates of €6700 in CKD stages 4 or 5 and €21,400 in patients on peritoneal dialysis are in line with the UK study. Although the majority of patients in their dialysis group were patients on hemodialysis (83%) our cost estimates are higher when combining the hemodialysis and peritoneal dialysis groups (€68,800), mainly due to different methodologies for collecting costs related to dialysis sessions in outpatient care. In our study, we used prospectively recorded visit data from outpatient care, or annualized estimates for those who did not have a full year of follow-up, while they assumed thrice weekly hemodialysis sessions using £25,000 as a per patient annual cost. Our estimated 2.9 dialysis outpatient visits per week (and additional dialysis sessions in inpatient care for some patients), resulted in substantially higher annual cost of dialysis delivered in the outpatient setting (€60,400), indicating challenges when comparing study results between different health care settings.

Cost ratios of hemodialysis and peritoneal dialysis have recently been reported in a comprehensive review including 78 publications from 46 countries.[5] Based on 37 studies between 1998 to 2011 from Europe, the authors conclude that hemodialysis is 30-60% more expensive than peritoneal dialysis, while the cost ratio based on 5 studies from the US from 2005-2012 was estimated to 1.29, results that are less than our estimated ratio (adjusted cost ratio 1.49 [95% CI 1.38-1.60]).

Recent estimates (2010) from the US have reported a mean annual health care cost of US$12,386 in patients in CKD 4 (n=413) and US$23,445 in patients in CKD 5 (n=138) using health insurance claims data.[10] These estimates are higher than our result in the CKD 4 or 5 group (€9600). Although both studies used the same eGFR intervals when defining CKD stage 4 and CKD stage 5, our result was more similar to their estimated mean annual cost in patients in CKD 3 (US$10,100). The differences appeared to be driven by 2-3 times higher cost of outpatient care in CKD stages 4 and 5 and 3 times higher cost of inpatient care in patients in CKD 5 in their study, while our drug cost estimates were higher.

Another study from the US from 2004 reported a mean annual cost in patients in CKD stage 4 (n=777) to US$7600, which was 2.6 times the cost as compared to age and sex matched controls without CKD, results that are in line with our estimates when restricting the CKD 4 or 5 group to CKD stage 4 only (€8500 and 3.5 times the cost in comparators).

With respect to previous cost estimates from Sweden, a regional study from 2002, based on questionnaires in 136 patients, estimated the per patient mean annual cost related to peritoneal dialysis to US$34,600 and in hemodialysis to US$36,220 during the first 5 years after initiating treatment.[18] When taking inflation into account, our estimates are substantially higher, which may

partly be explained by increased costs due to technology development of medical equipment (their estimates were based on data from 1990-1993), and by more complete follow-up when using register data. However, when comparing our adjusted mean annual cost ratio of hemodialysis and peritoneal dialysis the results are similar.

Implications

With the lower cost in CKD stages 4 or 5 as compared to dialysis, our result highlight the importance of good secondary prevention of patients in CKD stages 4 or 5 to postpone or even prevent the progression to end stage renal disease, a strategy that may generate significant savings, while also reducing the risk of mortality among these patients.[2]

Conclusion

The annual health care costs in patients in CKD stages 4 or 5, dialysis or transplanted patients are substantial. Patients on hemodialysis incurred the highest cost, 45 times as compared to general population, and 50% higher than patients on peritoneal dialysis. Transplanted patients and patients in CKD stages 4 or 5 incurred lower but considerable costs with 11 and 4 times the cost in the general population, respectively. More attention to secondary prevention in CKD stages 4 or 5 may generate savings by reducing time and number of patients on dialysis.

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Competing interest statement

JE declares that the answer to the questions on your competing interest form (http://resources.bmj.com/bmj/authors/checklists-forms/competing-interests) are all No and therefore has nothing to declare. MN has received payment for a lecture from Baxter. CGE and BH have received a grant to their academic institution from Baxter to support the work with this publication. SHJ has acted on an advisory board for Baxter, and received lecture payments at scientific meetings.

Details of contributors

BH, CGE, JE and MN conceived the study hypothesis. JE conducted the statistical analyses. JE wrote the first draft of the manuscript. BH, CGE, JE, MN and SHJ critically reviewed and contributed to the final draft. All authors are guarantors.

Additional Contributions

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Ethical approval

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Statement of independence of researchers from funders

BH, SHJ and CGE are employed by Stockholm County Council. No person representing Baxter read or commented on any version of the manuscript.

Data sharing statement

Data sharing: No additional data available

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Table 1 Participant characteristics[a]

	CKD Stages 4 or 5 (not on dialysis)	Peritoneal dialysis	Hemo-dialysis	Trans-planted
N	1046	101	460	825
Sex (% men)	683 (65%)	53 (52%)	271 (59%)	513 (62%)
eGFR[b], Mean (SD)	18 (6)	-	-	-
- <15	338 (32%)	-	-	-
- 15-29.9	708 (68%)	-	-	-
Time since transplantation (years)				
- Mean (SD)	-	-	-	9.1 (7.5)
- Median (25th-75th)	-	-	-	7.1 (3.3-12.8)
Age (years)				
- Mean (SD)	68 (14)	64 (16)	65 (15)	52 (14)
- Median (25^{th}-75^{th})	71 (60-79)	68 (54-78)	68 (55-75)	54 (43-63)
n (%)				
- 18-49y	130 (12%)	19 (19%)	76 (17%)	336 (41%)
- 50-59y	126 (12%)	16 (16%)	71 (15%)	212 (26%)
- 60-69y	232 (22%)	22 (22%)	125 (27%)	224 (27%)
- ≥70y	558 (53%)	44 (44%)	188 (41%)	53 (6%)
Education level[c]				
- Patients <75y	636 (61%)	66 (65%)	343 (75%)	808 (98%)
- ≤9y	172 (27%)	14 (21%)	115 (34%)	173 (21%)
- 10-12y	260 (41%)	31 (47%)	137 (40%)	347 (43%)
- >12y	193 (30%)	19 (29%)	69 (20%)	278 (34%)
- Missing	11 (2%)	2 (3%)	22 (6%)	10 (1%)
- Patients ≥75y (no information)	410 (39%)	35 (35%)	117 (25%)	17 (2%)
First registration in 2009	260 (25%)	40 (40%)	120 (26%)	57 (7%)
Follow-up days in 2009				
- Mean (SD)	323 (89)	288 (113)	320 (90)	353 (52)
- Median (25th-75^{th} percentile)	365 (365-365)	365 (217-365)	365 (352-365)	365 (365-365)

[a] SD=standard deviation; 25^{th}-75^{th} = 25^{th} to 75^{th} percentile

[b] Most recent recorded eGFR in relation to January 1, 2010. Full distribution shown in **eFigure 1**.

[c] Education level only available in patients <75 years

Table 2 Mean (SD) annualized hospital admission, outpatient visits, and dispensed prescription drug costs (ICD and ATC codes are specified in eTable 1)

	CKD Stages 4 or 5 (not on dialysis)	Peritoneal dialysis	Hemo-dialysis	Trans-planted
Annual admissions	1.0 (1.9)	2.6 (3.3)	3.6 (3.8)	0.9 (1.7)
Annual hospital days	6.2 (16.4)	16.0 (25.1)	21.4 (40.6)	4.6 (11.5)
- Cardiovascular disease	2.3 (8.3)	5.4 (15.1)	8.2 (29.1)	0.7 (3.7)
- Malignancy	0.5 (3.8)	0.3 (2.2)	0.7 (7.1)	0.2 (2.9)
- Infection	1.1 (5.2)	2.6 (7.5)	6.7 (21.6)	1.5 (6.6)
Annual outpatient visits	7.8 (6.8)	28.6 (19.4)	159.4 (28.8)	9.6 (10.5)
- Dialysis	0	15.2 (18.5)	152.2 (27.4)	0.1 (0.7)
- Cardiovascular disease	0.3 (1.1)	0.3 (1.2)	0.3 (0.7)	0.2 (0.7)
- Malignancy	0.4 (2.0)	0.3 (1.2)	0.5 (3.3)	0.4 (2.6)
Prescription drug costs, €	2917 (3690)	7353 (6870)	8395 (4286)	6794 (5134)
- Erythropoietin stimulating agents (ESA)	957 (1805)	2913 (2510)	3911 (938)	268 (952)
- Antineoplastic and immunomodulating agents	189 (1105)	97 (449)	249 (973)	5137 (4115)
- Various	297 (1675)	1086 (1357)	1420 (1460)	23 (161)
- Cardiovascular system	434 (410)	399 (459)	285 (329)	371 (327)
- Antidepressant drugs	54 (330)	42 (179)	68 (171)	30 (177)
Fluids for peritoneal dialysis, €**	-	29,900	-	-

*For hemodialysis, costs related to Erythropoietin stimulating agents (ESA) were estimated from a smaller sample (n=85) of hemodialysis patients as ESA use in this patient group does not enter the Prescribed Drug Register as it is administrated in the hospital in conjunction with dialysis

**Based on a regional report of dialysis care in southern Sweden[31]

Table 3 Adjusted cost ratios* (95% CI) of annualized total costs between patients with chronic kidney disease (CKD) stages 4 or 5 not on dialysis, peritoneal dialysis, hemodialysis and transplanted patients, and their matched general population comparators

	CKD stages 4 or 5 (not on dialysis)	Peritoneal dialysis	Hemodialysis	Transplanted	General population
CKD 4 or 5	-	0.15 (0.14-0.17)	0.11 (0.10-0.11)	0.59 (0.52-0.66)	4.0 (3.6-4.5)
Peritoneal Dialysis	6.45 (5.81-7.17)	-	0.67 (0.62-0.73)	4.04 (3.58-4.56)	28.5 (21.8-37.4)
Hemodialysis	9.41 (8.74-10.1)	1.49 (1.38-1.60)	-	5.97 (5.49-6.50)	44.5 (38.5-51.4)
Transplanted	1.70 (1.51-1.92)	0.25 (0.22-0.28)	0.17 (0.15-0.18)	-	11.1 (9.7-12.7)

*Adjusted for age, sex and diabetes status

Figure 1 Distribution of annualized total costs in patients with chronic kidney disease (CKD) stages 4 or 5 (not on dialysis), peritoneal dialysis, hemodialysis and transplanted patients

Figure 2 Comorbidity status in patients with chronic kidney disease (CKD) stages 4 or 5 not on dialysis, peritoneal dialysis, hemodialysis and transplanted patients (bars), as well as in their matched general population comparators (black diamonds)

Comorbid conditions defined as having a visit in inpatient or outpatient care during the last 10 years with a main or contributory diagnosis of the respective ICD-codes used (specified in **eTable 1**);
CVD: Cardiovascular disease; MI: Myocardial infarction; COPD: Chronic obstructive pulmonary disease

Figure 3 Annualized mean and median costs in patients with chronic kidney disease (CKD) stages 4 or 5 not on dialysis, peritoneal dialysis, hemodialysis and transplanted patients, as well as mean total cost in matched general population comparators
(matched 5:1 by age, sex and index year)

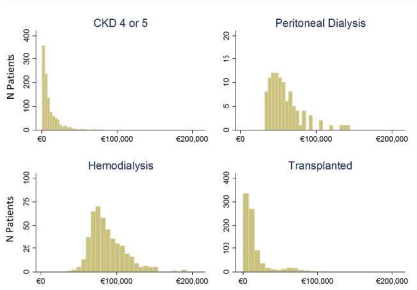

Figure 1 Distribution of annualized total costs in patients with chronic kidney disease (CKD) stages 4 or 5 (not on dialysis), peritoneal dialysis, hemodialysis and transplanted patients

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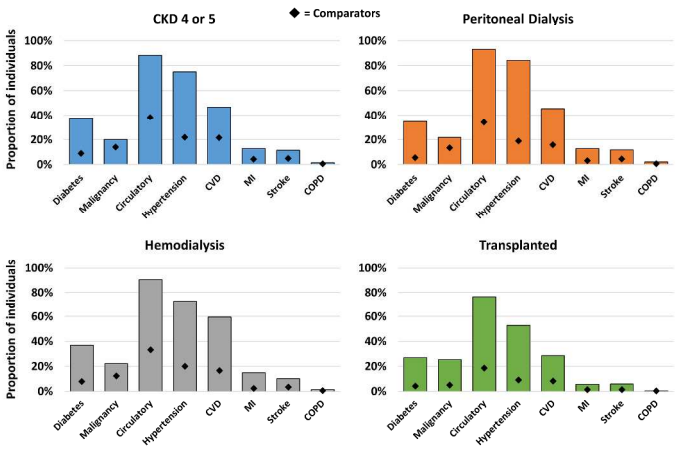

Figure 2 Comorbidity status in patients with chronic kidney disease (CKD) stages 4 or 5 not on dialysis, peritoneal dialysis, hemodialysis and transplanted patients (bars), as well as in their matched general population comparators (black diamonds)

Comorbid conditions defined as having a visit in inpatient or outpatient care during the last 10 years with a main or contributory diagnosis of the respective ICD-codes used (specified in eTable 1);
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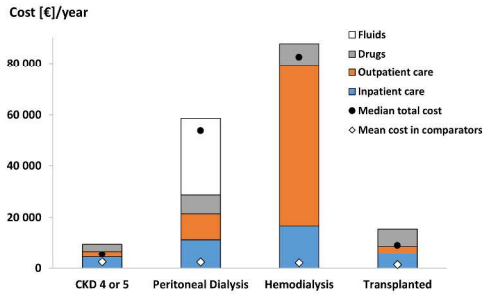

Figure 3 Annualized mean and median costs in patients with chronic kidney disease (CKD) stages 4 or 5 not on dialysis, peritoneal dialysis, hemodialysis and transplanted patients, as well as mean total cost in matched general population comparators
(matched 5:1 by age, sex and index year)

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Supplementary Web Appendix

Health Care Costs in Chronic Kidney Disease & Renal Replacement Therapy: A Population-Based Cohort Study

Jonas K Eriksson (PhD), Martin Neovius (senior researcher), Stefan H Jacobson (senior nephrologist, professor), Carl-Gustaf Elinder (senior nephrologist, professor) & Britta Hylander (senior nephrologist, associate professor)

eTable 1 International Classification of Diseases (ICD) codes for comorbidities[a] and Anatomic Therapeutic Chemical (ATC) codes for drug prescriptions

Group	Code
Comorbidities	**ICD-10 codes**
Diabetes	E10-E11
Malignancies	C00-C99
Circulatory	I00-I99
- Hypertension	I10-I15
- Cardiovascular Disease	I20-I51
- Myocardial Infarction	I21
- Stroke	I60-I64
Chronic Obstructive Pulmonary Disease	J41-J44
Uremia	N00-N19
Infection	A00-B99, G00-G02, G04.2, G05-G07, H66-H67, H70, J00-J22, J32, J34.0, J36, J38.3, J39.0-J39.1, K10.2, L00-L08, M00-M01, M46.2-M46.5, M86, N10, N30.0
Prescription drugs	**ATC codes**
Erythropoietin stimulating agents	B03XA
Antineoplastic and immunomodulating agents	Chapter L
Various	Chapter V
Cardiovascular system	Chapter C
Antidepressant drugs	N05A, N05B, N05C, N06A, N06B

[a] Comorbidities assessed from 10 years prior to January 1st, 2010, i.e. only ICD 10 codes used

eTable 2 Characteristics of matched general population comparators (matched by age, sex, and index year)[a]

	CKD Stages 4 or 5 (not on dialysis)	Peritoneal Dialysis	Hemodialysis	Transplanted
N	4 949	484	2153	3 872
Sex (% men)	3212 (65%)	251 (52%)	1265 (59%)	2391 (62%)
Age (Years)				
- Mean (SD)	68 (14)	64 (16)	64 (15)	52 (13)
- Median (25^{th}-75^{th})	71 (60-79)	67 (54-78)	67 (55-75)	53 (43-63)
n (%)				
- 18-49y	634 (13%)	95 (20%)	358 (17%)	1619 (42%)
- 50-59y	609 (12%)	78 (16%)	344 (16%)	1008 (26%)
- 60-69y	1165 (24%)	106 (22%)	611 (28%)	1026 (26%)
- ≥70y	2541 (51%)	205 (42%)	840 (39%)	219 (6%)
Education level[b]				
- Patients <75y	3121 (63%)	328 (68%)	1628 (76%)	3812 (98%)
- ≤9y	699 (22%)	54 (16%)	357 (22%)	713 (19%)
- 10-12y	1277 (41%)	150 (46%)	676 (42%)	1589 (42%)
- >12y	1094 (35%)	110 (34%)	562 (35%)	1455 (38%)
- Missing	51 (2%)	14 (4%)	33 (2%)	55 (1%)
- Patients ≥75y (no information)	1828 (37%)	156 (32%)	525 (24%)	60 (2%)
Start follow-up in 2009	1294 (26%)	200 (41%)	589 (27%)	279 (7%)
Follow-up days in 2009				
- Mean (SD)	321 (91)	285 (114)	318 (91)	352 (53)
- Median (25th-75th)	365 (351-365)	365 (203-365)	365 (336-365)	365 (365-365)
Comorbidity[c]				
- Diabetes	438 (9%)	27 (6%)	175 (8%)	164 (4%)
- Malignancies	698 (14%)	65 (13%)	270 (13%)	193 (5%)
- Circulatory disease	1898 (38%)	165 (34%)	723 (34%)	719 (19%)
- Hypertension	1089 (22%)	91 (19%)	438 (20%)	348 (9%)
- Cardiovascular disease	1063 (21%)	77 (16%)	365 (17%)	318 (8%)
- Myocardial Infarction[d]	211 (4%)	15 (3%)	53 (2%)	49 (1%)
- Stroke	237 (5%)	22 (5%)	76 (4%)	51 (1%)
- COPD[e]	34 (1%)	3 (1%)	11 (1%)	16 (0%)

[a] SD=standard deviation; 25^{th}-75^{th} = 25^{th} to 75^{th} percentile
[b] Education level only available in patients <75 years
[c] Comorbid conditions defined as having a visit in inpatient or outpatient care during the last 10 years with a main or contributory diagnosis of the respective ICD-codes used (specified in eTable 1)
[d] Myocardial infarction also included as a subgroup of cardiovascular disease
[e] Chronic obstructive pulmonary disease

eTable 3 Annualized mean (SD) costs in patients with chronic kidney disease (CKD) stages 4 or 5 not on dialysis, peritoneal dialysis, hemodialysis and transplanted

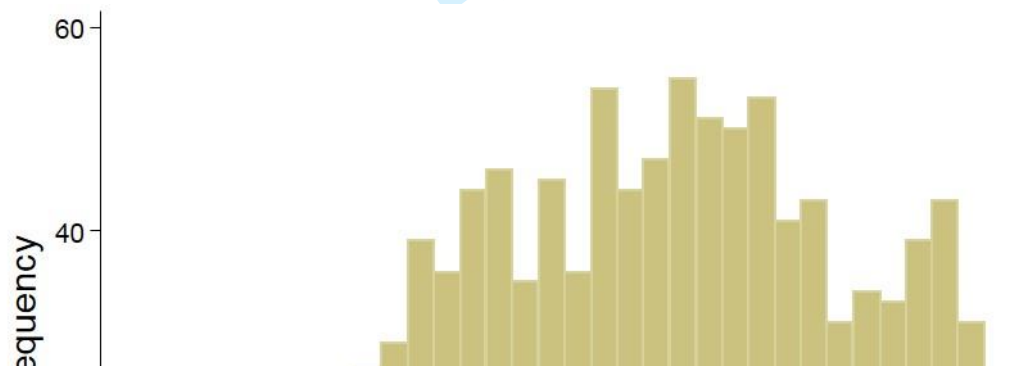
Costs	CKD Stages 4 or 5 not on dialysis (N=1046)	Peritoneal Dialysis (N=101)	Hemodialysis (N=460)	Transplanted (N=825)
Inpatient care	4338 (8404)	11 408 (15 079)	16 730 (18 674)	5889 (12 756)
- Cardiovascular disease	1770 (5422)	3702 (9990)	5508 (13 270)	879 (5191)
- Malignancy	403 (2641)	227 (1340)	396 (3145)	172 (1566)
- Infection	740 (3259)	1455 (4054)	3966 (9800)	1551 (8478)
Outpatient care	2326 (2093)	9987 (7304)	62 475 (11 542)	2834 (3180)
- Dialysis	10 (100)	5867 (7193)	60 357 (11 207)	25 (286)
- Cardiovascular disease	108 (526)	97 (363)	110 (475)	59 (285)
- Malignancy	120 (712)	98 (416)	119 (779)	100 (610)
Drugs	2917 (3690)	7353 (6870)	8395 (4286)	6794 (5134)
Fluids	0	29 900	0	0
Total	**9581 (10 828)**	**58 648 (22 027)**	**87 600 (22 339)**	**15 518 (18 608)**

eTable 4 Annualized mean (SD) costs in patients with chronic kidney disease (CKD) stages 4 or 5 not on dialysis, peritoneal dialysis, hemodialysis and transplanted **with treatment start before 2009**

Costs	CKD Stages 4 or 5 not on dialysis (N=786)	Peritoneal Dialysis (N=61)	Hemodialysis (N=340)	Transplanted (N=768)
Inpatient care	4383 (7962)	7946 (10159)	12 796 (14 363)	3251 (7196)
- Cardiovascular disease	1737 (5171)	2576 (5821)	3902 (8251)	754 (3775)
- Malignancy	435 (2420)	291 (1593)	258 (1660)	185 (1622)
- Infection	709 (2615)	1681 (4694)	3410 (7639)	883 (2975)
Outpatient care	2166 (1950)	8296 (5942)	63 704 (11 507)	2175 (1895)
- Dialysis	12 (114)	4318 (5549)	61 662 (11 096)	3 (79)
- Cardiovascular disease	84 (268)	96 (240)	130 (536)	63 (295)
- Malignancy	115 (562)	96 (338)	145 (896)	107 (631)
Drugs	3042 (3726)	6623 (6630)	8439 (3597)	5934 (3394)
Fluids	0	29 900	0	0
Total	**9592 (10 474)**	**52 764 (15 997)**	**84 939 (20 559)**	**11 361 (9519)**

eTable 5 Annualized mean (SD) costs in patients with chronic kidney disease (CKD) stages 4 or 5 not on dialysis, peritoneal dialysis, hemodialysis and transplanted **with treatment start in 2009**

Costs	CKD Stages 4 or 5 not on dialysis (N=260)	Peritoneal Dialysis (N=40)	Hemodialysis (N=120)	Transplanted (N=57)
Inpatient care	4201 (9632)	16 688 (19 413)	27 875 (24 246)	41 441 (17 404)
- Cardiovascular disease	1871 (6130)	5418 (14 098)	10 060 (21 378)	2562 (14 083)
- Malignancy	306 (3222)	130 (825)	784 (5487)	0 (0)
- Infection	834 (4702)	1109 (2836)	5540 (14 172)	10 546 (29 119)
Outpatient care	2809 (2415)	12 565 (8438)	58 995 (10 959)	11 714 (3663)
- Dialysis	2 (27)	8229 (8708)	56 659 (10 724)	314 (1012)
- Cardiovascular disease	182 (945)	99 (500)	55 (219)	0 (0)
- Malignancy	137 (1045)	102 (518)	47 (221)	6 (45)
Drugs	2540 (3560)	8467 (7161)	8269 (5829)	18 370 (9136)
Fluids	0	29 900	0	0
Total	**9550 (11854)**	**67 620 (26 715)**	**95 139 (25 360)**	**71 525 (20 591)**



eFigure 1 Distribution of estimated glomerular filtration rate (GFR; ml/min/1.73m^2) in patients with chronic kidney disease stages 4 or 5 (n=1046)[f]

[f] Estimated using the MDRD formula

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5, 6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6, 7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	6, 7
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) Summarise follow-up time (eg, average and total amount)	8, Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	8, 9, Table 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8, 9
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10, 11, 12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Health Care Costs in Chronic Kidney Disease & Renal Replacement Therapy: A Population-Based Cohort Study in Sweden

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Health Care Costs in Chronic Kidney Disease & Renal Replacement Therapy: A Population-Based Cohort Study in Sweden

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Figures:	3
eTables:	5
eFigures:	1

Key words: chronic kidney disease, cost, dialysis, renal replacement therapy, transplantation

ABSTRACT

Objective: To compare health care costs in chronic kidney disease (CKD) stages 4 or 5 not on dialysis (estimated glomerular filtration rate <30 ml/min/1.73m^2), peritoneal dialysis, hemodialysis, and in transplanted patients with matched general population comparators.

Design: Population-based cohort study.

Setting: Swedish national health care system.

Participants: Prevalent adult patients with CKD 4 or 5 (n=1046, mean age 68y), on peritoneal dialysis (n=101; 64y), on hemodialysis (n=460; 65y), and with renal transplants (n=825; 52y) were identified in Stockholm County clinical quality registers for renal disease on January 1st, 2010. Five general population comparators from the same county were matched to each patient by age, sex, and index year.

Primary and Secondary Outcome Measures: Annual health care costs in 2009 incurred through inpatient and hospital-based outpatient care and dispensed prescription drugs ascertained from nationwide health care registers. Secondary outcomes were annual number of hospital days and outpatient care visits.

Results: Patients on hemodialysis had the highest mean annual cost (€87,600), which was 1.49 (95%CI 1.38-1.60) times that observed in peritoneal dialysis (€58,600). The mean annual cost was considerably lower in transplanted patients (€15,500) and in the CKD group (€9600). In hemodialysis patients, outpatient care costs made up more than two-thirds (€62,500) of the total, while costs related to fluids ($29,900) was the largest cost component in peritoneal dialysis patients (51%). Compared to their matched general population comparators, the mean annual cost (95%CI) in hemodialysis, peritoneal dialysis, transplanted, and CKD patients was 45 (39-51), 29 (22-37), 11 (10-13), and 4.0 (3.6-4.5) times higher, respectively.

Conclusion: Mean annual costs were approximately 50% higher in hemodialysis than peritoneal dialysis patients. Compared to the general population, costs were substantially elevated in all groups, from 4-fold in CKD patients to 11, 29 and 45 times higher in transplanted patients, patients on peritoneal dialysis and hemodialysis, respectively.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- In this population-based study data were collected from routine clinical care to which there is universal access in Sweden
- By linking nationwide health care registers using the personal identity number, follow-up on an individual level was virtually complete regarding hospital days, hospital-based outpatient care and dispensed prescription drugs
- Costs related to in-hospital use of erythropoietin stimulating agents (ESA) for patients on hemodialysis were assessed using records from a smaller patient sample
- Costs related to fluids for patients on peritoneal dialysis were assessed using aggregated data, since these costs were not collected on an individual level in registers
- Although the proportion of undiagnosed individuals with CKD stage 4 or 5 have decreased with time, this group is still underdiagnosed and an unknown number of these patients were missed

INTRODUCTION

Chronic kidney disease (CKD) and end-stage renal disease are associated with substantial health care resource use and considerably higher mortality.[1 2] Although some reports suggest a decline in the incidence of CKD,[3] demographic changes together with increasing type 2 diabetes are likely to result in a higher prevalence of CKD.[4] To evaluate the value of therapeutic interventions in this patient group, an assessment of the economic burden related to CKD and end-stage renal disease is necessary, as is an available benchmark in terms of the corresponding costs in the general population.

Several studies have investigated the burden or costs in patients with different stages of CKD and renal replacement therapy, using different methods and in different settings.[5-7] The majority of cost studies from Europe and North America of patients on dialysis have reported higher health care costs of hemodialysis ranging from 1.0-1.9 times the cost in peritoneal dialysis.[5] Similarly, previous studies have reported increasing health care use and costs with higher CKD stages,[8-11] and estimates in patients with CKD that are 2-3 times the cost as compared to controls without CKD.[9 11] Recent studies from Europe, North America and Australia on the burden of CKD and renal replacement therapy with reported annual per patient cost have typically been based on small study samples or by using a modeling approach collecting data from published aggregated estimates.[12-21] Only a few studies have used individual data from larger study samples.[8-10]

To the best of our knowledge no study has from the same study population and on an individual level described health care use and costs in CKD stages 4 or 5 not on dialysis, hemodialysis, peritoneal dialysis, and transplanted patients separately, and compared the result to costs in the general population.

The aim of this population-based cohort study was to examine annual costs assessed from Swedish nationwide health care registers related to hospital days, outpatient care visits, and prescription of drugs in prevalent CKD stages 4 or 5 not on dialysis, peritoneal dialysis, hemodialysis, and transplanted patients, and to put these costs in relation to matched general population comparators.

METHODS

In this population-based cohort study we identified patients on CKD stages 4 or 5 not on dialysis, patients on dialysis and transplanted patients from clinical quality of care registers in Stockholm County and added data from national health registers. By using the personal identity number, a unique number assigned to all Swedish residents,[22] we enriched these data with inpatient and hospital-based outpatient care from the National Patient Register as well as data on dispensed drugs from the Prescribed Drug Register kept by the National Board of Health and Welfare.

Ethical approval was granted by the regional ethics committee at Karolinska Institutet, Stockholm, Sweden.

Chronic Kidney Disease and the Swedish National Health Service

Sweden had a population of 7.4 million ≥18 years on December 31, 2009 (www.scb.se), and comprised 21 counties. Stockholm County was the biggest with 1.6 million inhabitants ≥18 years, accounting for 22% of the population. The Swedish health care system was tax funded and offered universal access, while prescription drugs were provided free of charge above a threshold of around €200 annually.

Patients with renal replacement therapy were treated by nephrologists in inpatient and outpatient facilities,[23] rather than by general practitioners, while care for CKD patients was a mix of mainly hospital-based outpatient care, and to some extent primary care. The decision to initiate renal replacement therapy was made by nephrologists from clinical evaluations based on the Swedish guidelines[24] originating from the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) guidelines[25] and the corresponding European guidelines.[26]

Identification of Patients in Quality Register Sources

CKD Patients: From the Stockholm County CKD Register we identified adult prevalent CKD patients in stages 4 or 5 who were not on dialysis, on January 1st, 2010, registered at Karolinska and Danderyd University Hospital in the outpatient setting. This does not include all CKD stages 4 and 5 patients in the county, as some may get care elsewhere and some remain undetected. Furthermore, patients in CKD stages 1-3B were generally not registered and were for this reason not included in the study. Stages 4 and 5 were defined as an eGFR of 15-29.9 and <15, respectively. GFR was estimated using the abbreviated Modification of Diet in Renal Disease equation (MDRD; ml/min/1.73m^2) using serum creatinine levels.[27] Individuals with missing eGFR at baseline were excluded from CKD analyses (n=5). Data on albuminuria were incomplete and therefore no analyses by albuminuria status were performed.

Renal Replacement Therapy Patients: Prevalent patients on hospital-based dialysis or with a kidney transplant on January 1st, 2010, were identified in the Swedish Register of Renal Replacement Therapy, which includes all adult patients on renal replacement therapy in Stockholm County.[28 29]

General Population Comparators from the Register of the Total Population

From the Register of the Total Population held by Statistics Sweden, up to five general population comparators from the Stockholm County were sampled and matched on age, sex and index year to each patient (exact matching). The matched comparators received the same index date as their corresponding patient. Data on emigration and highest attained education were also retrieved from the Register of the Total Population.

The National Patient Register

Data on inpatient and hospital-based outpatient care were retrieved from the Swedish National Patient Register in 2009. This register contains the personal identity number, visit/admission date (and discharge date for the inpatient component), diagnostic related group (DRG) associated with the visit, and main as well as contributory diagnoses coded according to the International Classification of Diseases version 10 (ICD-10).[30] Comorbid conditions were defined as having a visit in inpatient or outpatient care during the last 10 years with a main or contributory diagnosis of the respective ICD-codes used (**eTable 1)**.

Hospital days and outpatient visits were converted into costs using the DRG coding system, where clinically similar hospitalizations or outpatient visits are grouped together. The price per DRG is fixed for a specific year, and is a weighted average for all the health care delivered in that group and year. In 2009 the inpatient and outpatient component of the National Patient Register included around 580 and 400 DRG groups, respectively.

The Prescribed Drug Register

From the Prescribed Drug Register we collected data on dispensed prescriptions in ambulatory care in 2009. Data on in-hospital drug use are not recorded on a patient level in the Prescribed Drug Register. Among other variables the register includes the personal identity number, date of prescription and dispensation, costs (total cost, patient cost, reimbursed cost), dosage, route of administration, and name as well as the of Anatomic Therapeutic Chemical (ATC) code of the drug.

Outcome and follow-up

The main outcome was annual health care costs incurred through inpatient and outpatient care, as well as dispensed prescription drugs. Secondary outcomes were annual number of hospital days and outpatient visits. Costs were assessed during 2009 and converted to euros (€1=SEK9.54 Swedish kronor in 2010). Patients were followed in the same health state as when they were identified in January 1st, 2010, with estimated annualized costs in those patients who did not have 1 year of follow-up.

Annualized Costs: Health care use and costs in patients who were not in CKD stages 4 or 5, on dialysis, or did not yet have a kidney transplant on January 1st, 2009, and hence were not followed the complete year of 2009 (all patients were identified on January 1st, 2010), were annualized from the time of entry into the respective health states. To have enough data available for each patient, we restricted the study population to patients with at least 1 month of follow-up, i.e. patients who were exposed on or before December 1st, 2009. For example, if a patient started hemodialysis on July 1st, 2009, we doubled that patient's health care use and costs to achieve an annualized estimate. For transplanted patients who received a kidney transplant in 2009, the cost for the kidney transplant procedure were included. However, costs related to the transplantation procedure were not annualized.

Costs Related to Hemodialysis Visits: As a data quality control, patients on hemodialysis that had less than 2 registered dialysis visits per week (n=135) in the National Patient Register were scrutinized using the patient registration database at the clinic. In most of these patients, visits that were found in the clinical database and that for some reason were not registered in the National Patient Register, were added. In total of 88 (65%) of the scrutinized patients on hemodialysis we added information from the registration database at the clinic. For a few patients (n=17) with unreasonable few registered hemodialysis visits in the clinical database, visits were imputed. For patients having

missing visit data for time periods ≥3 months and where extrapolation was not possible due to few visits (n=14) the number of visits were imputed with 156 hemodialysis visits per year (3 visits/week). In three patients with missing data for time periods <3 months (n=3), number of visits per week were extrapolated over time for these short time periods.

Costs Related to Erythropoietin stimulating agents (ESA) in Hemodialysis and Fluids in Peritoneal Dialysis: As the Prescribed Drug Register does not include in-hospital use of drugs, the cost for ESA is underestimated in hemodialysis patients when using this data source. We retrieved data on ESA use in a sub-sample of hemodialysis patients (n=85) and calculated the cost using 2009 drug prices in Sweden (http//:www.tlv.se). In this sub-sample the annual cost per patient related to ESA was estimated to €3911, which we applied to all hemodialysis patients. Further, the cost of fluids for peritoneal dialysis is also not covered by the Prescribed Drug Register. This cost has previously been estimated to SEK 200,000-370,000 (€21,000-€38,800) per patient and year.[31] We used the mid-value (€29,900) in this range and applied it on all patients on peritoneal dialysis.

Statistical Analysis

Cost distributions were non-normal in patients with CKD stages 4 or 5, patients on peritoneal dialysis, and transplanted patients, but approached a normal distribution in patients on hemodialysis (**Figure 1**). As the arithmetic mean has been described to be the most informative measure for cost and resource use data,[32] we report the mean annual cost (complemented by the median for descriptive purposes). Mean annual cost ratios, when comparing costs in CKD stages 4 or 5, peritoneal dialysis, hemodialysis and transplanted patients, or when comparing patients vs their matched general population comparators, were adjusted for age, sex, and diabetes status using a generalized linear regression model with negative binomial distribution, and 95% confidence intervals were estimated using robust standard errors. In sensitivity analysis we fitted a generalized linear model with log-gamma distribution, as well as in addition to age, sex and diabetes status adjusted for malignancy, circulatory disease, hypertension, cardiovascular disease, myocardial infarction, stroke, and chronic obstructive pulmonary disease (eTable 1).

Statistical analyses were performed using SAS (version 9.3).

RESULTS

A total of 2432 prevalent patients who were alive on January 1st, 2010, were included (**Table 1**). CKD stages 4 or 5 patients (n=1046) were on average 68 years old, while dialysis patients (n=101 on peritoneal dialysis; n=460 on hemodialysis) were younger (64y and 65y, respectively), and transplanted patients (n=825) much younger (52 years). All groups were predominantly male, and the education level was broadly similar to that in the general population (Table 1, **eTable 2**). The vast majority of transplanted patients had complete follow-up through 2009 (93%), while one quarter of the CKD stage 4 or 5 and hemodialysis patients did not have the full year of follow-up, and 40% of the patients in the peritoneal dialysis group were also followed for less than one year (Table 1).

Regarding selected register-identified comorbidities, approximately 90% of the patients had circulatory disease history, with about 15% having had a myocardial infarction and 10% a stroke (except transplanted patients; **Figure 2**). The CKD stages 4 or 5 and dialysis patients were similar, with the exception of a higher prevalence of cardiovascular disease in the hemodialysis patient group. The younger transplanted patients displayed lower prevalence, as compared to the CKD and dialysis patients, for most of the selected comorbidities, but a higher occurrence of malignancies. All groups had similar prevalence of chronic obstructive pulmonary disease as the general population comparators, but displayed higher or much higher prevalence in the other selected comorbidities, including diabetes where more than 30% of patients (except the transplanted group) had diabetes, compared to 6-9% in the matched general population (eTable 2).

Total Costs

The highest mean annual cost was observed in the hemodialysis group with €87,600, out of which 71% were accounted for by outpatient care costs (€62,500; **Figure 3**; **eTable 3**). Of the total outpatient care cost, 97% (€60,400) were costs for visits listing dialysis.

Patients on peritoneal dialysis incurred a mean annual cost of €58,600 which was about two thirds of the cost compared to hemodialysis patients (adjusted ratio [hemodialysis vs peritoneal dialysis] 1.49, 95% CI 1.38-1.60; **Table 3**). The largest cost component in the peritoneal dialysis group was costs related to fluids (€29,900; 51% of total cost), while costs related to inpatient and outpatient care were similar (€11,400 and €10,000, respectively).

In contrast, transplanted patients was the only group where dispensed prescription drugs made up the largest cost component (€6800; 44% of total cost), while the mean annual cost in this group of €15,500 was a fourth of the estimated cost in peritoneal dialysis patients (adjusted ratio [peritoneal dialysis vs transplanted] 4.04, 95% CI 3.58-4.56; Table 3).

Patients in CKD stages 4 or 5 displayed the lowest mean annual costs at €9600, where 45% (€4300) was accounted for by inpatient care. The adjusted mean annual cost ratio for transplanted vs CKD stages 4 or 5 was 1.70 (95% CI 1.51-1.92; Table 3). This difference was primarily explained by greater use of immunosuppressive drugs but also partly due to more expensive inpatient care among transplanted patients (**Table 2**, Figure 3).

In a stratified analysis on treatment start before or during 2009, similar total cost estimates, as compared to the overall patient group, were observed in patients in CKD stages 4 or 5, hemodialysis and peritoneal dialysis, while transplanted patients who received a kidney transplant in 2009 had considerably higher costs (**eTable 4 & 5**).

In sensitivity analysis, where we in addition to age, sex, and diabetes status adjusted for malignancy, circulatory disease, hypertension, cardiovascular disease, myocardial infarction, stroke, and chronic obstructive pulmonary disease, similar mean annual cost ratio estimates as compared to the main analysis were observed. Likewise, when we fitted a generalized linear model with log-gamma distribution, instead of using a negative binomial distribution, the estimates were similar between the models.

Drug Costs

Prescription Drug Costs: The mean annual cost of dispensed prescription drugs was €7400 in the peritoneal dialysis group, €6800 in transplanted patients, €8400 (of which €3911 on ESA) in hemodialysis patients, and €2900 in the CKD 4 or 5 group (Table 2, Figure 3).

Costs related to Fluids in Peritoneal Dialysis: Based on a regional report of dialysis care in southern Sweden, the annual cost of fluids in patients on peritoneal dialysis were estimated to €29,900.[31]

Health Care Use

Annual Hospital Days: Mean annual hospital days in patients on hemodialysis was 21.4, with the majority of hospital days listing a main or contributory diagnosis for cardiovascular disease (8.2 days) or infection (6.7 days; Table 2). Patients on peritoneal dialysis displayed lower overall mean hospital days (16.0), with 5.4 days and 2.6 days related to cardiovascular disease and infection, respectively. Transplanted patients and patients in CKD stages 4 or 5 had similar level of inpatient care use with 4.6 and 6.2 annual hospital days, respectively.

Outpatient Care: In hemodialysis patients, 152 out of a mean 159 annual visits were due to dialysis. The corresponding number in peritoneal dialysis patients was 29 visits per year with 15 visits listing dialysis. Again, transplanted patients and patients in CKD stages 4 or 5 had similar numbers with 10 and 8 visits, respectively.

Health Care Use and Costs Compared to the General Population

Mean annual health care use in the matched general population comparators to CKD stages 4 or 5, peritoneal dialysis, and hemodialysis patients were 0.2-0.3 hospital days, 1.8-2.2 outpatient visits, and €500-€600 in prescription drug costs, which resulted in a mean annual total cost of €2000-€2400 (Figure 3).

The corresponding health care use in general population comparators matched to the younger transplanted patients were 0.1 hospital days, 1.4 outpatient visits, and $400 in drug costs, resulting in a mean annual total cost of €1300.

Compared to their matched general population comparators, the mean annual cost in the hemodialysis group was 45 (95% CI 39-51) times higher, 29 (95% CI 22-37) times higher in the peritoneal dialysis group, 11 (95% CI 10-13) times higher in transplanted patients, and 4.0 (95% CI 3.6-4.5) times higher in patients with CKD stages 4 or 5 (Figure 3; Table 3).

DISCUSSION

Principal Findings

In this population-based cohort study we found that CKD stages 4 or 5 and renal replacement therapy are associated with substantial health care costs ranging from 4 to 45 times that expected in the general population. With 3.1 visits per week in outpatient care, patients on hemodialysis had the highest health care costs (€87,600) with dialysis care making up more than two thirds of the total cost. The total health care cost in hemodialysis was about 50% higher than in peritoneal dialysis patients, where similar costs of inpatient and outpatient care were observed, while cost of fluids was a major cost driver in peritoneal dialysis (€29,900). The mean annual costs in transplanted patients was €15,500, where prescription drugs constituted almost 50%, and in CKD stages 4 or 5 €9600, with inpatient care making up almost half of the total cost.

Strengths and limitations

Strengths of this study include the population-based data collected from routine clinical care in the Swedish health care system where registered individuals in Sweden have universal access. No comorbidity-based inclusion restrictions were used. Instead, we reported comorbidity status among included patients, as well as prescription drug costs in drug groups, and costs of hospital admissions and outpatient visits for specific diagnoses (e.g. cardiovascular disease). Furthermore, using individual level data from several nationwide registers, linked together by using the personal identity number, follow-up was virtually complete regarding outcome data for hospital days, hospital-based outpatient visits and prescription drug cost, as well as data on comorbidities, death and migration. Available registers enabled analysis of health care use in CKD stages 4 or 5, as well as in hemodialysis, peritoneal dialysis, and transplanted patients during the same year and at the same hospitals using the same data sources. Finally, we had the possibility to match comparators from the general population to each patient as a benchmark for health care resource utilization.

One limitation was that not all health care cost components were included in the available register sources. Fluids used for patients on peritoneal dialysis were not included in the Prescribed Drug Register, and these costs were therefore assessed using aggregated data.[31] Similarly, costs related to ESA for patients on hemodialysis is usually administered in the hospital, resulting in individual level data for ESA not being recorded in the Prescribed Drug Register. Using a smaller sample of patients on hemodialysis we could assess the costs related to ESA and apply this estimate to all hemodialysis patients in the study. Applying these aggregated costs to all patients on peritoneal dialysis (fluids) and hemodialysis (ESA) will most likely result in smaller variation and overestimated precision of the cost estimates than would have been observed in data including these cost components. Other costs not included were costs related to primary care and certain laboratory services, probably leading to an underestimation of the actual cost. Furthermore, patients on hemodialysis with few registered dialysis visits were scrutinized using the patient registration databases at the clinics. While a few patients for some reason had apparent missing data on dialysis visits also in this system, we imputed data with the mean. However, we cannot know whether hemodialysis visits were missing in the patients who were not scrutinized, which may result in an underestimation of the true hemodialysis cost.

Although all renal replacement therapy patients in Stockholm County were included, and the proportion of individuals with undiagnosed CKD stages 4 or 5 may have decreased with time, some patients are identified at start of dialysis, or die before identification. An unknown number of these

individuals were missed, and our results should only be generalized to CKD stages 4 or 5 patients in nephrology care. Finally, an important underlying assumption with the methodology used in this study, where a mix of patients with short and long treatment duration were included, the proportion of patients starting their treatment have to be constant over time, in this case by calendar year. This assumption is particularly important in transplanted patients who have a high initial cost with the kidney transplant procedure.

Previous Research

A recent study from the UK (costs in £UK2011) recruited 7246 patients with CKD or patients who were receiving dialysis in Europe, North America and Australasia, and hospital admissions were recorded every 6 month at clinic visits.[8] They reported a mean hospital cost (drug cost not included) in patients with CKD 4 to £3700, £12,952 in CKD 5, and £20,511 in patients on dialysis. Excluding drug costs, our estimates of €6700 in CKD stages 4 or 5 and €21,400 in patients on peritoneal dialysis are in line with the UK study. Although the majority of patients in their dialysis group were patients on hemodialysis (83%) our cost estimates are higher when combining the hemodialysis and peritoneal dialysis groups (€68,800), mainly due to different methodologies for collecting costs related to dialysis sessions in outpatient care. In our study, we used prospectively recorded visit data from outpatient care, or annualized estimates for those who did not have a full year of follow-up, while they assumed thrice weekly hemodialysis sessions using £25,000 as a per patient annual cost. Our estimated 2.9 dialysis outpatient visits per week (and additional dialysis sessions in inpatient care for some patients), resulted in substantially higher annual cost of dialysis delivered in the outpatient setting (€60,400), indicating challenges when comparing study results between different health care settings.

Cost ratios of hemodialysis and peritoneal dialysis have recently been reported in a comprehensive review including 78 publications from 46 countries.[5] Based on 37 studies between 1998 to 2011 from Europe, the authors conclude that hemodialysis is 30-60% more expensive than peritoneal dialysis, while the cost ratio based on 5 studies from the US from 2005-2012 was estimated to 1.29, results that are less than our estimated ratio (adjusted cost ratio 1.49 [95% CI 1.38-1.60]).

Recent estimates (2010) from the US have reported a mean annual health care cost of US$12,386 in patients in CKD 4 (n=413) and US$23,445 in patients in CKD 5 (n=138) using health insurance claims data.[10] These estimates are higher than our result in the CKD 4 or 5 group (€9600). Although both studies used the same eGFR intervals when defining CKD stage 4 and CKD stage 5, our result was more similar to their estimated mean annual cost in patients in CKD 3 (US$10,100). The differences appeared to be driven by 2-3 times higher cost of outpatient care in CKD stages 4 and 5 and 3 times higher cost of inpatient care in patients in CKD 5 in their study, while our drug cost estimates were higher.

Another study from the US from 2004 reported a mean annual cost in patients in CKD stage 4 (n=777) to US$7600, which was 2.6 times the cost as compared to age and sex matched controls without CKD, results that are in line with our estimates when restricting the CKD 4 or 5 group to CKD stage 4 only (€8500 and 3.5 times the cost in comparators).

With respect to previous cost estimates from Sweden, a regional study from 2002, based on questionnaires in 136 patients, estimated the per patient mean annual cost related to peritoneal dialysis to US$34,600 and in hemodialysis to US$36,220 during the first 5 years after initiating treatment.[18] When taking inflation into account, our estimates are substantially higher, which may

partly be explained by increased costs due to technology development of medical equipment (their estimates were based on data from 1990-1993), and by more complete follow-up when using register data. However, when comparing our adjusted mean annual cost ratio of hemodialysis and peritoneal dialysis the results are similar.

Implications

With the lower cost in CKD stages 4 or 5 as compared to dialysis, our result highlight the importance of good secondary prevention of patients in CKD stages 4 or 5 to postpone or even prevent the progression to end stage renal disease, a strategy that may generate significant savings, while also reducing the risk of mortality among these patients.[2]

Conclusion

The annual health care costs in patients in CKD stages 4 or 5, dialysis or transplanted patients are substantial. Patients on hemodialysis incurred the highest cost, 45 times as compared to general population, and 50% higher than patients on peritoneal dialysis. Transplanted patients and patients in CKD stages 4 or 5 incurred lower but considerable costs with 11 and 4 times the cost in the general population, respectively. More attention to secondary prevention in CKD stages 4 or 5 may generate savings by reducing time and number of patients on dialysis.

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Competing interest statement

JE declares that the answer to the questions on your competing interest form (http://resources.bmj.com/bmj/authors/checklists-forms/competing-interests) are all No and therefore has nothing to declare. MN has received payment for a lecture from Baxter. CGE and BH have received a grant to their academic institution from Baxter to support the work with this publication. SHJ has acted on an advisory board for Baxter, and received lecture payments at scientific meetings.

Details of contributors

BH, CGE, JE and MN conceived the study hypothesis. JE conducted the statistical analyses. JE wrote the first draft of the manuscript. BH, CGE, JE, MN and SHJ critically reviewed and contributed to the final draft. All authors are guarantors.

Additional Contributions

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Ethical approval

Ethical approval was granted by the regional ethics committee at Karolinska Institutet, Stockholm, Sweden (DNR: 2009/1225-31/5).

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Statement of independence of researchers from funders

BH, SHJ and CGE are employed by Stockholm County Council. No person representing Baxter read or commented on any version of the manuscript.

Data sharing statement

Data sharing: No additional data available

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Table 1 Participant characteristics[a]

	CKD Stages 4 or 5 (not on dialysis)	Peritoneal dialysis	Hemo-dialysis	Trans-planted
N	1046	101	460	825
Sex (% men)	683 (65%)	53 (52%)	271 (59%)	513 (62%)
eGFR[b], Mean (SD)	18 (6)	-	-	-
- <15	338 (32%)	-	-	-
- 15-29.9	708 (68%)	-	-	-
Time since transplantation (years)				
- Mean (SD)	-	-	-	9.1 (7.5)
- Median (25th-75th)	-	-	-	7.1 (3.3-12.8)
Age (years)				
- Mean (SD)	68 (14)	64 (16)	65 (15)	52 (14)
- Median (25^{th}-75^{th})	71 (60-79)	68 (54-78)	68 (55-75)	54 (43-63)
n (%)				
- 18-49y	130 (12%)	19 (19%)	76 (17%)	336 (41%)
- 50-59y	126 (12%)	16 (16%)	71 (15%)	212 (26%)
- 60-69y	232 (22%)	22 (22%)	125 (27%)	224 (27%)
- ≥70y	558 (53%)	44 (44%)	188 (41%)	53 (6%)
Education level[c]				
- Patients <75y	636 (61%)	66 (65%)	343 (75%)	808 (98%)
- ≤9y	172 (27%)	14 (21%)	115 (34%)	173 (21%)
- 10-12y	260 (41%)	31 (47%)	137 (40%)	347 (43%)
- >12y	193 (30%)	19 (29%)	69 (20%)	278 (34%)
- Missing	11 (2%)	2 (3%)	22 (6%)	10 (1%)
- Patients ≥75y (no information)	410 (39%)	35 (35%)	117 (25%)	17 (2%)
First registration in 2009	260 (25%)	40 (40%)	120 (26%)	57 (7%)
Follow-up days in 2009				
- Mean (SD)	323 (89)	288 (113)	320 (90)	353 (52)
- Median (25th-75^{th} percentile)	365 (365-365)	365 (217-365)	365 (352-365)	365 (365-365)

[a] SD=standard deviation; 25^{th}-75^{th} = 25^{th} to 75^{th} percentile

[b] Most recent recorded eGFR in relation to January 1, 2010. Full distribution shown in **eFigure 1**.

[c] Education level only available in patients <75 years

Table 2 Mean (SD) annualized hospital admission, outpatient visits, and dispensed prescription drug costs (ICD and ATC codes are specified in eTable 1)

	CKD Stages 4 or 5 (not on dialysis)	Peritoneal dialysis	Hemo-dialysis	Trans-planted
Annual admissions	1.0 (1.9)	2.6 (3.3)	3.6 (3.8)	0.9 (1.7)
Annual hospital days	6.2 (16.4)	16.0 (25.1)	21.4 (40.6)	4.6 (11.5)
- Cardiovascular disease	2.3 (8.3)	5.4 (15.1)	8.2 (29.1)	0.7 (3.7)
- Malignancy	0.5 (3.8)	0.3 (2.2)	0.7 (7.1)	0.2 (2.9)
- Infection	1.1 (5.2)	2.6 (7.5)	6.7 (21.6)	1.5 (6.6)
Annual outpatient visits	7.8 (6.8)	28.6 (19.4)	159.4 (28.8)	9.6 (10.5)
- Dialysis	0	15.2 (18.5)	152.2 (27.4)	0.1 (0.7)
- Cardiovascular disease	0.3 (1.1)	0.3 (1.2)	0.3 (0.7)	0.2 (0.7)
- Malignancy	0.4 (2.0)	0.3 (1.2)	0.5 (3.3)	0.4 (2.6)
Prescription drug costs, €	2917 (3690)	7353 (6870)	8395 (4286)	6794 (5134)
- Erythropoietin stimulating agents (ESA)	957 (1805)	2913 (2510)	3911 (938)	268 (952)
- Antineoplastic and immunomodulating agents	189 (1105)	97 (449)	249 (973)	5137 (4115)
- Various	297 (1675)	1086 (1357)	1420 (1460)	23 (161)
- Cardiovascular system	434 (410)	399 (459)	285 (329)	371 (327)
- Antidepressant drugs	54 (330)	42 (179)	68 (171)	30 (177)
Fluids for peritoneal dialysis, €**	-	29,900	-	-

*For hemodialysis, costs related to Erythropoietin stimulating agents (ESA) were estimated from a smaller sample (n=85) of hemodialysis patients as ESA use in this patient group does not enter the Prescribed Drug Register as it is administrated in the hospital in conjunction with dialysis

**Based on a regional report of dialysis care in southern Sweden[31]

Table 3 Adjusted cost ratios* (95% CI) of annualized total costs between patients with chronic kidney disease (CKD) stages 4 or 5 not on dialysis, peritoneal dialysis, hemodialysis and transplanted patients, and their matched general population comparators

	CKD stages 4 or 5 (not on dialysis)	Peritoneal dialysis	Hemodialysis	Transplanted	General population
CKD 4 or 5	-	0.15 (0.14-0.17)	0.11 (0.10-0.11)	0.59 (0.52-0.66)	4.0 (3.6-4.5)
Peritoneal Dialysis	6.45 (5.81-7.17)	-	0.67 (0.62-0.73)	4.04 (3.58-4.56)	28.5 (21.8-37.4)
Hemodialysis	9.41 (8.74-10.1)	1.49 (1.38-1.60)	-	5.97 (5.49-6.50)	44.5 (38.5-51.4)
Transplanted	1.70 (1.51-1.92)	0.25 (0.22-0.28)	0.17 (0.15-0.18)	-	11.1 (9.7-12.7)

*Adjusted for age, sex and diabetes status

Figure 1 Distribution of annualized total costs in patients with chronic kidney disease (CKD) stages 4 or 5 (not on dialysis), peritoneal dialysis, hemodialysis and transplanted patients

Figure 2 Comorbidity status in patients with chronic kidney disease (CKD) stages 4 or 5 not on dialysis, peritoneal dialysis, hemodialysis and transplanted patients (bars), as well as in their matched general population comparators (black diamonds)

Comorbid conditions defined as having a visit in inpatient or outpatient care during the last 10 years with a main or contributory diagnosis of the respective ICD-codes used (specified in **eTable 1**);
CVD: Cardiovascular disease; MI: Myocardial infarction; COPD: Chronic obstructive pulmonary disease

Figure 3 Annualized mean and median costs in patients with chronic kidney disease (CKD) stages 4 or 5 not on dialysis, peritoneal dialysis, hemodialysis and transplanted patients, as well as mean total cost in matched general population comparators
(matched 5:1 by age, sex and index year)

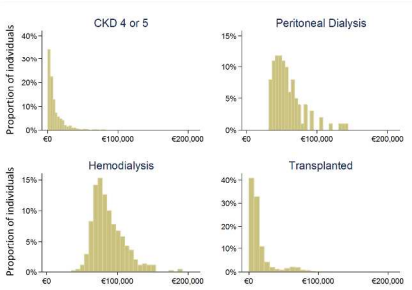

Figure 1 Distribution of annualized total costs in patients with chronic kidney disease (CKD) stages 4 or 5 (not on dialysis), peritoneal dialysis, hemodialysis and transplanted patients

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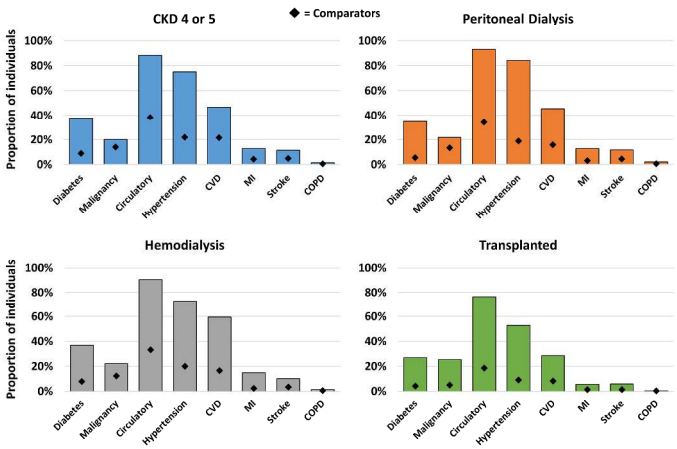

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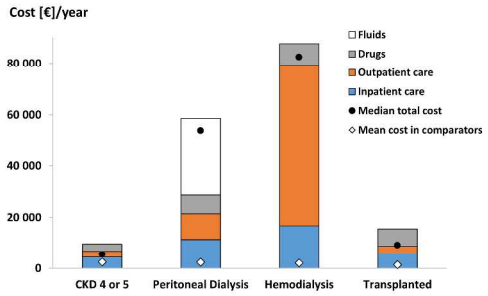

Figure 3 Annualized mean and median costs in patients with chronic kidney disease (CKD) stages 4 or 5 not on dialysis, peritoneal dialysis, hemodialysis and transplanted patients, as well as mean total cost in matched general population comparators
(matched 5:1 by age, sex and index year)

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Supplementary Web Appendix

Health Care Costs in Chronic Kidney Disease & Renal Replacement Therapy: A Population-Based Cohort Study

Jonas K Eriksson (PhD), Martin Neovius (senior researcher), Stefan H Jacobson (senior nephrologist, professor), Carl-Gustaf Elinder (senior nephrologist, professor) & Britta Hylander (senior nephrologist, associate professor)

eTable 1 International Classification of Diseases (ICD) codes for comorbidities[a] and Anatomic Therapeutic Chemical (ATC) codes for drug prescriptions

Group	Code
Comorbidities	**ICD-10 codes**
Diabetes	E10-E11
Malignancies	C00-C99
Circulatory	I00-I99
- Hypertension	I10-I15
- Cardiovascular Disease	I20-I51
- Myocardial Infarction	I21
- Stroke	I60-I64
Chronic Obstructive Pulmonary Disease	J41-J44
Uremia	N00-N19
Infection	A00-B99, G00-G02, G04.2, G05-G07, H66-H67, H70, J00-J22, J32, J34.0, J36, J38.3, J39.0-J39.1, K10.2, L00-L08, M00-M01, M46.2-M46.5, M86, N10, N30.0
Prescription drugs	**ATC codes**
Erythropoietin stimulating agents	B03XA
Antineoplastic and immunomodulating agents	Chapter L
Various	Chapter V
Cardiovascular system	Chapter C
Antidepressant drugs	N05A, N05B, N05C, N06A, N06B

[a] Comorbidities assessed from 10 years prior to January 1st, 2010, i.e. only ICD 10 codes used

eTable 2 Characteristics of matched general population comparators (matched by age, sex, and index year)[a]

	CKD Stages 4 or 5 (not on dialysis)	Peritoneal Dialysis	Hemodialysis	Transplanted
N	4 949	484	2153	3 872
Sex (% men)	3212 (65%)	251 (52%)	1265 (59%)	2391 (62%)
Age (Years)				
- Mean (SD)	68 (14)	64 (16)	64 (15)	52 (13)
- Median (25^{th}-75^{th})	71 (60-79)	67 (54-78)	67 (55-75)	53 (43-63)
n (%)				
- 18-49y	634 (13%)	95 (20%)	358 (17%)	1619 (42%)
- 50-59y	609 (12%)	78 (16%)	344 (16%)	1008 (26%)
- 60-69y	1165 (24%)	106 (22%)	611 (28%)	1026 (26%)
- ≥70y	2541 (51%)	205 (42%)	840 (39%)	219 (6%)
Education level[b]				
- Patients <75y	3121 (63%)	328 (68%)	1628 (76%)	3812 (98%)
- ≤9y	699 (22%)	54 (16%)	357 (22%)	713 (19%)
- 10-12y	1277 (41%)	150 (46%)	676 (42%)	1589 (42%)
- >12y	1094 (35%)	110 (34%)	562 (35%)	1455 (38%)
- Missing	51 (2%)	14 (4%)	33 (2%)	55 (1%)
- Patients ≥75y (no information)	1828 (37%)	156 (32%)	525 (24%)	60 (2%)
Start follow-up in 2009	1294 (26%)	200 (41%)	589 (27%)	279 (7%)
Follow-up days in 2009				
- Mean (SD)	321 (91)	285 (114)	318 (91)	352 (53)
- Median (25th-75th)	365 (351-365)	365 (203-365)	365 (336-365)	365 (365-365)
Comorbidity[c]				
- Diabetes	438 (9%)	27 (6%)	175 (8%)	164 (4%)
- Malignancies	698 (14%)	65 (13%)	270 (13%)	193 (5%)
- Circulatory disease	1898 (38%)	165 (34%)	723 (34%)	719 (19%)
- Hypertension	1089 (22%)	91 (19%)	438 (20%)	348 (9%)
- Cardiovascular disease	1063 (21%)	77 (16%)	365 (17%)	318 (8%)
- Myocardial Infarction[d]	211 (4%)	15 (3%)	53 (2%)	49 (1%)
- Stroke	237 (5%)	22 (5%)	76 (4%)	51 (1%)
- COPD[e]	34 (1%)	3 (1%)	11 (1%)	16 (0%)

[a] SD=standard deviation; 25^{th}-75^{th} = 25^{th} to 75^{th} percentile
[b] Education level only available in patients <75 years
[c] Comorbid conditions defined as having a visit in inpatient or outpatient care during the last 10 years with a main or contributory diagnosis of the respective ICD-codes used (specified in eTable 1)
[d] Myocardial infarction also included as a subgroup of cardiovascular disease
[e] Chronic obstructive pulmonary disease

eTable 3 Annualized mean (SD) costs in patients with chronic kidney disease (CKD) stages 4 or 5 not on dialysis, peritoneal dialysis, hemodialysis and transplanted

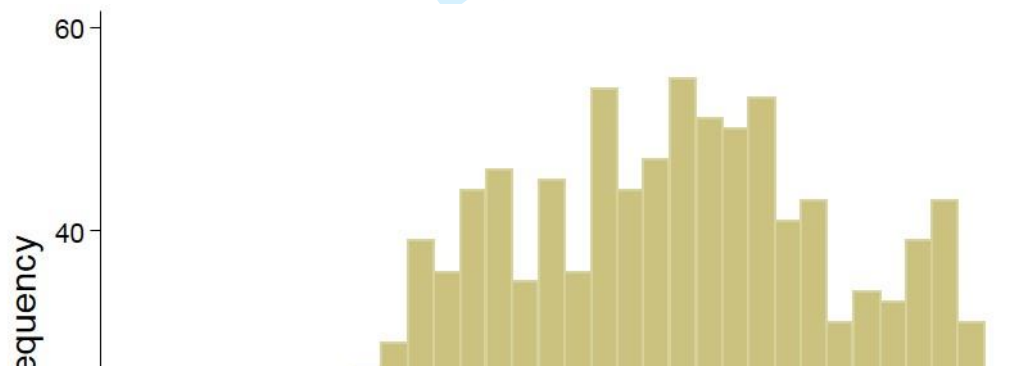
Costs	CKD Stages 4 or 5 not on dialysis (N=1046)	Peritoneal Dialysis (N=101)	Hemodialysis (N=460)	Transplanted (N=825)
Inpatient care	4338 (8404)	11 408 (15 079)	16 730 (18 674)	5889 (12 756)
- Cardiovascular disease	1770 (5422)	3702 (9990)	5508 (13 270)	879 (5191)
- Malignancy	403 (2641)	227 (1340)	396 (3145)	172 (1566)
- Infection	740 (3259)	1455 (4054)	3966 (9800)	1551 (8478)
Outpatient care	2326 (2093)	9987 (7304)	62 475 (11 542)	2834 (3180)
- Dialysis	10 (100)	5867 (7193)	60 357 (11 207)	25 (286)
- Cardiovascular disease	108 (526)	97 (363)	110 (475)	59 (285)
- Malignancy	120 (712)	98 (416)	119 (779)	100 (610)
Drugs	2917 (3690)	7353 (6870)	8395 (4286)	6794 (5134)
Fluids	0	29 900	0	0
Total	**9581 (10 828)**	**58 648 (22 027)**	**87 600 (22 339)**	**15 518 (18 608)**

eTable 4 Annualized mean (SD) costs in patients with chronic kidney disease (CKD) stages 4 or 5 not on dialysis, peritoneal dialysis, hemodialysis and transplanted **with treatment start before 2009**

Costs	CKD Stages 4 or 5 not on dialysis (N=786)	Peritoneal Dialysis (N=61)	Hemodialysis (N=340)	Transplanted (N=768)
Inpatient care	4383 (7962)	7946 (10159)	12 796 (14 363)	3251 (7196)
- Cardiovascular disease	1737 (5171)	2576 (5821)	3902 (8251)	754 (3775)
- Malignancy	435 (2420)	291 (1593)	258 (1660)	185 (1622)
- Infection	709 (2615)	1681 (4694)	3410 (7639)	883 (2975)
Outpatient care	2166 (1950)	8296 (5942)	63 704 (11 507)	2175 (1895)
- Dialysis	12 (114)	4318 (5549)	61 662 (11 096)	3 (79)
- Cardiovascular disease	84 (268)	96 (240)	130 (536)	63 (295)
- Malignancy	115 (562)	96 (338)	145 (896)	107 (631)
Drugs	3042 (3726)	6623 (6630)	8439 (3597)	5934 (3394)
Fluids	0	29 900	0	0
Total	**9592 (10 474)**	**52 764 (15 997)**	**84 939 (20 559)**	**11 361 (9519)**

eTable 5 Annualized mean (SD) costs in patients with chronic kidney disease (CKD) stages 4 or 5 not on dialysis, peritoneal dialysis, hemodialysis and transplanted **with treatment start in 2009**

Costs	CKD Stages 4 or 5 not on dialysis (N=260)	Peritoneal Dialysis (N=40)	Hemodialysis (N=120)	Transplanted (N=57)
Inpatient care	4201 (9632)	16 688 (19 413)	27 875 (24 246)	41 441 (17 404)
- Cardiovascular disease	1871 (6130)	5418 (14 098)	10 060 (21 378)	2562 (14 083)
- Malignancy	306 (3222)	130 (825)	784 (5487)	0 (0)
- Infection	834 (4702)	1109 (2836)	5540 (14 172)	10 546 (29 119)
Outpatient care	2809 (2415)	12 565 (8438)	58 995 (10 959)	11 714 (3663)
- Dialysis	2 (27)	8229 (8708)	56 659 (10 724)	314 (1012)
- Cardiovascular disease	182 (945)	99 (500)	55 (219)	0 (0)
- Malignancy	137 (1045)	102 (518)	47 (221)	6 (45)
Drugs	2540 (3560)	8467 (7161)	8269 (5829)	18 370 (9136)
Fluids	0	29 900	0	0
Total	**9550 (11854)**	**67 620 (26 715)**	**95 139 (25 360)**	**71 525 (20 591)**



eFigure 1 Distribution of estimated glomerular filtration rate (GFR; ml/min/1.73m^2) in patients with chronic kidney disease stages 4 or 5 (n=1046)[f]

[f] Estimated using the MDRD formula

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5, 6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6, 7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	6, 7
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) Summarise follow-up time (eg, average and total amount)	8, Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	8, 9, Table 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8, 9
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10, 11, 12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.