Can routinely collected hospital admission data be used to study temporal morbidity and mortality trends in maintenance renal replacement patients?

Analyses from the Oxford Record Linkage Study and all-England Hospital Episode Statistics, 1965-2011

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Intellectual Property and Publication Statements

"I confirm that the work submitted is my own, except where work which has formed part of jointly authored publications which has been included. My contribution and the other authors work has been explicitly indicated below. I confirm that appropriate credit has been given within the thesis where reference has been made to the work of others."

Jointly authored publications directly relevant to MD

Chapter 5 – Jointly published manuscript

Storey BC, Staplin N, Harper CH, et al. Declining comorbidity-adjusted mortality rates in English patients receiving maintenance renal replacement therapy. *Kidney Int.* 2018;93(5):1165-1174. **See Appendix section 1.2**

My contributions: This jointly published manuscript is the main published work from my MD thesis. I finalized the conception of the study; approached the curator of the datasets to gain his for his approval to use it; sourced and converted hard copies of historical diagnostic and procedural manuals into usable forms; interrogated these manuals and extracted relevant codes which could potentially identify an ESRD cohort. I identified all accompanying terms used to identify comorbid illness, primary renal diagnosis and categories of causes of death. I designed, iteratively tested and adapted the clinical algorithms used to identify the final end-stage renal disease patient cohort. I led, but worked alongside, statistical colleagues (NS, CS) to design the relevant mortality analyses, decided on what sensitivity analyses would be worthwhile and choose the final tables and figures in the manuscript. CH and NS were the lead statistical contributors who handled and processed the data. I fully drafted, revised and later finalized after contributions (WH, NS, CH, MJL, RH) from other before submission.

Chapter 6- Jointly published manuscript

Judge PK, Harper CHS, **Storey BC**, et al. Biliary Tract and Liver Complications in Polycystic Kidney Disease. *J Am Soc Nephrol.* 2017;28(9):2738-2748 **See Appendix section 1.3**

My contribution: I solely performed the direct validation work of patients primary renal diagnosis in 3C. I also designed (as above) the ESRD algorithm used in the main analyses. I was part of the clinical team (PJ, RH, WH and CGW) which decided which diseases we thought relevant to investigate and then I extracted the clinical codes in conjunction with PJ. I performed a literature research on the established disease associations of PKD which was relevant to the final manuscript. I helped draft, revise and finalise the final manuscript and was privy to all the decisions and work which led its core team (WH, PJ, NS, CH and BS) including deciding on the final illustrative materials. CH and NS were the lead statistical contributors who handled and processed the data.

Dedication

This work is dedicated to my immediate family [wife “Liz” and two daughters “Isobel” and “Jesca” who have always encouraged, and occasionally necessarily cajoled me to persevere and complete this project. The love and support I receive from “my girls” surpasses any work hereafter.

Acknowledgements/Contributions

“This body of work has been led by me within a small and dedicated team which has principally included Associate Professor William Herrington, (WH; Oxford supervisor), Dr. Natalie Staplin (NS; senior statistician), Charlie Harper (CH; medical statistician) being overseen by Professor Martin Landray (ML; Oxford supervisor) and Professor Chris Gale (CP; Leeds supervisor) with input from Associate Professor Richard Haynes (RH).

The thesis solely contains my own words and any errors I take full responsibility.

Contributions in more detail and by chapter, can be found at Chapter 8.3 at page 217.

Prologue to thesis/Abstract

Maintenance dialysis programmes for end-stage renal disease (ESRD) began in the United Kingdom in the 1960s.[1-3] Until the 1980s, renal replacement therapy (RRT, i.e., dialysis or kidney transplantation) was restricted to ESRD patients who were considered the most economically active and those with diabetes or other comorbidities were often not referred or treated.[4] This contrasts with the situation 50 years later when the median age of patients starting maintenance RRT is 65 years and diabetes is the leading cause of ESRD.[5]

Examining long-term temporal mortality trends helps describe past and current serious health risks. Their interpretation is difficult in RRT populations as comparisons between treated ESRD and other populations need to take account of the substantial secular changes in the prevalence of comorbid illnesses which influence both mortality[6-8] and the likelihood of receiving RRT. To date, no large study has standardized mortality rates in treated ESRD and general population cohorts to the same comorbidity as well as age/sex structure. Therefore, although data from ESRD registries in the United States 1977-2007,[9] Europe 1998-2007,[10] Australasia 1992-2005,[11] and UK 2002-2011[5] have all shown modest improvements in mortality for people with treated ESRD, it is unclear whether the magnitude of this change is comparable to those observed in the general population during the same period.[12]

The Oxford Record Linkage Study (ORLS) was established in 1963 and recorded information about all hospital inpatient admissions in Oxfordshire and the surrounding counties.[13] Hospital Episode Statistics (HES) succeeded ORLS and established nationwide coverage from 1998. Mortality trends among new maintenance RRT patients and a set of general population controls, extracted from these two datasets were performed. Novel approaches ensured that both cohorts could be corrected for changes in prior comorbidity over time and the effects of transplantation, and stratified analyses in patients with and without diabetes could be performed.

Key aims of thesis

1) **Derive and validate a cohort of end-stage renal disease (ESRD) patients exclusively from anonymised, individually-linked prospectively collected hospital inpatients datasets**

2) **Analyse the temporal trends of age, sex and comorbidity adjusted mortality rates in the ESRD cohort**

3) **Concurrently derive a comparative general population to provide an opportunity to compare trends between the ESRD and general populations**

4) **Demonstrate other uses of routinely collected hospital inpatients datasets in renal epidemiology**

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List of abbreviations

AKI	Acute kidney injury
ANZDATA	Australia and New Zealand Dialysis and Transplant Registry
AVF	Arterio-venous fistula
AVG	Arterio-venous graft
CI	Confidence interval
CKD	Chronic kidney disease
COPD	Chronic obstructive airways disease
CV	Cardiovascular
eGFR	Estimated glomerular filtration rate
ERA/EDTA	European Renal Association/European Dialysis and Transplant Association
ESRD	End stage renal disease
HD	Haemodialysis
HES	Hospital Episode Statistics
HSCIC	Health and Social Care Information Centre, now called NHS Digital
ICD	International Statistical Classification of Diseases and Related Health Problems
K/DOQI	Kidney Disease Outcomes Quality Initiative
KDIGO	Kidney Disease Improving Global Outcomes
NHS	National Health Service
NHSBT	National Health Service Blood and Transplant
OKU	Oxford Kidney Unit
ONS	Office of National Statistics
OPCS	Office of Population Censuses and Surveys Classification

	of Surgical Operations and Procedures
ORLS	Oxford Record Linkage Study
PD	Peritoneal dialysis
PRD	Primary renal disease
RR	Relative risk
RRT	Renal replacement therapy
UHCE	Unit of Healthcare Epidemiology
UK	United Kingdom
UK-RR	United Kingdom Renal Registry
UK-TR	United Kingdom Transplant Registry
USRDS	United States Renal Data System

Chapter 1 Introduction

Introduction to end-stage renal disease and the historical context of its treatment by renal replacement therapy

1.1 Introduction to end-stage renal disease

End-stage renal disease (ESRD) is the culmination of injurious processes which renders the kidneys unable to perform at a level which keeps patients from developing a heterogeneous constellation of signs and symptoms, caused principally by the accumulation of ‘uraemic’ toxins which are not able to be excreted in the urine.

Renal replacement therapy (which includes dialysis and kidney transplantation) are two treatments that have transformed the life prospects of patients suffering from ESRD. Before their introduction, death from irreversible renal disease was inevitable and unpleasant. Dialysis is a medical treatment, based on physical, chemical and engineering principles and is applicable in severe acute (often reversible) kidney injury and irreversible ESRD. It requires a semi-permeable membrane and there are two types of dialysis; haemodialysis which uses extracorporeal blood and dialyses this against a dialysate solution across the (semi-permeable) dialyser. Alternatively, peritoneal dialysis harnesses the semi-permeable properties of the peritoneal lining and cavity into which dialysate fluid is inserted via a specialized catheter into the abdominal cavity, left to allow convective and diffusive processes to occur, before being drained and replaced with fresh dialysate fluid. Kidney transplantation emerged from a surgical and immunological background and involves implanting another human’s kidney into a recipient with ESRD, reconnecting the vasculature and its outflow tube, the ureter, into the bladder. It is only ever used to treat ESRD and has no role in the management of acute kidney injury (AKI).

Transplantation and dialytic therapies (RRT) are the only life-prolonging treatments for ESRD and both have only emerged as viable options over the last half century and their historical perspective merits discussion to contextualise some of the inherent challenges there are when attempting to study long term mortality trends in this population.

1.2 Early historical aspects: Haemodialysis

The term “dialysis” was coined by a Glaswegian chemist called Thomas Graham (1805-1869). He observed the sieving properties of vegetable parchment which when floated on water permitted the passage of small crystalloid molecules but prevented larger colloid molecules to pass through.[14] Graham pursued other interests and it was another 50 years before John J. Abel (1857-1938) and his team at John Hopkins University investigated this principle on nephrectomized animals. Their research on “vividiffusion” using an “artificial kidney” came to a halt with World War One as they could no longer source hirudin, an anticoagulant needed to stop blood clotting on the dialysis membrane.[15,16] After the Great War the first experiments of haemodialysis on human patients emerged, performed by George Haas (1886-1971). His fractionated method involved repeatedly withdrawing venous blood and then dialysing it against a physiological solution and then returning it through the same channel. He was unsuccessful though, writing in 1925, that severe uraemia was “a condition against which the doctors stands otherwise powerless.”[17] This disheartening reality remained so until the first successful haemodialysis was performed in the context of the Second World War by Wilheim Johan (Pim) Kolff (1911-2009) in Kampen, Netherlands. Sourcing his raw materials for a dialysis drum from a local enamel factory, buying sausage skins to use as a dialysis membrane, and deceiving German authorities to employ skilled staff was a remarkable and enduring feat.[18-20] From early 1943 onwards Kolff and his dedicated small team performed a series of unsuccessful attempts on a variety of acute and chronic renal failure patients but his first ‘success’ came in September 1945, with “patient number 17”. Sophie Schafstadt was a 67 year old suffering from septicaemia caused by cholecystitis (acute severe inflammation of the gallbladder), and sulphonamide crystal anuria. Ironically, she was being imprisoned in the military barracks outside Kampen for being a Nazi collaborator yet the barrack’s commander-in-chief was an acquaintance of Kolff and so he allowed her to be treated. In Kolff’s infamous doctorate he wrote:

"I am convinced that she would have died if the treatment with the artificial kidney had not taken place. If others agree with me this would have made it likely that it is possible to save the life of patients suffering from acute uraemia with the help of vividialysis. An incitement to continue along this course"

His efforts have forever changed the treatment of acute and chronic renal failure. His achievements though would not have been possible without the prior discovery of two other key materials: heparin and cellophane. The credit for the discovery of heparin has been disputed but Jay Maclean (1890-1957) and William Howell (1860-1945) both clearly contributed.[21] Cellulose, was first regenerated into its sheet form by Jacques Brandenburger (1872-1954) yet it was William Thalhimer (1884-1961) who saw its potential applications as a dialysis material.[22]

Two other pioneers, working on different sides of the Atlantic deserve mention for their contributions. Kolff was insulated to other contemporary work as he was isolated in war-torn mainland Europe. In Canada, D.W.G. "Gordon" Murray, (1894-1976), was a talented cardiac surgeon who brought heparin into the routine clinical use,[23,24] inserted the first homologous aortic valve replacement,[25] and was first to use haemodialysis on human subjects in North America in 1946. Nils Alwall's (1906-1986), based in Lund, Sweden research was not interrupted by events of the Second World War as Sweden had remained neutral. His methodical nature and understated demeanour has meant his legacy to the history has perhaps been undervalued. He not only developed an early dialysis machine which had a more controlled mechanism of ultrafiltration (the process by which excess salt and water is removed), he envisioned an arteriovenous shunts before Scribner[26] and begun performing diagnostic renal biopsies, now an integral component of renal care.[27] His diligent and conscientious animal experiments led him to use haemodialysis in human subjects by June 1946.

The view that maintenance dialytic therapies offered realistic prospects for patients with ESRD remained contentious throughout 1960s with an anonymous Lancet editorial typifying the attitude of non-specialist physicians stating, “It had little to offer.”[2] This began to change when the bedevilling problem of reliable access to the blood stream was solved. The invention of a conduit to remove arterialised blood from the wrist or ankle and replace it, via a connecting piece of tubing to an upstream vein, was termed an arterio-venous or ‘Scribner/Quinton’ shunt after its creators.[28] First implanted in 1960 by surgeon David Dillard in Seattle its effect was beyond the technical as it removed a psychological barrier to haemodialysis being a viable longer term therapy. The concept was updated and re-worked by New York physicians, Brescia and Cimino, who fashioned an autologous arterial venous connection positioned subcutaneously at the wrist. This causes the draining vein to arterialise and hypertrophy (swell), providing adequate blood flows and negating the need of the external connectors that the original shunt relied.[29] An admiring editorial by Scribner[30] ensured that within the dialysis community, its use spread quickly. Indeed a mature, good quality arterio-venous fistula remains the optimal and recommended type of haemodialysis access.[31]

1.3 Early historical aspects: Peritoneal dialysis

In 1923 Georg Ganter, working in Würzburg, published the first animal trials of peritoneal dialysis to treat advanced renal disease. He ligated the ureters of guinea pigs and rabbits and showed that biochemical parameters could be improved by instilling solute into the abdominal cavity. He took this experience onto the first human patient. Over the following 20 years there were little progress in the field until interest was again sparked after reports of an ‘artificial kidney machine’ being used by Kolff, Alwall and Murray. The technical difficulties of this early form of intermittent haemodialysis drove others researchers to develop alternatives. In 1946, Frank, Seligman and Fine reported the first successful use of peritoneal lavage in a patient, yet became frustrated by a supply shortage in the materials

required and in the unacceptable peritonitis (infection within the lining of the abdomen) rates. Different techniques and improved catheter design helped somewhat but practical peritoneal dialysis remained elusive. Arthur Grollman, working in Dallas, developed and extolled the concept of a 'dwell-time': leaving the fluid in the abdominal cavity for a period of time before exchanging it and performed a lot of experiments on dogs and humans.[32] However it was Morton Maxwell, based in Los Angeles, who commercialised the process and made its reproducible as he approached local manufactures to supply reliable, sterilised fluid, tubing and used a standardized catheter.

Incremental developments occurred over the next few decades before the innovation of the semi-permanent indwelling peritoneal catheter opened the opportunity for patients to dialyse at home and underlined that peritoneal dialysis was a long-term option for patients with ESRD. The introduction of a Tenckhoff catheter, with its two anchoring cuffs, is still used in modern practice.

1.4 Early historical aspects: Kidney transplantation

"Seldom in the history of medicine" has a pair "two differing life-saving treatments for the same previously fatal disease appeared almost simultaneously."[33] Alexis Carrel (1873-1944), in 1906, tried xeno-transplantation by transplanting a kidney from a goat and a pig into 2 renal failure patients' brachial vessels. Neither patient survived. In 1936 the first human transplants (allotransplantation) was performed by an Ukranian surgeon called Yuri Yurijevich Voronay (1895-1961) on a series of 6 patients. As he had not appreciated the deleterious effects of harvesting kidneys long after death; none of the grafts functioned.

The momentous first successful kidney transplant was performed by Murray and colleagues in Boston on a pair of identical twins on the 23rd December 1954.[34] The first in the UK was performed in Edinburgh in 1960.[35] However the lack of effective immunosuppressants meant that transplants other than those between identical twins remained experimental for some

time.[36] A major breakthrough in transplantation came with the introduction of azathioprine[37,38] and then cyclosporine (a calcineurin inhibitor) in the 1980s.[39-41] These provided more consistent and tolerable immunosuppression thereby avoiding the problems associated with prolonged courses of high dose cortico-steroids and significantly reducing the morbidity from acute rejection.[41] The technical aspects of the transplant operation itself has changed little over time but the organisational structure of clinical transplantation, with all it ancillaries stakeholders (implanting surgeons, explanting retrieval teams, transplant immunology, nephrologists, NHS Blood and Transplant and critical care clinicians) have all contributed to improving transplantation rates and outcomes. Wolfe showed that even in high-risk individuals, including patients with diabetes, there were mortality benefits of a successful kidney transplantation which surpassed the risks of continuing dialytic therapies: a report which increased the numbers considered suitable for a transplant.[42]

1.5 Developments of dialytic therapies in the United Kingdom

In the United Kingdom, the 'artificial kidney machine' were brought to London by Kolff himself in 1946 as he wanted to share his experiences with Eric Bywaters (1910-2003) and Jo Joekes (1914-2010) who had had seen the devastating effects of renal failure from crush injuries during the Blitz.[43] However their early experiences were comparable to conservative therapies, colloquialized to the "Bull regime", consisting of a vile cocktail of fluid and nutrients ingested via a nasogastric tube. The treatment even recommended that vomitus from the patient was dutifully collected, filtered through lint, and then returned.[44] Other than brief experimentation by Dr. E. M. Darmady (1906-1989), a Portsmouth based pathologist turned renal physician, who travelled and used a self-built dialyser between 1947-1948,[45] there would be no more dialysis offered in the NHS for about 10 years.

Dialytic therapies re-surfaced in Leeds, where Dr. Frank Parsons (1918-1989) had been appointed Registrar to Professor Pyrah who had recently acquired a flame photometer to allow more accurate fluid replacement in the setting of oligo-anuric renal disease. Parsons

felt “dejected and disillusioned” at the fatal outcomes of many patients in acute renal failure and so he studied the work of a team based in Boston who were using the artificial kidney.[46] With Pyrah support he was sent on a secondment and over 4 months in 1954 he learnt the practical aspects of dialysis and even supervised the treatment of a young man in his twenties who would later that year receive the first living renal transplant from his identical twin brother.[46] He returned to Leeds and persuaded the governors of the hospital to purchase a Kolff-Bingham machine alongside co-founding a research unit, funded by the Medical Research Council (MRC). At the meeting the MRC secretariat stated that they had been advised that “there was no place for an artificial kidney in British medicine.” However once Parsons had described his experiences of its lifesaving potential of haemodialysis in America he was told, “Parsons, try it, but remember that the country is against you.”[46] Parsons’ unit in Leeds grew and whilst it probably did dialyse patients with ESRD as well as acute renal failure, the first *dedicated* chronic dialysis unit for ESRD was opened in the Spring of 1961 at Royal Free Hospital in London under the direction of Stanley Shaldon.[47] Others units, mainly based at university hospitals, followed across the country. These early English pioneers were working in a sceptical atmosphere, in which their trade was considered not cost-effective neither viable in the long term, a sentiment epitomised in a second Lancet editorial in 1965 which commented that, “limited resources should not be squandered on mass-dialysis.”[2]

Nevertheless, there was an obvious demand for a therapy that had life-preserving qualities. The Oxford Kidney Unit (OKU) was formally opened in 1967 although its first chronic patient, Jean Tarver, began peritoneal dialysis, on Christmas Eve in 1966.[27,48] Jean was supported by her husband and local Member of Parliament who lobbied the then Regius Professor of Medicine at Oxford to buy a kidney dialysis machine which was sourced in the Summer of the units’ inaugural year. Jean duly switched to haemodialysis, a treatment which she relied exclusively upon for the next 35 continuous years, out-surviving the founder of OKU.

By the 1970s and early 1980s there was a recognisable, albeit small, network of university based hospitals offering dialytic therapies to acute and chronic renal patients and the number of these centres and the types of patients that were taken on for dialysis programs was set to grow considerably.

1.6 Progress from the 1980s to date

These early dialysis units were dealing with high demand and struggled to grow their service as they were constrained by the limited public sector financial settlement witihn the socio-political context of Thatcherite Britain. This led to some selection of patients who received RRT, often excluded due to old age or comorbidity. Patients were also required to be self-caring in order to be able to dialyse themselves at home.[49] A controversial and rather sensationalist audit performed by the Medical Services Study Group of the Royal College of Physicians, published in 1981 gave some examples of why patients, under the age of 50, were not being offered RRT;

> *"Orphan. Neuropathy. Severe retinopathy and poor vision"*
>
> *"Very unintelligent"*
>
> *"Blind. Insulin dependent diabetes 21 years. Other diabetic complications*."[4]

This audit received stern rebukes from the practising nephrologists[50-55] and indeed the accompanying editorial said the conclusions were, "wrong and may mislead" but felt the British Medical Journal had a duty to publish it.[56] A nihilistic attitude, held by clinicians outside nephrology may have contributed to another factor of late (or indeed no) referral to RRT services as they held the belief that RRT did not offer a long term option.[57,58] Furthermore, this report followed heightened public awareness of the issues around procuring organs for transplantation, generated from a BBC *Panaroma* programme on brain death, which had a motif of,

"If the patient wasn't dead, when he was wheeled into the operating theatre, he certainly is now."[59]

However, despite the benefits of treatment, there was an under-resource of RRT facilities. The Office of Health Economics reporting that, in 1980, there was a need to grow capacity in the system, suggesting a need for an initial increase from about thirty to forty new persons per million population (pmp). Yet even in 1982 there was recognition by the chief medical officer that the 40 pmp figure was "an underestimate."[60] The 1980s saw renal units squeeze extra capacity into their RRT programs by promoting home therapies (principally peritoneal dialysis) to all new patients. In the 1980s the benefits of a successful kidney transplant started to become apparent, relieving pressure on limited dialysis funding.[61]

Across the 1980s and 1990s dialysis technology evolved, with newer better machines and updated materials such as the introduction of biocompatible membranes,[62] the move from acetate to bicarbonate based dialysate solutions[63,64], identification of toxic effects of aluminimum[65-67] and increasing ease by which machines could monitor the ultrafiltration rate all helped improve the tolerability of the therapy. Another advance was the introduction of recombinant erythropoietin, which solved the perpetual anaemia that these early patients suffered, helping them avoid the risks of multiple risk of blood transfusions.[68,69] Viable alternatives to dialysis access also became available in the form of tunnelled central venous catheters.[70] The kidney's critical role in calcium homeostasis was also discovered in the 1970s and derviations of activated 1,25 di-hydroxycholecaliferol[71-73] was introduced into clinical practice in the late 1970s early 1980s, helping to alleviate some of the adverse effects of the bone disease characterised in ESRD patients.[74]

Since the turn of the century modern renal services have included designated facilities in all acute hospitals with universal and open referral pathways to specialists renal units for all General Practitioners. Age and comorbid illnesses are rarely barriers to referral for

consideration for RRT; these decisions are now individualised to the patient needs and indeed are increasingly becoming a patient led decision.

1.7 Background literature

Patients with ESRD are known to have higher overall mortality rates than that observed in general population.

Linder first described the accelerated vascular disease which pertains to advanced CKD[75], and subsequent work has focused on confirming 'traditional' vascular risk factors are too contributory to this heightened risk; namely smoking[76], LDL-C[77] and hypertension.[78] The association of hypertension, (defined variably in the literature) are more complicated in advanced CKD, especially with patients on dialysis. Echocardiographic studies of patients with CKD stages 4 and 5 (i.e. eGFR <30mls/min/1.73m^2) have been shown to have evidence of abnormal cardiac function, yet many patients have no overt symptoms. One other surrogate of subclinical cardiac disease, is the cardiac biomarker troponin. Herrington et al. used the SHARP dataset and after the adjustment of usual confounders, found a 'U-shaped' relationship of reverse causality, between systolic blood pressure and cardiovascular disease.[78] Yet, after stratifying patients into those with a raised troponin or not they observed a strong log-linear relationship: each 10 mmHg higher systolic BP corresponding to a 27% increased risk of cardiovascular disease (hazard ratio, 1.27; 95% confidence interval, 1.11–1.44).

CKD stage 5 also has a host of other inter-related factors which likely contribute towards overall mortality risk, compared to the general population. Increasingly recognised is fluid overload, with a large international demonstrating a cumulative 1-year fluid overload exposure to be predictive of a higher death rate across pre-defined BP categories; (<130 mmHg: HR, 1.94; 95% CI, 1.68 to 2.23; 130–160 mmHg: HR, 1.51; 95% CI, 1.35 to 1.69; >160 mmHg: HR, 1.62; 95% CI, 1.39 to 1.90.[79]

The ERA reported that *non*-vascular mortality had a 8.1 times higher age-adjusted risk of mortality, similar to the 8.8 increase for vascular mortality) and this aspect of increased risk is often overlooked.[80,81] It is common knowledge that non-vascular causes of death such as malignancy share a number of shared risk factors, namely smoking, adiposity, and physical inactivity, yet RRT itself does exposure patients to additional insult on their immune systems and in the transplant setting and in the treatment of autoimmune disease its overt manipulation with immuno-suppressants.

1.7.1 Temporal trends in all-cause mortality in ESRD patients

Temporal trends analyses of treated ESRD populations have been generally limited to registry-based reports. These previous studies have been over a relative short period of time, have been unable to adjust for co-morbidity, or have been unable to identify a directly comparable control population.[9,11,81,82]

The UK-Renal Registry does report age-stratified survival percentages for incident cohorts since 1997 in its annual reports. These has shown steady improvements in survival, but the UK-Renal Registry is unable to adjust these analyses by any comorbidity metric, as no appropriate data were recorded in earlier cohorts and the UK-RR has no data before 1997.[83]

Longitudinal data from the United States Renal Data System (US RDS) used abridged life tables to report improvements in the survival of dialysis patients over the last 40 years (1977-2007) with the average life-years lost reducing from 23.6 years (95% CI, 23.1-24.0) in 1977 to 19.7 (19.5-19.8) years in 2007.[9] Although reporting the age-specific life years lost partially controls for the changes in the age structure of the RRT population there was no adjustment for changes in comorbidity profile despite reporting increases in the prevalence of diabetes from 9 to 38% in the ESRD.[9]

Similarly, in a Japanese prevalent dialysis population the age-standardized rates of all-cause mortality fell from 184 per 1000 person years between 1988 to 97 in 2013, but again no adjustment for co-morbidity was performed.[84] This lack of comorbidity adjustment may lead to underestimates of temporal declines in mortality rates and makes assessment of the magnitude of excess risk to a general population much less reliable.[85]

Data from the European Renal Association/European Dialysis Transplant Association (ERA/EDTA) reports includes information from 18 national and regional renal registries. They calculated unadjusted and adjusted 5-year survival probabilities between an early era of 1998-2002 and a more modern era from 2003-2007. A 15% improvement (HR=0.85, 95%CI, 0.84-0.86) from the earlier to more modern period was reported. They were able to adjust age, sex, country and primary renal disease (PRD), a surrogate that is often used as a proxy for some comorbid illness but reported missing information in upto 15% of its incident ESRD patients have an unknown cause to their renal failure.[10] Furthermore, reporting rates of PRD differ in each country and key comorbidities such as vascular disease or diabetes which were not the PRD were not captured.[10]

1.7.2 Vascular and non-vascular mortality in ESRD patients

Lindner first described an accelerated atherosclerosis process in haemodialysis patients in 1974[75] and established that ESRD patients have considerably higher absolute risks of cardiovascular (CV) disease than age-matched general population individuals.[86,87] Indeed cardiovascular disease as a group is the commonest reported cause of the death for ESRD patients.[83] Exploring this, Australian renal registry data studied medium-term temporal trends in CV mortality and included general population data for comparison. The age-specific relative risks (RR) of CV mortality in the dialysis population versus to the general population (whose rates were derived from Australian national mortality data) rose over the 14 year

period (1992-2005) amongst 55-64 years olds, from 32 to 50/100 persons years.[11] There was, however, no opportunity to adjust for any differences or temporal changes in the comorbidity profile of these two populations.

There is recognition that adjustment for comorbidity, often referred to as "case-mix" provides fairer comparisons of mortality, and the collection of a standardized comorbidity dataset for ESRD patients is advocated in the UK and Europe.[88-90] The lack of comorbidity data for English ESRD patients has prevented the UK-RR adjusting its survival data and it has no data prior to 1998 so cannot provide longer term temporal trends.[5] The reported paucity of baseline co-morbidity data for incident RRT led the UK-RR them to augment patient level data from the UK-RR with directly linked data from all-England Hospital Episode Statistics (HES).[88] This demonstrated a reduction in the number of renal-centres designated as prior "outliers" for their respective three-year mortality rates in incident patients when the HES-derived co-morbidity variables were incorporated into the adjustment model. Furthermore, this data showed that even in the limited period for which it had data, 2002-2006, there was an improvement in survival with an adjusted hazard ratio being 22% lower in 2006 compared the 2002 reference group. [88]

1.8 Detailed thesis aims

This thesis with its access to the unique resource of ORLS and all-England HES proposes to identify and then calculate mortality rates for a treated ESRD population across almost 40 years and compare the proportional changes in mortality to a general population using standardisation techniques which includes a comorbidity adjustment. The complete aims are to:-

1. **Derive and validate a cohort of end-stage renal disease (ESRD) patients exclusively from anonymised, individually-linked prospectively collected hospital inpatients datasets**

   Oxford has the earliest national resource of this kind allowing the inclusion of patients from the early and modern era of renal medicine offering a unique opportunity to study morality trends over the long term. Comorbidities, identified from prior inpatient hospitalisations prior to start of RRT will be extracted to permit their use as covariates in subsequent mortality analyses. As no prior study has used the proposed derivation method before, the baseline characteristics will be validated (using both direct and indirect methods) against other repositories which holds data on English ESRD patients.

2. **Analyse the temporal trends of age, sex and comorbidity adjusted mortality rates in the ESRD cohort**

3. **Concurrently derive a comparative general population to provide an opportunity to compare trends between the ESRD and general populations**

   The opportunity for analogous standardization between two different populations, that of an ESRD and general population helps assess whether any trends in mortality rates

observed in the ESRD are greater, similar or smaller to those observed in a corresponding general population.

4. **Demonstrate other uses of routinely collected hospital inpatients datasets in renal epidemiology**

1.9 Bullet Points of Chapter 1

- Treatment for ESRD in the form of transplantation and dialysis are relatively new therapies to the NHS, being cautiously introduced into the NHS in the 1960s and 1970s.

- The demographics of these early patients were much younger and less comorbid than what is seen in current nephrology practice.

- The short to medium term trends of modern RRT patients have shown modest improvements.

- Prior mortality trends have not, and indeed not been able to, compare any changes observed in an ESRD population to that of a comparable general population.

Chapter 2 Cohort derivation

Method of cohort derivation of English newly treated end-stage renal disease patients and contemporaneous general population hospital controls from the Oxford Record Linkage Study (1970-1996) and all-England Hospital Episode Statistics (2000-2008)

2.1 Abstract

Background

Patients receiving treatment for end-stage renal disease are frequently admitted to hospital which offers an opportunity to identify a cohort of treated ESRD patients derived exclusively from hospital inpatient datasets. The methodology used to derive such a cohort and similar methods to identify a comparative general population cohort are presented.

Methods

An incident cohort of treated ESRD patients was identified retrospectively from two routinely collected hospital inpatients datasets, the Oxford Record Linkage Study (ORLS; 1970-1996) and all-England Hospital Episode Statistics (HES; 2000-2008), using specifically designed algorithms which incorporated clinical codes relevant to renal disease, transplantation and dialysis from International Statistical Classification of Diseases and Related Health Problems (ICD) versions 7-10, and Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS) versions 2-4. A large set of contemporaneous general population hospital controls were also identified from the same datasets identified from the time of an index hospital admission for a variety of minor ailments or procedures.

Results

In all-England HES 56.3 million individual patient records were scrutinised of which 140,616 had mention of a renal replacement therapy (RRT) related code. A clinical algorithm then searched the linked records of these patients to confirm whether they were receiving *maintenance* RRT (dialysis or transplant), differentiating them from patients admitted with presumed admissions with dialysis-dependent acute kidney injury. Basic demographic details, and uniquely prior major comorbidities, identified in a fixed period of retrospective follow-up from the start date of RRT were also extracted. Patients under 18 years old, those dying within 90 days of starting RRT, or those identified as having prevalent RRT were then excluded. 42,730 such patients were finally identified in all-England HES and with similar methods ORLS identified a further 2,192 patients.

To permit subsequent comparative analyses, 5.6 million contemporaneous general population hospital controls were identified from the same datasets over the same period.

Conclusions

Deriving a large cohort of incident ESRD commencing RRT from linked routinely collected hospital inpatient data in Oxford and England between 1970-2008 is technically feasible.

2.2 Introduction

The term ‘record linkage’ was first coined by H.L. Dunn in 1946.[91] He introduced it with the following metaphor,

“Each person in the world creates a book of life. This book starts with birth and ends with death. Its pages are made up of the records of the principal events in life. Record linkage is the name given to the process of assembling the pages of this book in to a volume.”

For the purpose of this body of work the term “linked” or “linkage” requires further clarification. Individuals’ consecutive hospital admission records need linking together (intra-individual linkage) and hospital admission datasets as a whole require linkage to other healthcare datasets, such as the national mortality data (inter-dataset linkage). With both these components a storybook of health, disease and ultimately death can be assembled.

2.3 Datasets

2.3.1 Oxford Record Linkage Study, 1963-1998

The systematic collection of prospectively, routinely collected, individually-linked hospital inpatient data hospitals began, in Oxford, and has evolved into its current form, all-England Hospital Episode Statistics (HES). Sir Ernest Donald Acheson pioneered its use, envisaging a construct to inform, track and potential treat society from a unit of individuals, families or the community as whole.[92] Importantly he foresaw the importance of linked data as opposed to Hospital In-Patient Enquiry (HIPE) which only recorded a random sample of unlinked admissions which was unable to distinguish events at a person level. Acheson founded the Oxford Record Linkage Study (ORLS) in 1962 whilst working at the Nuffield Department of Medicine at the Radcliffe Infirmary.[93] It was conceived with four aims:[94]

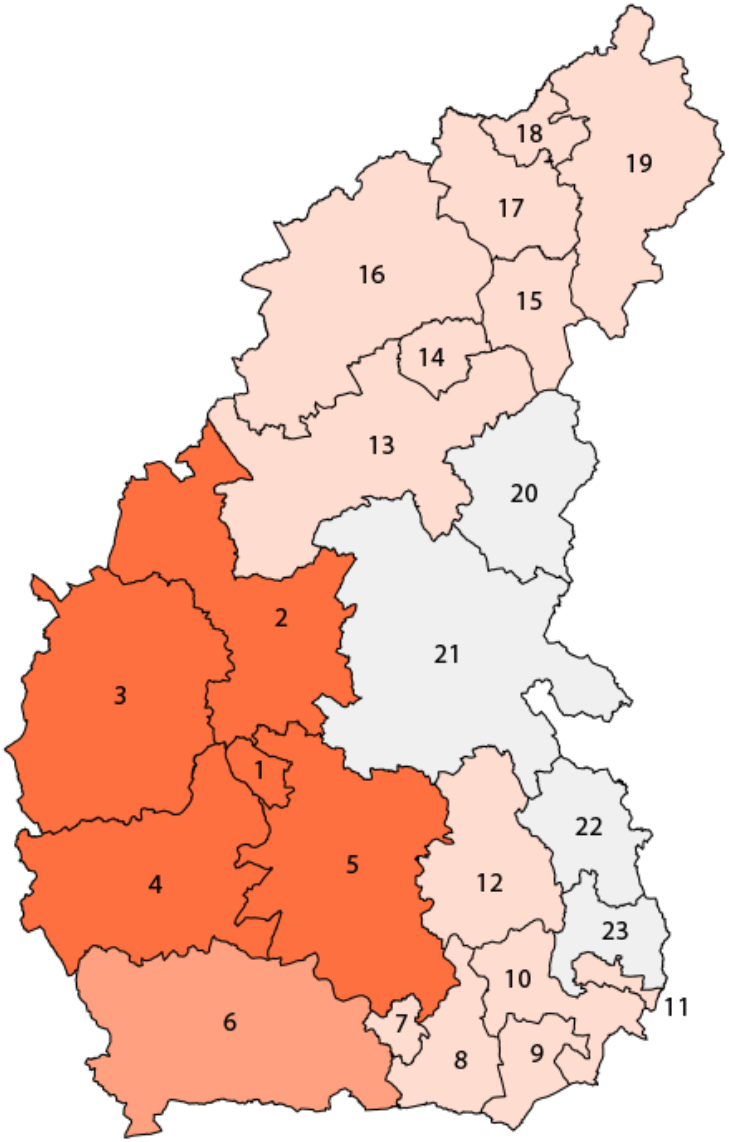
1. To study the feasibility and cost of prospectively accumulating information on key health events in cumulative personal files
2. Develop computer methods capable of record linkage across medical disciplines
3. To study applications of the files in medical and operational research
4. If successful as a pilot study, promote its extension on a national basis

At its inception, ORLS only collected data on hospital admissions from central Oxfordshire but it expanded and enveloped neighbouring counties as depicted in Figure 2-1.

1963-1965	Oxfordshire
1966-1974	East Berkshire
1975-1986	Wycombe Kettering West Berkshire Northamptonshire
1987-1998	Aylesbury Milton Keynes

By 1998, these eight districts covered a total population of 2.5 million with high quality data being manually and then electronically imputed by a dedicated set of clinical coders.[95] These data are now archived, computerised and fully anonymised. It is curated by the Unit of Health Care Epidemiology, now embedded within the Big Data Institute, Li Ka Shing Centre for Health Information and Discovery, University of Oxford. All its data are anonymised but encrypted identifiers were used to link successive records for the same individual.[96] No access to the original patient identifiers is possible and was never sought.

Figure 2-1: Expanding coverage of Oxford Record Linkage Study



ORLS by Period

1963 onwards	(5)
1966 onwards	(1)
1975 onwards	(13)
1991 onwards	(4)

ORLS by Area

Oxford	1
Cherwell	2
West Oxfordshire	3
Vale of White Horse	4
South Oxfordshire	5
West Berkshire UA	6
Reading UA	7
Wokingham UA	8
Bracknell Forest UA	9
Windsor and Maidenhead UA	10
Slough UA	11
Wycombe	12
South Northamptonshire	13
Northampton	14
Wellingborough	15
Daventry	16
Kettering	17
Corby	18
East Northamptonshire	19
Milton Keynes UA	20
Aylesbury Vale	21
Chiltern	22
South Buckinghamshire	23

UA=Unitary authority

2.3.2 All-England Hospital Episode Statistics, 1998-2011

Hospital Episode Statistics (HES) is a vast warehouse of clinical and administrative data which records hospital inpatient admissions with complete nationwide coverage of all National Health Service (NHS) institutions in England, including acute hospitals, primary care trusts and mental health trusts. HES was conceived after a report of a working group, chaired by Edith Körner was convened to make recommendations on health service informatics, as the need for high quality national admission data on hospital was increasingly recognised. The Körner commission published a series of reports between 1982 and 1987 envisaging a system analogous to a "well-made jigsaw", which would accurately reflect the evolving informatics needed by healthcare management, auditors and researchers. It would have to perform the complex tasks of efficient administration, effective healthcare planning and genuine accountability across the entire NHS.[97,98] In 1987 the implementation phase of the so-called Körner recommendations began, on a regional basis only, with each local health authority collecting and storing their own records. From 1996, these local reservoirs of data were abolished and a nationwide cleaning service (NWCS) was provided to pool and collate the records nationally, achieving Acheson fourth aim. This process continues to date and is co-ordinated by Secondary Users Service (SUS) under the auspices of the NHS Digital.

Over the period where the national systems were being harmonised, ORLS researchers steadfastly maintained two key elements. First, as it already had an existing system of reliable linkage with an experienced and dedicated team of clinical coders capable of capturing admissions across all inpatient disciplines, it could integrate the Körner recommendations into its normal work platforms. Secondly and unlike other regions in England ORLS did not destroy its regional data between 1987 and 1998, and so uniquely it has uninterrupted linked data from the 1960s to the 1990s. Its data offers important and unique opportunities for epidemiological research.

This combined resource of ORLS and all-England HES has long-standing ethical approval in place from the Central and South Bristol Multi-Centre Research Ethics Committee (04/Q2006/176; Figure 8-2) for epidemiological analyses, including those proposed in this thesis.

2.3.3 Data acquisition, Information security and safeguarding data

The Unit of Healthcare Epidemiology (UHCE) is a department within Nuffield Department of Population Health (NDPH) in the Division of Medical Sciences, at the University of Oxford. UHCE designed and owns the data collected in ORLS. It was curated by Professor M. Goldacre until his retirement on 31St March 2015 whereby formal custodianship of the dataset transferred to Professor M. Landray, who is one of my co-supervisors.

When UHCE started receiving *national*, all-England, data from HES, a System Level Security Policy (SLSP) was established for the so-called "UHCE National Linked Database." All the data UHCE received was and remains fully encrypted with all identifiable personal data (NHS number, local hospital number, postcode, date of birth) having been pseudo-anonymised, with the encryption key held by NHS Digital. The SLSP listed the security measures which UHCE conformed to.

2.3.4 Physical measures of security

1. The UHCE is situated on a University research campus. This campus is patrolled by University security staff 24 hours per day, 365 days per year.

2. There are CCTV cameras on the campus monitored by the security staff.

3. When the offices are closed, the building is securely locked. The building is protected with an intrusion alarm installed by a security company and connected to the security patrol staff and the local police station. Infra-red motion sensors which trigger the alarm are in place throughout the building.

4. When the offices are closed, there is full coverage and full weekend coverage of the site by the University security staff. The University security services conduct full external site patrols during the day and night.

5. Out of normal working hours, access to the building requires the use of an electronic key card which is allocated to a specified person, and its use can be audited.

6. During working hours, access to the offices from the outside requires the use of an electronic key card.

7. The two Windows servers were kept in the development office, since they were used on a daily basis while the database is being developed and populated. This room was securely locked when empty and accessible only by physical key lock.

2.3.5 Logical measures for access control and privilege management

1. Login identities and passwords are required to access to the Servers and are restricted to those staff authorised by the Director. No default users (e.g. GUEST) are permitted.

2. Any datasets that contain the encrypted partial identifiers or sensitive data (e.g. HES) are stored and processed only on the UHCE Development server. (Note: such data were not necessary to complete this thesis)

3. Only authorised users using desktop PCs within the UHCE have access to the data on the UHCE Live server. Further logins and extra passwords are required to access the data.

4. The media access control (MAC) of every personal computer on the local-area network (LAN) was registered centrally in the departmental firewall. No other machines could connect to the network. This required me to have virtual desktop as my office was not located in UHCE premises.

5. All partial identifier fields were encrypted at source before they were received them from the Data Supplier.

6. Windows Servers stored and processed the data. The operating system and data drives were and remain encrypted with BitLocker which is built in to the operating system. BitLocker requires a combination of a Trusted Platform Module (TPM) chip, which is unique to every machine, and a USB Key which must be present in the machine to decrypt the drives, ensuring that the disks cannot be used in any other machine. A recovery key is also created when the files are encrypted which can be used on its own to decrypt the files – this is kept in a secure location on site in a separate location to any data-files including backups, and is only to be used to recover backup data in case of server failure.

7. After daily use, each BitLocker USB Key was removed and stored in a key-coded safe. The secure code is known only to authorised members of staff and changed on a three monthly basis.

8. Access is granted to each user individually and appropriate permissions assigned on a per-person basis, allowing access rights to be tightly controlled and monitored.

9. All staff, employed in NPDH are mandated to complete online information governance training and assessment.

NDPH reconfigured and erected a new premises during my thesis and with this a review of the unit's information security policy was undertaken to align itself to the Information Governance Toolkit now updated by HSCIC/NHS Digital. This transition was completed in Spring 2016. UHCE servers are now currently stored in specifically designed server storage units within the Li Ka Shing Centre for Health Information and Discovery's Big Data Institute. The servers continue to use "BitLocker", a form of full-disc encryption aforementioned. UHCE information governance standards have been assessed by NHS digital, a report of which is in the Supplemental material, Figure 8-1: Information Governance Toolkit from NHS Digital.

2.4 Nomenclature used in hospital inpatient datasets

ORLS and HES datasets recorded demographic, clinical and administrative data. The clinical data included types of admissions (emergency, day case, elective), dates of any admission and discharge, specialty of the supervising consultant and principal or 'primary' diagnosis which led to the admission together with upto 17 other secondary diagnoses. The codes of any procedures performed were recorded alongside its date (i.e. Procedures were only ever incident events). Other pertinent data included codes ascribed to specific hospitals/providers. For this thesis these additional codes were used in the derivation algorithm for the ORLS era, 1965-1999.

In HES, a hospital "spell" is made up of one or more contiguous finished consultant episodes (FCE), hereafter referred to as "episodes". A spell is a complete inpatient admission from the date of admission and discharge from the hospital/provider. An episode is defined as the complete time a patient has under a specific consultant and their speciality.

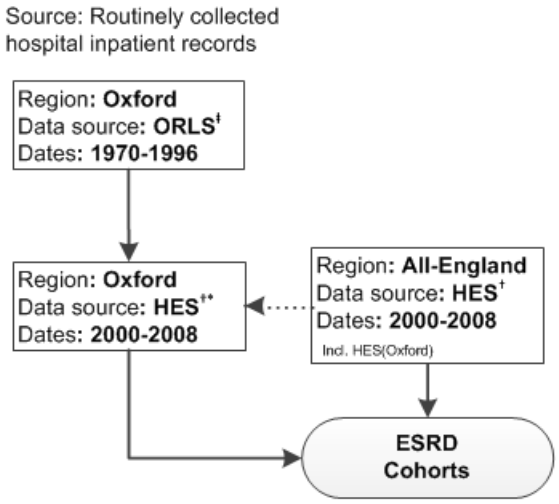
The inpatient records in ORLS also captured the complete time a patient was admitted in hospital or under a specific provider (from admission to discharge) but there was only a single record per admission (i.e. ORLS records captured all episodes in one record). For synchronisation purposes, an ORLS inpatient record was seen as equivalent to a complete HES spell.

Information on mortality for both datasets was made possible because of their linkage to the Office of National Statistics (ONS) which provided, as Dunn would have described it, a robust and reliable "end chapter" to a patient's story.

2.5 Time periods covered by the cohorts

The derivation of the treated ESRD cohort included adults (≥18 years old) who commenced maintenance RRT between 1st January 1970 - 31st December 1996 in ORLS, and between 1st January 2000 - 31st December 2008 in HES, which included a regional subset, termed HES Oxford. HES Oxford closely approximates the area previously covered by ORLS. All patients had a fixed period of upto 5 years of retrospective follow-up to identify prior co-morbidities and upto three years of follow-up, meaning observations began from 1st January 1965 and finished on 31st December 2011 (Figure 2-2).

Figure 2-2: Summary of datasets used to derive study populations



‡ORLS=Oxford Record Linkage study. ORLS region includes Oxfordshire, Berkshire, Buckinghamshire and Northamptonshire. ESRD= end-stage renal disease. ESRD cohort includes new treated end-stage renal disease patients surviving 90 days. †HES=Hospital episode statistics. *=Termed HES (Oxford) in figures. All patients had upto three years follow-up; end date for ORLS was 31st Dec 1999 and 31st Dec 2011 for HES.

2.6 Diagnostic and procedurals manuals

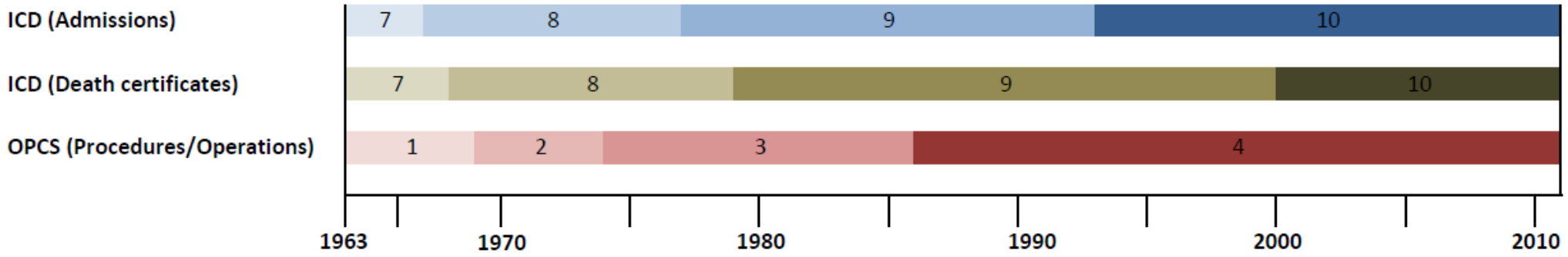
The versions of the diagnostic and procedural coding systems used by the datasets to record deaths, diagnoses and operations changed through the decades from ICD (International Statistical Classification of Diseases and Related Health Problems) versions 7 to 10 and OPCS (Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures) versions 2 to 4 (Figure 2-3).

Clinical diagnostic terms relevant to renal disease were manually mapped through these various versions. Clinical terminology in nephrology has evolved and modern terms such as “acute kidney injury” are not even listed in ICD-v10, an analogous term “acute renal failure” is preferred. However, in older manuals, for example in ICD-v8 (used in ORLS for hospital admission diagnoses between 1968-1978) the preferred term was “acute nephritis”.

Similarly the modern classification and grading of “chronic kidney disease” was introduced by K/DOQI (Kidney Disease Outcomes Quality Initiative) in 2002[99] and last updated by KDIGO (Kidney disease; Improving Global Outcomes) in 2012[100] and is embedded into ICD-v10 at the fourth character level (N18.0, N18.1, N18.2, N18.3, N18.4, N18.5, N18.9, which designates CKD not otherwise specified, stage 1, stage 2, stage 3, stage 4, stage 5 and unspecified respectively). In ICD-v7 to 9, the diagnostic term would have been “chronic renal failure”. This singular overarching term would have included all dialysis-dependent ESRD patients and any pre-dialysis patients with established renal disease as there was no fourth character to the code which could differentiate between the two. Hard copies of all appropriate ICDs manuals were available for review. A second clinician (WH), familiar with managing patients with ESRD cross checked all the derivation code that were proposed to be used in the extraction process.

The Unit of Healthcare Epidemiology provided hard copies of OPCS versions 1, 2 and 3 which were scanned to preserve the resource and then reviewed before being converted, by me, into a format which enabled them to be integrated into the derivation procedures. An electronic version of OPCS version 4 was used.

Figure 2-3: Time periods covered by clinical coding manuals used to record death, diagnoses and procedures



ICD=International Statistical Classification of Diseases and Related Health Problems, OPCS=Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures

2.7 Procedures performed to identify an ESRD cohort in HES, 2000-2008

This involved three steps:

1. Identifying patients *likely* to have been receiving renal replacement therapy

2. Confirming that renal replacement therapy was for the treatment of ESRD, rather than recoverable AKI

3. Restricting the cohort to an *adult* and *incident* cohort of *treated* ESRD patients all with upto three years follow-up (i.e. removing prevalent ESRD patients; those who had started RRT before the HES dataset began)

A summary flowchart of the procedures is found in Figure 2-4.

2.7.1 1st HES Step: Identifying codes and potential patients treated with ESRD and/or renal replacement therapy

For the first step, diagnostic and procedural codes relevant to RRT and ESRD were manually cross-mapped through the versions of coding manuals. The diagnostic RRT codes were identified from the ICD versions 7-10 and categorised into terms relating to transplantation (incident or prevalent) or dialysis (including terms for haemodialysis, peritoneal dialysis and dialysis 'unspecified'). Procedural codes relevant to RRT were identified from the OPCS versions 2-4 and categorised into similar categories: dialysis and transplantation. A summary list of the descriptions of these codes is shown in Table 2-1.

In the HES derivation, the codes for ESRD and renal replacement therapy were searched for in all patients at the episode level of each hospital admission. Patients with no mention of any of these 'RRT-related codes' were excluded, reducing potential patients to from 56 million to 140,616. Patients identified as having residency (identified through postal districts)

outside England (n=1,598) were then excluded as there was potential of discontinuity of follow-up.

Table 2-1: Diagnostic and procedural codes used to identify patients with renal disease in versions of A) International Statistical Classification of Diseases and Related Health Problems and B) Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures

A) International Statistical Classification of Diseases and Related Health Problems [ICD]

	ICD-10	ICD-9	ICD-8	ICD-7
Renal Disease				
Acute renal disease	N17x	584	580	590
Chronic renal disease	N18x	585	582, 584	592, 594
End-stage renal disease*	N18.0, N18.5, Q60.1	5856, 753.0	753	-
Indicator of advanced CKD†	-	403, 582, 583, 585, 586, 587 590.0	403, 582, 583, 584, 593.2, 590.0	592,593,594
Renal Replacement Therapy				
Transplantation				
Incident transplant	-	-	-	-
Prevalent transplant	N16.5, T86.1, Z94.0	996.81, V42.0	-	-
Dialysis				
Haemodialysis	T82.4, Z49.1	V560	-	-
Peritoneal dialysis	Z49.2	V568	-	-
Dialysis, unspecified	E85.3, Y60.2, Y61.2, Y62.2, Y84.1, Z99.2	996.73, E879.1	-	-

*Including codes for renal agenesis †In ORLS, clinical coding was less refined and so a broadened category of 'renal disease terms' was used to initially screen potential patients for the ESRD cohort.

B) Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures [OPCS]

	OPCS-4	OPCS-3	OPCS-2
Renal Replacement Therapy			
Dialysis			
Haemodialysis	X40.3, X40.4	950.3	950.3
Peritoneal dialysis	X40.2, X40.5, X40.6	401.3	401.3
Dialysis, unspecified	X40.1		
Transplantation			
Incident transplant	M01.2, M01.3, M01.4, M01.5, M01.8, M01.9	566	566
Prevalent transplant	M02.6, M08.4, M17.4, M17.8, M17.9		
Dialysis access codes			
Insertion of peritoneal dialysis catheter	X41.1		
Insertion of tunnelled venous catheter	L91.5		
Insertion of an arterio-venous conduit	L74.1, L74.2, L74.6, L47.8, L47.9	889.1	889

2.7.2 2nd HES Step: Distinguishing maintenance from temporary RRT

Thereafter, the records of the remaining 139,018 patients were interrogated using steps designed at confirming that the pre-defined criteria of "maintenance RRT" were satisfied. This was necessary as clinical coding manuals have not reliably distinguished between dialysis that was delivered in the setting of severe acute kidney injury and *regular* dialysis provided as part of maintenance treatment for ESRD. It would have been wrong to assume that the co-existence of clinical discharge codes for CKD and dialysis represented maintenance dialysis as CKD is itself a strong risk factor for AKI.[101] A series of hierarchical rules designed to confirm whether maintenance RRT had occurred were therefore employed.

Rules for defining 'maintenance RRT' in all-England HES

Maintenance RRT Rule 1, Kidney transplantation:

The occurrence of any code included in RRT type = 'Prevalent kidney transplantation' or 'Incident kidney transplantation' (Table 2-1).

Explanatory note: Transplantation is only ever performed in patients with ESRD.

This was the first rule satisfied in 21,485 patients.

Maintenance RRT Rule 2, Maintenance peritoneal dialysis:

The occurrence of a RRT code = Peritoneal Dialysis, or survival of at least 90 days from the insertion of a peritoneal dialysis catheter (Table 2-1).

Exception to maintenance RRT Rule 2: Those who fulfilled rule 2 (peritoneal dialysis) as their first RRT event, but did not subsequently fulfil any of the other rules and had a diagnosis of AKI associated with all their PD spells were not considered a maintenance RRT patient.

Explanatory note: Peritoneal dialysis is rarely used to treat AKI and the insertion of a peritoneal dialysis catheter, in the absence of term for AKI, was considered maintenance RRT.

This was the first rule satisfied in 21,384 patients.

Maintenance RRT Rule 3, Definite maintenance dialysis:

The occurrence of a hospital inpatient episode with any code which included in RRT type 'Dialysis' in a participant who had:

3.1) A diagnosis of ESRD (Table 2-1) any time prior to, or within 365 days after the start of the episode

Or

3.2) The insertion of an arterio-venous (AV) fistula or graft (Table 2-1) any time prior to, or within 365 days after the start of the episode

Explanatory note: Patients who were identified as having a code for dialysis in the context of a prior mention of end-stage renal disease or evidence of permanent haemodialysis access creation were considered to have commenced maintenance RRT. Tunnelled central venous catheters were deliberately not included in rule 3.2 as these can be inserted for a variety of other reasons whereas an AV fistula or graft is almost only used for long-term dialysis. Similarly, including patients with only a record of permanent haemodialysis access (i.e. a arteriovenous fistula or graft) but without a record of RRT was not considered appropriate as these conduits are inserted upto 12 months before patients are anticipated to start maintenance and may never be subsequently used.

This was the first rule satisfied in 46,895 patients.

Maintenance RRT Rule 4, Probable maintenance dialysis:

> The occurrence of at least two episodes with any code included in RRT type = 'Dialysis', with at least 90 days between the start of the first 'Dialysis' episode and the start of any subsequent spell containing a 'Dialysis' code that did not have a record of a acute renal disease diagnosis in that hospital spell (Table 2-1).
>
> *Explanatory n*ote: Those who fulfilled rule 4 (probable dialysis) as their first RRT event and did not subsequently go on to fulfil any of the other rules should be considered 'Possible dialysis'.

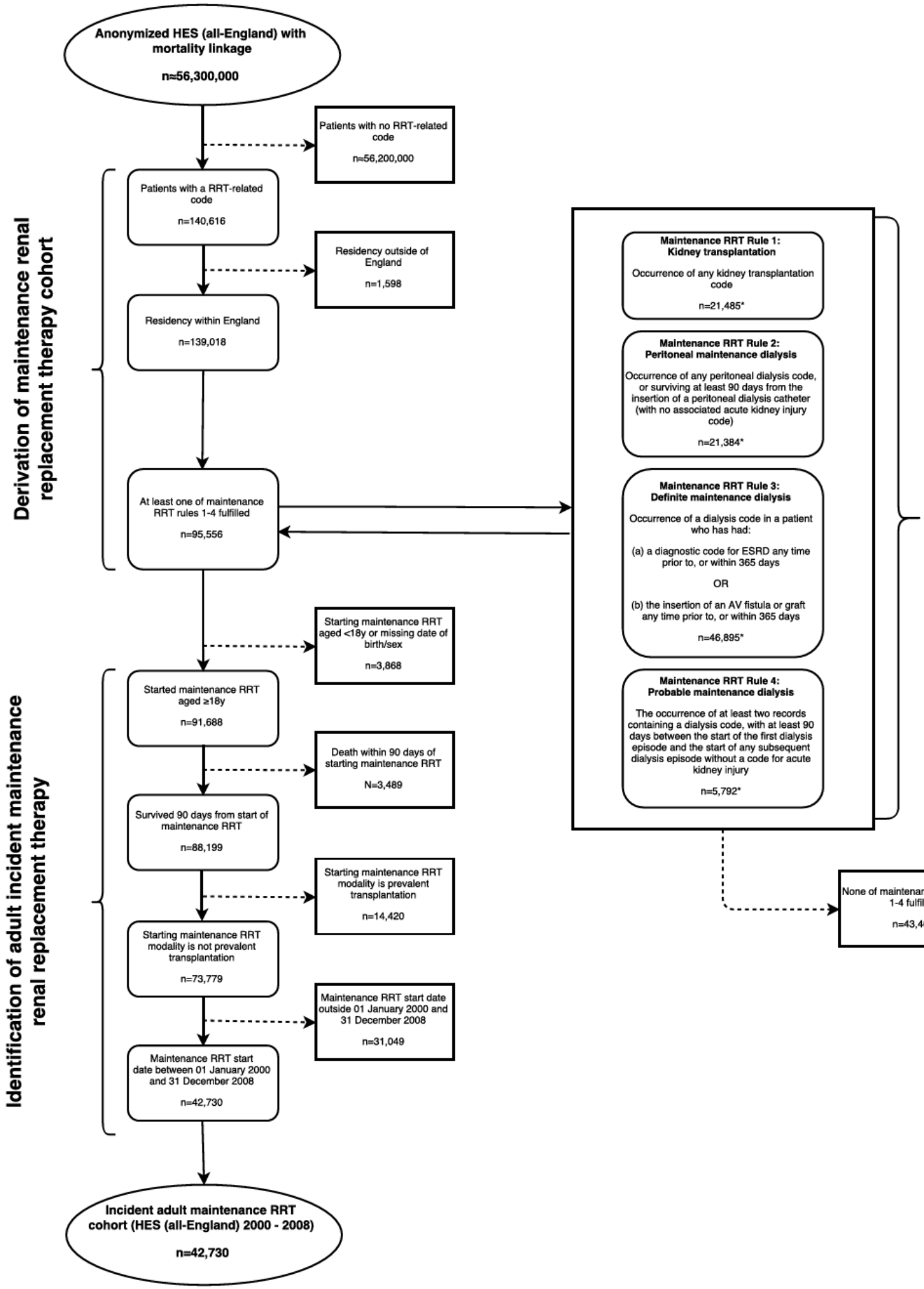
This was the first rule satisfied in 5,792 patients.

This series of rules was applied to the 139,018 patients of which 43,462 did not fulfil any rule and were therefore excluded, leaving a total of 95,556 patients who were confirmed to be receiving maintenance RRT.

2.7.3 3rd HES Step: Distinguishing incident from prevalent RRT patients

The cohort was then restricted to incident RRT patients by excluding those who were identified as having as prevalent transplant (n=14,420). The cohort was then also restricted to patients starting maintenance RRT between 2000 and 2008, removing a further 31,049 patients, leaving 42,730 patients. A flowchart of the derivation steps for the HES ESRD cohort is provided in Figure 2-4.

Figure 2-4: Treated end-stage renal disease cohort derivation (all-England HES 2000-2008)



AV = Arteriovenous. ESRD = End-stage renal disease. HES = Hospital Episode Statistics. RRT = Renal replacement therapy. (Code) refers to diagnostic or procedural codes. *Participants could fulfil mo
one rule, but only the first rule which was fulfilled is counted.

Co

2.7.4 Exclusion criteria applied to All-England HES derivation, 2000-2008

The cohort was then restricted to adults (≥ 18 years old) only.

In less than 5% of patients, missing demographic data at the defined start date of the cohort prevented their inclusion.

Incident RRT patients who died within 90 days of starting maintenance RRT were excluded (see Figure 2-4).

2.7.5 Defining entry date to the cohort

For each patient that met the criteria that defined maintenance RRT, the date of first maintenance RRT was defined as the earliest date of:

- The date of first incident transplantation code

- The start date of the episode for first record of peritoneal dialysis, or the date of insertion of a peritoneal catheter, when not in the context of acute kidney injury

- The start date of the first episode of dialysis that was used to define maintenance dialysis

2.8 Procedures performed to identify an ESRD cohort in ORLS, 1970-1996

Analogous steps from those in all-England HES were performed to derive the earlier cohort of incident ESRD patients with some modifications required because of differences in the datasets. The full steps and rules are described below:

2.8.1 1st ORLS Step: Identifying codes associated with advanced renal disease, ESRD and/or renal replacement therapy

An initial screen for potential patients was performed by searching all hospital records held in ORLS for a 'renal-related code'. This included a broader range of terms from that used in the HES derivation and included terms for advanced CKD, applicable in the earlier coding manuals (Table 2-1). Of a total of 4.1 million records, 3.2 million patients had no renal-related code, reducing the potential number of patients to 955,089. Of these, 36,475 were excluded as they had residency outside the area covered by ORLS, leaving 918,614 patients whose records were scrutinised further to find evidence which could confirm maintenance RRT.

Additional variables used only in ORLS to identify potential ESRD patients

Alongside renal-related codes, other variables that were recorded in ORLS were also extracted. This included various combinations of speciality and locality/provider codes. These additional variables were included, in addition to the broader inclusion of terms used in the initial screen of records, to minimise the chances of missing maintenance RRT patients. The additional variables included inpatients records with a speciality code of "33" which referred to 'intermittent haemodialysis' and was only ever observed in patients with hospital admissions to the Churchill hospital, between 1970-1978, the regional RRT centre at that time. Two provider codes, "3215" and "1208" referred to Northampton and Dellwood satellite dialysis units respectively and the dates from which these codes were used were consistent when these units opened, (1989-1994 and 1979-2000 respectively). Any patients with these provider codes were entered into the confirmation or 2nd step. The combination of

a speciality code “361” [Nephrology] was frequently observed to co-exist with regular hospital admissions where there was a primary diagnosis of ‘79993’. 79993 was a code used by the coders between 1987-1994 and was observed to be very common in patients who were having regular admissions under a nephrologists at the Churchill hospital. As there was a high degree of suspicion these represented possible ESRD patients, they were all progressed in the subsequent steps. Before the speciality code of nephrology was ascribed, two other speciality codes (-99 and 13) appeared to be common in patients attending Oxford hospitals. Therefore in conjunction with diagnostic codes indicative of advanced CKD (as defined in Table 2-1), any patients with this combination of codes were also put forward into the subsequent steps. See summary Table 2-2 for full details of the additional variables used to screen ORLS data for any potential maintenance RRT patients.

Table 2-2: Additional information extracted from hospital records used in place of missing variables in Oxford Record Linkage Study (1970-1998)

RRT Type	Consultant Speciality Code	Provider or Hospital Code	ICD-9 term	Description of additional variable and dates of application
Haemodialysis	33	-	-	Haemodialysis treatment specific to the Churchill Hospital, Oxford (1970-78)
Haemodialysis	-	3215, 1208	-	Treatment provided by satellite dialysis units Northampton (1989-1994) and West Berkshire/Dellwood (1979-1998)
Haemodialysis	361	-	79993	Treatment provided at non-Oxford hospitals under a Nephrologist where missing dialysis code substituted with error code 79993 (1987-1994)
Haemodialysis	-99 or 13	4102, 9002	CKD ORLS	Treatment provided at the Churchill Hospital prior to nephrology being an established speciality which has its own code. In the presence of a CKD diagnosis deemed reasonable to assume were under the care of renal physician (1979-1986)

RRT= renal replacement therapy ICD=International Statistical Classification of Diseases and Related Health Problems

2.8.2 2nd ORLS Step: Distinguishing maintenance from temporary RRT

918,614 entered from step one (see subsections 2.8.1 and Figure 2-5) in this confirmatory step designed to ensure that "maintenance RRT" was being satisfied. The series of rules were analogous to the HES rules but when modified, an explanatory note is provided.

Rules for identifying maintenance RRT rules in ORLS 1970-1996

Maintenance RRT Rule 1, ORLS-Kidney transplantation:

The occurrence of any code included in RRT type = 'Prevalent kidney transplantation' or 'Incident Kidney Transplantation' (see Table 2-1)

Explanatory note: No difference to the rules in the HES derivation.

This was the first rule satisfied 553 patients.

Maintenance RRT Rule 2, ORLS-Maintenance peritoneal dialysis:

The occurrence of a record RRT = Peritoneal Dialysis with a code for CKD any time prior to or within 365 days of the start of the record (Table 2-1).

Explanatory note: This differed subtlety from the rule applied in HES as there was not a procedural code for peritoneal dialysis catheter insertion and there was limited use of the fourth character codes specific to ESRD in ICD-9, so the clinical term was widened to include all CKD codes. Again, when AKI codes were mentioned in the same hospital episode, this did not satisfy the criteria of maintenance RRT.

This was the first rule satisfied 640 patients.

Maintenance RRT Rule 3, ORLS-Definite maintenance dialysis:

The occurrence of a record with any code included in RRT type = ‘Dialysis’ (Table 2-1) in a participant who has had:

ORLS Rule 3.1) A diagnosis of ESRD (Table 2-1) any time prior to, or within 365 days after the start of the record

Or

ORLS Rule 3.2) The insertion of an AV fistula or graft (AVF_AVG) (see Table 2-1) any time prior to, or within 365 days after the start of the record

Explanatory note: No difference to the rules in the HES derivation.

This was the first rule satisfied 933 patients.

Maintenance RRT Rule 4, ORLS-Probable dialysis:

The occurrence of at least two episodes with any code included in RRT type = ‘Dialysis’, with at least 90 days between the start of the first ‘Dialysis’ record and the start of any subsequent record containing a ‘Dialysis’ code that did not have a record of acute renal failure diagnosis in the record (see Table 2-1)

Explanatory note: Those patients who fulfilled criteria of ‘probable dialysis’ as their first RRT event and do not subsequently go on to fulfil any of ORLS Rule 3 should be considered ‘Possible dialysis’.

This was the first rule satisfied 1,614 patients.

Maintenance RRT Rule 5, ORLS-Dialysis with mention of CKD:

The occurrence of an episode with any code included in RRT type = 'Dialysis' (Table 2-1) in a participant who has had:

ORLS Rule 5.1 A diagnosis indicative of advanced CKD (see Table 2-1) any time prior to, or within 365 days after the start of the episode.

Explanatory note: Those who fulfilled ORLS rule 5 as their first RRT event and who did not subsequently go on to fulfil any of the other rules ORLS rules 1 to 4 should be considered as 'possible' dialysis.

This was the first rule satisfied 1,238 patients.

2.8.3 Modifications of the rules for identification of maintenance RRT patients in the ORLS

Age restriction

Due to restrictions in chronic dialysis provision early within the cohort, an age exclusion was applied to patients entering the cohort before 1990.

1970-1975	exclude those starting RRT with age >=60 years
1975-1979	exclude those starting RRT with age >=70 years
1980-1984	exclude those starting RRT with age >=80 years
1985-2008	no age restriction was applied

Of the 918,614 patients whose records were interrogated to confirm of maintenance RRT 913,636 were excluded with a further 1,569 excluded after clinician review. This review subjected records of individualised patients to be reviewed to inform the presence of ESRD and start date of RRT.

Clinical adjudication of all ORLS patients

All potential patients identified in ORLS were subject to a manual review of all their linked anonymised hospital admissions that were stored in ORLS.

This additional step was designed to ensure that the pattern of admissions was consistent with an RRT patient and allowed manual attribution of the fact or start date of RRT in ORLS when agreed with two clinicians familiar with the care of patients with renal disease. This was necessary because of aspects of selection which are difficult to set as automated rules. For example it became apparent during the review that the 'Dellwood' centre, as well have having some inpatient beds for haemodialysis was a rehabilitation hospital where some patients were admitted for convalescence following an injury or illness.

2.8.4 3rd ORLS Step: Distinguishing incident from prevalent RRT patients

3,409 patients entered the third step where only adults or patients with patients were identified, (removing 483 patients) and any patient dying within the first 90 days of their RRT start date were removed.

Then patients identified as entering the cohort with a functioning transplant, termed "prevalent transplantation" were also excluded, a total of 278 more patients.

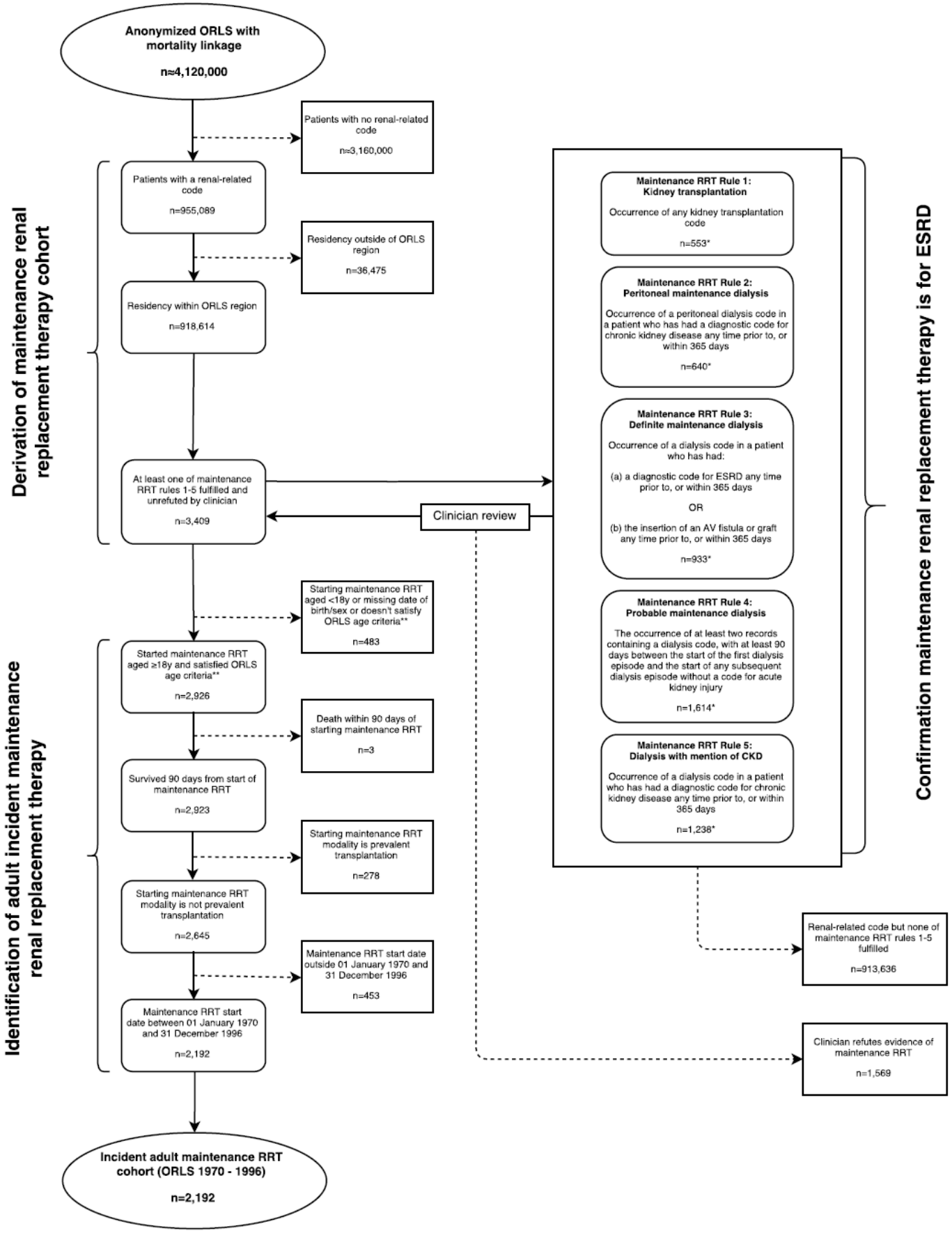
Explanatory note: It is likely that these patients may have moved from outside the catchment of ORLS, where they had their incident transplant operation, to then moving into the catchment area of the ORLS where subsequent admissions were captured.

2.8.5 Defining entry date to the cohort

For each patient that met the criteria that defined maintenance RRT, the date of first maintenance RRT was as per the derivation in HES but had the additional oversight of a clinical review of all hospital inpatients records.

A summary of the derivation flowchart applied to ORLS is provided in Figure 2-5.

Figure 2-5: Treated end-stage renal disease cohort derivation (ORLS 1970-1996)



AV = Arteriovenous. CKD = Chronic kidney disease. ESRD = End-stage renal disease. ORLS = Oxford Record Linkage Study. RRT = Renal replacement therapy. (Code) refers to diagnostic or procedural codes. *Participants could fulfil more than one rule, but only the first rule which was fulfilled is counted. **If RRT start date between 1970 - 1974 then age<60, if RRT start date between 1975 - 1979 then age<70, and if RRT start date between 1980 - 1984 then age<80. To ensure reliable derivation of the ORLS cohort, a broad range of diagnostic and procedural codes was used and combined with clinician review of individual patient records.

2.9 Internal validation of the rules which defined maintenance RRT

To assess the validity of these specific algorithms or 'rules' designed to confirm maintenance RRT subsequent hospital admissions of patients included into the final cohort were reviewed to see if they ever fulfilled any of the other rules in their future hospital episodes. Patients first identified in 'rule 1' (i.e. kidney transplantation) were not tested as this unambiguously defines ESRD.

Table 2-3: Internal validation of the rules which confirmed maintenance RRTTable 2-3 describes the proportion of patients identified as undergoing maintenance dialysis and subsequent not fulfilling any other rule.

Table 2-3: Internal validation of the rules which confirmed maintenance RRT

First rule satisified	Number satisfying this rule	Number (%) of patients NOT subsequently fulfilling another criteria of maintenance RRT
all England HES Rules		
HES Rule 2-Peritoneal dialysis	11,687	327 (2.6%)
HES Rule 3-Definite dialysis	25,516	1,122 (4.4%)
HES Rule 4-Probable dialysis	3,042	55 (1.8%)
ORLS Rules		
ORLS Rule 2-Peritoneal dialysis	392	16 (14.1%)
ORLS Rule 3-Definite dialysis	343	3 (0.9%)
ORLS Rule 4-Probable dialysis	606	47 (7.8%)
ORLS Rule 5-Dialysis with mention of CKD	696	299 (43%)

In all-England HES, consistently less than 5% of patients, no matter what maintenance RRT rule (2:'peritoneal', 3:'definite', 4:'probable') was used to initially identify them as receiving maintenance RRT did not, in any future inpatient hospital admissions, satisfy other criteria of maintenance RRT. In ORLS period of derivation, this proportion was larger constituting mainly patients identified by rule 4:'probable' and ORLS rule 5:'dialysis with mention of CKD'. However all patients identified in ORLS had the advantage of individual clinical review

of hospital episodes. Furthermore external and some direct validation of the cohorts is described in Chapter 4 Validation.

2.10 Procedures performed to identify general population hospital controls, 1970-2008

To permit comparative analyses of the ESRD cohorts with the general population, a large set of contemporaneous general population hospital controls were derived from the same datasets using a method previously developed described and adopted previously by UHCE.[96] Patients admitted to hospital for a minor medical condition or procedures were selected across the whole cohort as these are more likely to be representative of the general population than those admitted for serious diseases. Any hospital control who ever underwent maintenance RRT was excluded. A list of the mapped codes used to identify the general population hospital controls is found in Table 2-4.

The benefit of this approach is that the comparative population has the same opportunities to have prior co-morbid illnesses identified from their respective prior hospitalisations, and any such illnesses would have been captured in a consistent way, by the same body of trained clinical coders, allowing more reliable mortality trend analyses.

Defining the index date for the general population hospital controls

Entry into the cohort was defined as the start date of the episode in which a specified diagnosis was recorded or the date of the minor procedure. In patients where there was more than one control event, the episode of care which was included in the analysis as the control event was selected at random (i.e. a control participant could only be included once).

Other criteria applied to general population controls, 1970-2008

To ensure consistency with the ESRD cohort, general population controls had to be aged 18 years or older as were those patients who died within 90 days of their index event.

Table 2-4: Diagnoses and procedures used to identify the index admission for control population, by coding manual

Diagnoses	ICD-10	ICD-9	ICD-8	ICD-7
Ophthalmic				
Squint	H49:H51	378	373	384
Cataract	H25	366	374	385
General surgical				
Gallbladder disease	K80:K81	574:575	574:575	584:585
Hernia	K40	550	550	560:561
Varicose veins	I84	455	455	461
Haemorrhoids	I83	454	454	460
Otorhinolaryngology				
Otitis externa/media	H60:H67	380:382	380:382	390:392
Nasal polyp/deflecting septum	J33, J34.2	470:471	504:505	514:515
Injuries				
Limb fractures	S42, S52, S62, S82, S92	810:816, 823:826	810:816, 823:826,	810:816, 823:826,
Dislocations sprains and strains	S03, S13, S23, S33, S43, S53, S63, S73, S83, S93	830:839, 840:848	830:839, 840:848,	830:839, 840: 848,
Head injury	S06	850:854	850:854,	852:856
Superficial injury and contusion	S00, S10, S20, S30, S40, S50, S60, S70, S80, S90	910:919, 920:924	910:918, 920:929	910:918, 920:929
Miscellaneous				
Nail diseases	L60	703	703	712
Sebaceous cyst	L72.1	7062	7062	7142
Knee-internal derangement	M23	717	724	734
Bunion	M20.1	7271	730	740
Contraception management	Z30	V25	Y43	-
Upper respiratory tract infection	J00:J06	460:466	460:466	470:475
Teeth disorders	K00:K03	520:521	520:521	530:535

Procedures/Operations	OPCS-4	OPCS-3	OPCS-3	OPCS-1
Appendiectomy	H01:H03	441:444	441:444	441
Dilation and curettage	Q10.3:Q11.4	703:704	703:704	731:732
Total hip replacement	Y37:Y39	810	810	-
Total knee replacement	Y40:Y42	812	812	-
Tonsillectomy/adenoidectomy	E20, F34, F36	230:236	230:236	260:264

ICD=International Statistical Classification of Diseases and Related Health Problems, OPCS=Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures

2.11 Extraction of baseline characteristics for ESRD and general population

Age

Patients' exact ages were calculated from their date of birth as identified at the start date of maintenance RRT or, for hospital controls, the admission date for the minor conditions or procedure.

Sex

The sex of the patient (male or female) was captured at the first hospital admission.

Ethnicity

Ethnicity was not recorded in ORLS. In all-England HES the UK-Renal Registry ethnicity categories were applied to the 18 data variables of ethnic categories in HES. There were classified into groups as per Table 2-5.

Table 2-5: Categories of ethnicity coding used in Hospital Episode Statistics

Ethnic group ID	Description
1	White (including British White, Irish White and Any other White background)
2	Black (including White and Black Caribbean [Mixed], White and Black African [Mixed], Caribbean [Black or Black British], African [Black or Black British] and Any other Black background)
3	South Asian (Indian [Asian or Asian British], Pakistani [Asian or Asian British], Bangladeshi [Asian or Asian British])
4	Chinese
5	Other (including any other Asian background, White and Asian (Mixed) and Any other Mixed background and any other ethnic group)
9	Unknown or not stated

Comorbidities

Comorbidities were extracted from hospitalizations prior to the index date with a fixed period of 5 years of retrospective follow-up in ORLS and 2 years in HES. Comorbidities based on

the Charlson[102,103] index were identified from any diagnostic and procedure codes on admission records at the time of entry into the cohort and for a 'fixed period' of retrospective follow-up (i.e. interrogating admission data over a set number of years which preceded the defined start date of maintenance RRT).

Comorbidities were grouped into: (i) diabetes mellitus (type 1 and 2 combined); (ii) vascular disease, including major coronary disease, heart failure, cerebrovascular disease and peripheral arterial disease; and (iii) non-vascular disease including liver disease, cancer, chronic obstructive pulmonary disease (COPD), peptic ulcer disease, hemi- or paraplegia and connective tissue disease. A table of codes which defined the comorbidities and its mapped terms is provided in Table 2-6. For further details, including the rationale for the duration of the retrospective follow-up and how clinical coding practices have changed see section Chapter/Section 3.5.1, starting at page 103.

Index of Multiple Deprivation

The socio-economic status of participants was only possible to identify in HES. Here, the Index of Multiple Deprivation (IMD) was used. IMD is a measure of multiple deprivation assessments at the super-local level. It has seven domains:

1) Income
2) Employment
3) Health and disability
4) Education
5) Crime
6) Barriers to housing and services
7) Living environment

IMD version 2004, ranked the 32,482 geographical areas in England by deprivation (rank 1 being the highest deprivation).[104] The IMD rank score was extracted using data recorded on the episode when maintenance RRT was deemed to have begun or on the admission for the minor comorbidities/procedures for hospital controls.

Table 2-6: Coding of comorbidity by International Classification of Disease (ICD) diagnoses and Office of Population Censuses and Surveys (OPCS) procedures

	ICD-10	ICD-9	ICD-8	ICD-7
Diabetes	E10:E14	250[†]	250	260
Vascular				
Major coronary disease	I21:I23, I252, I25.6	410, 412, 414.8	410, 412	420
Congestive heart failure	I42:I43, I50, I11.0, I13.0, I13.2, I25.5, P29.0	402, 404, 425, 428	402, 404, 425, 427	434
Cerebrovascular disease	I60:69, G45, G46, H34.0	430:431, 434:436, 438, 432.0, 432.1	430:431, 433:436	330:334
Peripheral vascular disease	I70:I74, K55.0, K55.1, K55.8, K55.9, R02, Z95.8, Z95.9, E10.5, E11.5, E12.5, E13.5, E14.5	440:444, 250.6	440:445	450:454
Non-Vascular				
Liver	B18, K70:K76, I85, I86.4, I98.2	570:573	571, 573	581
Cancer	C00:C97	140:208, V10	140:239	140:239
COPD*	J41:J47, J60:J67, J68.4, J70.1,J70.3, J84, I27.8, I27.9	416.8, 416.9, 491:496, 500:506, 515, 508.1	490:493, 515:518	241, 501:502, 523:526, 527.1
Peptic ulcer disease	K25:K28	531:534, 530.3	531:534	540:542
Hemi- or paraplegia	G81:G83, G04.1, G11.4, G80.1, G80.2	342:344	343:344	351:352
Connective tissue disease	M05: M06, M30:M36	517, 710, 714, 446.0, 446.4, 446.7, 447.6	712, 716, 734, 695.4, 696.0	722

	OPCS-4	OPCS-3	OPCS-2	OPCS-1
Vascular				
Major coronary disease[‡]	K40:K47, K49, K50, K75	304.1, 304.3	304.1, 304.2	312
Peripheral vascular disease[¶]	X07:X12, J10.4, K33, L04, L12:L13, L16, L18:L21, L25:L31, L33:L35, L37:L39, L41:L54, L56:L60, L62:L63, L65:L66, L68:L71, L76, L89, L97, O20	304, 320:321, 325, 552, 822:826, 861:866, 870:871, 873:875, 878, 880:884, 887:888, 890	860:875, 884, 8811	880:886

*COPD=chronic obstructive pulmonary disease
[‡]Includes codes for coronary artery bypass surgery or percutaneous coronary interventions (angioplasty +/- stent)
[¶]Includes codes for (non-traumatic) limb amputations and non-coronary arterial interventions

2.11.1 Renal characteristics pertinent to ESRD cohort only

Initial RRT modality

The modality assumed at the start date of maintenance RRT depended on the rule that defined the start of maintenance RRT:

> If rule 1 (i.e. kidney transplantation) in HES or ORLS identified the start of maintenance RRT then the patient was assumed to have received a pre-emptive renal transplant.
>
> If rule 2, 3 or 4 identified the start of maintenance RRT then the patient was assumed to be receiving dialytic therapies.

Attempts were made to try and reliably establish which dialytic therapy (haemo- or peritoneal dialysis) was the initial modality first but this was not possible. Current data suggests that once differences in case-mix are adjusted for, then the survival is not modified by dialysis modality.[105,106]

Primary renal disease

For each identified participant a primary renal diagnosis (PRD) was derived using episode diagnoses reported in the admission that defined maintenance RRT and any preceding spell (with the exception of polycystic kidney disease (PKD) and other hereditary causes which could have been identified in any episode).

If more than one PRD was present then the PRD which was selected based on the following hierarchy:

> Polycystic kidney disease
> Other hereditary
> Glomerulonephritis
> Diabetic kidney disease

Systemic disease
Tubulo-interstitial disease (including cases of obstructive uropathy)
Miscellaneous
Hypertension/ischaemic
Unknown

If none of these diagnoses were present, and the patient had diabetes mellitus as a comorbidity at the date of the start of maintenance RRT, then diabetic kidney disease was selected, otherwise the PRD was considered to be 'unknown'.

For the purposes of subsequent presented data: Other hereditary, Systemic disease, Tubulo-interstitial disease, Miscellaneous and Hypertension/ischaemic should be considered as an 'Other known diagnosis' category. A table showing the mapped terms for the main groups of primary renal disease is presented in Table 2-7.

Table 2-7: Diagnostic codes used to identify main groups of primary renal disease

	ICD-10	ICD-9	ICD-8	ICD-7
Diabetic kidney Disease	E10.2, E11.2, E12.2, E13.2, E14.2, N08.3	250.4	-	-
Polycystic kidney disease	Q61.1, Q31.2, Q61.3	753.0, 753.1	753.0, 753.0	757
Glomerulonephritis	D69.0, M30.1, M31x, N00x:N07x	582, 591, 592, 593, 598	580, 581	590, 591
Other Known	A98.5, B52.0, B65.0, C88.0, C90.0, D57.0, D59.3, D89.1, E72.0, E74.0, E75.2, E78.6, E83.0, E85.0, G63.8, I12.0, I13,I70.1, N08.0, N08.1, N08.2, N08.4, N08.5, N08.8, N11, N28.0, N13:N16, K76.7, M30.0, M31.1, M35.0, P96.0, Q27.1, Q27.2, Q60, Q61.4, Q61.5, Q61.8, Q61.9, Q62, Q63, Q87.2, Q87.8	84.8, 120, 203, 270.0, 274.1, 273, 283, 403:405, 421, 446, 590:593, 598, 593.8, 710, 753.2:753.9	84.8, 12.0, 203.0, 275.4, 275.5, 404, 403, 421.0, 440.1, 446, 590:595, 753.2:753.9, 759.6, 762.0	115, 123, 203, 430, 442, 600:607, 642

2.12 Extraction of outcomes; mortality data

ORLS and all-England HES have linked data from the national mortality data held by the Office for National Statistics (ONS). This provided the fact of death, date of death, and the proscribed underlying cause of death (UCD) for all patients. The UCD is defined by the World Health Organization (WHO) as, “the disease or injury that initiated the train of events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury.” In addition, HES and ORLS held ancillary data on the codes recorded in the various parts of the medical certificate of death, but did not distinguish whether diagnoses were in Part I and Part II (i.e. whether they were direct or contributory causes).

For the proposed cause-specific mortality analyses, deaths were grouped as in Figure 2-6 using the mapped codes in Table 2-8. These categories were chosen to be clinically relevant and large enough to generate enough events.

Figure 2-6: Coding of death categories by International Classification of Disease (ICD) version

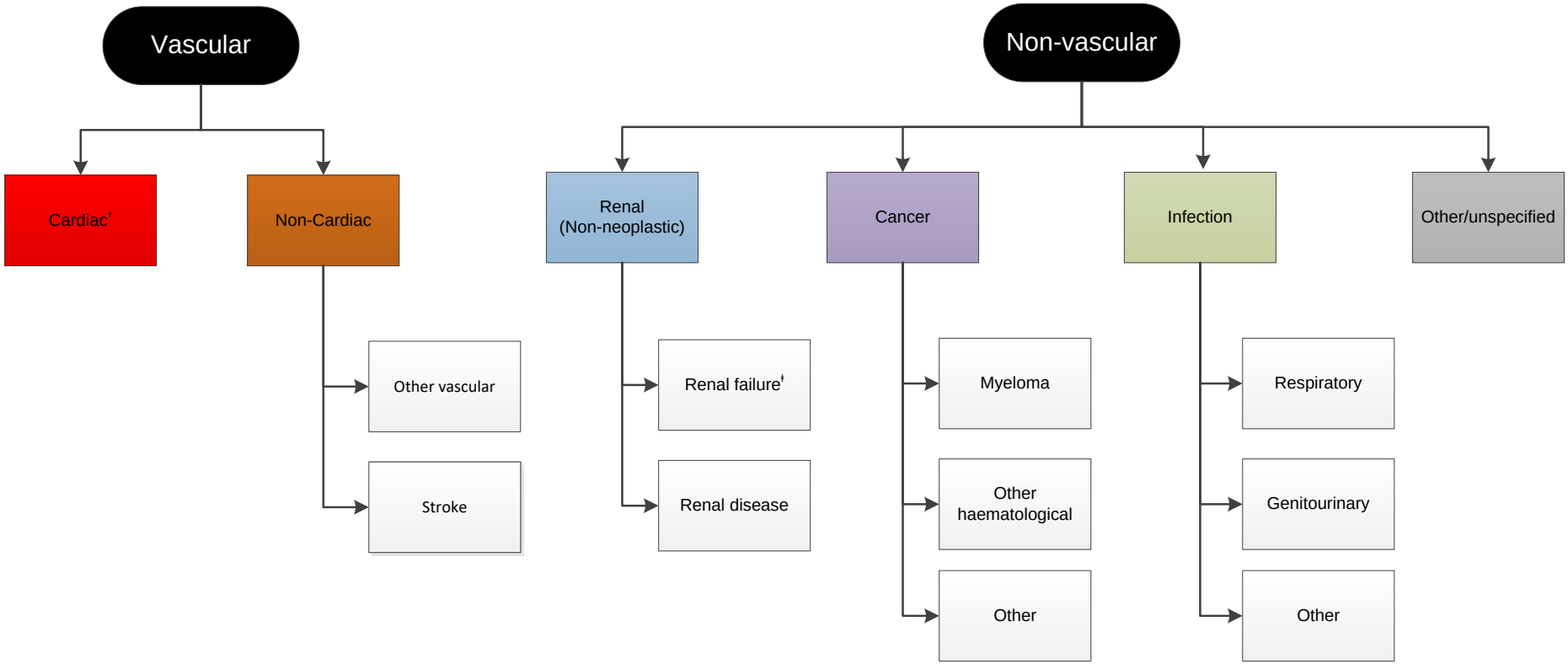


Table 2-8: Coding of death categories by International Classification of Disease (ICD) version

	ICD-10	ICD-9	ICD-8	ICD-7
Vascular				
Cardiac[†]	I00:I09, I11, I20:I25, I27:I52, R96, R98	390:399, 402, 410:414, 416:429, 7981, 798.2, 798.9	390:399, 402, 410:414, 420:429, 795.2, 796.2	400:416, 420:422, 430:434, 795.2, 795.3
Non-cardiac vascular				
Other vascular terms	I10, I14:I15, I26, I70:I84, I86:I99, E10.5, E11.5, E12.5, E13.5, E14.5	401, 405, 415, 440:459, 250.6	400:401, 440:448, 450:458	440:441, 443:445, 450:468
Cerebrovascular	I60:I69	430:438	430:438	330:334
Non-Vascular				
Renal (non-neoplastic)				
Renal failure[‡]	A98.5, E10.2, E11.2, E12.2, E13.2, E14.2, I12:I13, N17:N19, N25:N27, O08.4, O90.4, P96.0, R39.2, Y60.2, Y61.2, Y622, Y841, T82.4, T82.7, T82.8, T82.9	403:404, 584:589, V45.1, V56.0, V56.8, 250.3, 639.3, 794.4	403:404, 580, 582:584, 792	442, 446, 590, 592:594, 792,
Renal disease[#]	E85, N00:N08, N14:N16[¶], N20:N23, N28:N29, Q60:Q63, M30:M36, C88.0:C88.3, D47.2, D89.0:D89.2, M10.3, O10.2, O10.3, Q27.1, Q27.2,	273, 580:583, 591:593, 710, 753, 2766, 277.3, 652.1, 652.2, 747.6,	446, 581, 591:593, 753, 519.1	522, 591, 601:604, 757
Cancer				
Myeloma	C90	203	203	203
Other haematological	C81:C89, C92:C96	200:202, 204:208	200:202, 204:208	200:202, 204:208
Other	C00:C80, C97	140:199, 230:239	140:199, 230:239	140:189, 191:199, 230:239
Infection				
Respiratory	J09:J18, J85:J86	480:487, 510, 513	470:474, 480:486, 510, 513	480:493, 518, 521
Genitourinary	N10:N13, N30, N34, N41, N45, N39.0	590, 595, 597, 601, 604, 599.0	590, 595, 597, 601, 604, 680:686, 710, 599.0	600, 605, 607, 611, 614
Other[*]	A00:B99, L00:L08, M00:M03, M46, M49, M73, M86, K35:K37, K57, K61, K65, K80:K81, K83, G00:G09, N70:N77	001:139, 680:686, 711, 730, 540:542, 562, 566:567, 572, 574, 320:326, 614:616	000:136, 720, 540:543, 562, 566, 567, 574, 575, 320:324, 612, 620, 622	001:138, 690:698, 720,730, 550:552, 575, 576, 584, 585, 340:344, 622, 630
Other/unspecified	All other ICD-10 codes	All other ICD-9 codes	All other ICD-8 codes	All other ICD-7 codes

[†]Includes codes for sudden death
[‡]Includes codes for AKI, CKD, renal sclerosis, renal failure unspecified, uraemia, diabetes mellitus with renal complications, hypertension with mention of renal failure, misadventures/complication during dialysis. ICD-7 & ICD-8 terms chronic nephritis are also included
[#]Includes terms for glomerular disease, tubulo-interstitial disorders, obstructive uropathies, urolithiasis, congenital abnormalities affecting the kidney, amyloid, paraproteinaemias, fluid overload and autoimmune/vasculitis/connective tissue disorders
[¶]Excludes urinary tract infection ("N160") which is included in the infection category
[*]Includes skin and soft tissue, bone and joint, abdominal, central nervous system, gynaecological (not during puerperium) infection and generic infection chapters.

2.13 Discussion and conclusions

This chapter has described the specific procedures, which identified a combined cohort of 44,922 Oxford and English incident ESRD patients who survived 90 days from starting maintenance RRT. This is unique, as no reports of other ESRD cohorts, identified exclusively from routinely collected hospital inpatient datasets has been found in the literature. Furthermore the concurrent identification of over 5 million general population hospital control patients will permit comparative analyses. The datasets have linkage to national mortality registry data providing an opportunity to analyse longitudinal mortality trends, an invaluable epidemiological tool providing an assessment of health risk and provide evidence whether there has been progress of a given period of time. Mortality trends assist in identifying factors that are related to differences in patient mortality, although can only yield these results based on variables which are measured. Almost uniquely in ESRD epidemiology, has the disease of interest seen such a change in the characteristics of patients selected to receive treatment and this poses certain challenges. As age and certain comorbidities are both determinants of selection to receive RRT and mortality in patients with ESRD,[6-8,107-110] any longitudinal analyses should ideally be adjusted for these secular changes in order to be informative.

Defining the actual study population that is being studied is critical as there are large differences in mortality rates between those who receive treatment for ESRD, as oppose who do not. The death rates among those with patients with *untreated* ESRD, either because they have no access to renal replacement services or have chosen to have non-dialysis care in the setting of symptomatic uraemia is unsurprisingly high, with patients generally dying in a matter of days or weeks, depending on residual renal function. Therefore including untreated patients into any mortality statistics of an entire ESRD population would therefore increase the overall death rates. In contrast, if the deaths of those withdrawing from dialysis were excluded, or patients with a stable

eGFR<15mls/min/1.73m^2 (which would fulfil the recent formal biochemical definition of ESRD) but who have not begun RRT then the deaths rates would be lower as this level of renal function rarely directly leads to death.

Isolated standardized mortality statistics of ESRD populations are rarely useful – it is only when there are compared to death rates in other populations and/or have a longitudinal component that they become more informative. This thesis proposes to do both of these things, making its results more reliable. For example, the age stratified cardiovascular mortality rates (per 1000 person-years) for dialysis patients aged 35-44 years RRT was reported to be 21.2 yet it is only when you know the same age specific rates in a comparative general population of 0.2 per 1000py that the magnitude of the absolute excess for age-matched dialysis patients is apparent.[81] Furthermore comparing relative indices, in this narrowly focussed example would give a '100 fold' increase in age specific rates, which is rather sensationalist.[111] There were small numbers of deaths and other than age, no attempt was made to adjust for the other comorbidities of such patients such as a presumed significantly higher rate of type 1 diabetes. Moreover, these analyses did not have data to describe changes in rates over time as the data were analysed at a single time point.

2.13.1 Limitations of using routinely collected healthcare data

This thesis includes ESRD patients who have been *positively* selected onto a RRT programme and survived 90 days from the start of maintenance RRT. It does not include ESRD patients that have been refused or declined RRT whereby non-dialysis/'conservative has been decided upon. Hospital inpatient records do not provide such a distinction as often these decisions are made in the outpatient setting. The exclusion of patients who died within the first 90 days of starting maintenance RRT is typically done in registry data and will allow fairer comparisons of this English data to other resources. The 90 day period is clinically (yet arbitrarily) chosen, as the actual start date of *maintenance* dialysis can be rather difficult

to determine. Many patients begin in the setting of an acute illness from which their prior remaining renal function is lost and they do not recover or in the case of peritoneal dialysis at what point patients training finishes and they begin full therapy is a matter of debate.

This observational data does not hold other common variables which are known to effect mortality, LDL-C, blood pressure, smoking habits and measures of adioposity.

This thesis therefore proposes to study the mortality trends of incident patients receiving treatment for ESRD (in the form of maintenance dialytic therapies or a kidney transplant). It will exclude maintenance RRT patients who died within 90 days (an arbitrary period used in nephrology to remove biases introduced by early mortality on RRT) and compare mortality rates to a set of contemporaneously derived general population hospital controls.

2.14 Bullet points of Chapter 2

- Permission to access fully anonymised and encrypted, prospectively-collected, individually-linked hospital admission data from ORLS (1965-1999) and all-England HES (1998-2011) data were obtained

- Diagnostic (ICD) and procedural (OPCS) coding manuals covering the period 1965-2011 period of proposed study were sourced and transcribed into usable formats

- Diagnostic and procedural codes relevant to renal disease and its' treatment were identified

- A three stage process of **a)** identifying potential ESRD patients, **b)** confirming *maintenance* RRT and then **c)** identifying adults starting *incident* RRT was developed. This was applied to HES (2000-2008) and adapted to ORLS (1970-1996) periods of study.

- Major comorbidities grouped into **a)** diabetes, **b)** vascular and **c)** non-vascular were identified in a fixed period of retrospective follow-up from the index date to the cohort.

- An extraction of a contemporaneous general population controls was also performed

Chapter 3 Baseline characteristics

Baseline characteristics of cohorts of 45,000 treated ESRD patients and 5.6 million general population hospital controls from Oxfordshire and England 1970-2008

3.1 Abstract

Background

The characteristics of patients starting renal replacement therapy (RRT) has changed substantially over the 40 years since 1970. A description of these changes for a cohort of treated end-stage renal disease (ESRD) patients are presented in parallel to secular changes observed in a contemporaneous set of general population hospital controls. The impacts of changes in datasets over time on the ascertainment of comorbidities are also explored.

Methods

The baseline demographics, comorbidities and renal characteristics of an incident cohort of treated ESRD adults derived from routine hospital inpatients datasets; Oxford Record Linkage Study (ORLS; 1970-1996) and all-England Hospital Episode Statistics (HES; 2000 2008) are presented. The characteristics of a large set of contemporaneous general population hospital controls are reported for comparison.

Results

In total 44,922 new treated ESRD RRT patients were identified: 2,192 from ORLS and 42,730 from HES. The median age at start of RRT for Oxfordshire patients rose from 46 years (IQR 36-60) in 1970-1985 to 61 years (IQR 46-72) in 2006-2008. The proportion of females receiving RRT has remained largely unchanged at about 40%. The proportion of ESRD patients identified as having comorbid illness at the start of RRT increased steeply. The crude prevalence of diabetes increased from 6.7% in 1970-1990 to 33.9% in 2006-2008; vascular disease prevalence from 10.0% to 28.3%; and non-vascular disease from 7.8% to 27.5%. Similar changes were observed in the Oxfordshire and all-England ESRD cohorts.

Among 5.6 million general population hospital controls, median age at entry into the cohort increased from 40 years (29-57) in 1970-1990 to 47 years (33-64) in 2006-2008. The prevalence of major comorbidities also increased in this population: diabetes prevalence

rose from 0.8% to 4.1%, vascular disease from 2.0% to 3.6% and non-vascular disease 3.6% to 9.8%.

Conclusions

Since 1970, when RRT was introduced in Oxfordshire, the age structure and comorbidity profile of treated ESRD patients has changed dramatically, reflecting the increased provision and access to RRT. The magnitude of the secular changes observed in the ESRD and general population hospital controls, especially with respect to age and the prevalence of comorbid illnesses, means that any assessment of mortality trends needs to adjust for these key determinants of mortality to be interpretable.

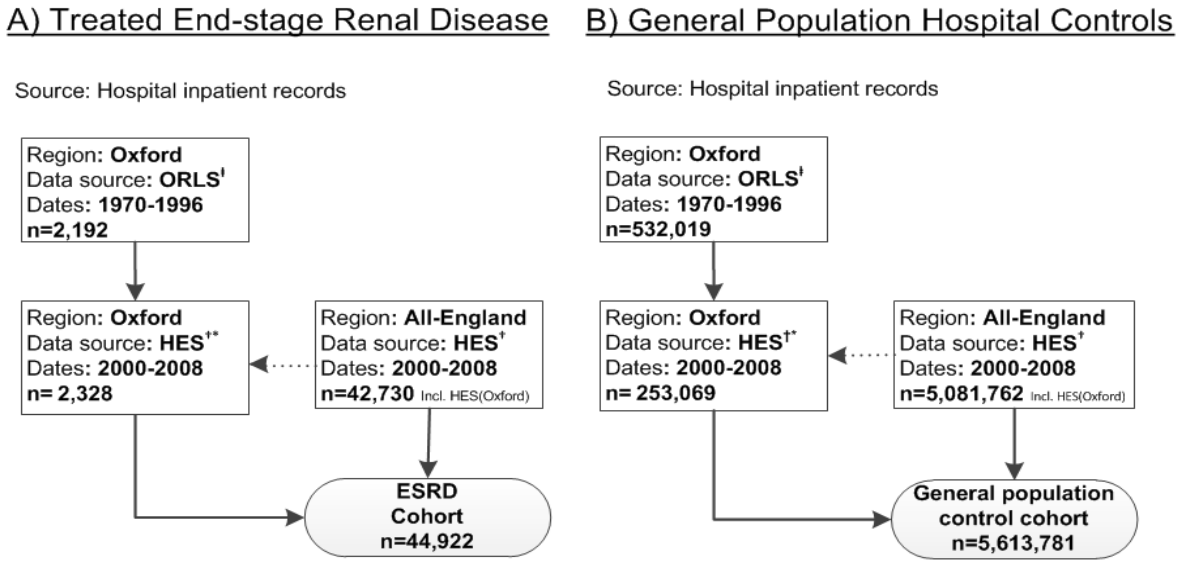
3.2 Introduction

A retrospective adult cohort of incident ESRD patients, receiving renal replacement therapy (RRT) has been derived from routinely collected hospital inpatients datasets over a period of 40 years. Their baseline demographic characteristics are presented and discussed alongside baseline characteristics of a large set of general population hospital controls.

3.3 Methods

For a full description of the cohort derivation, see Chapter 2 In brief, an algorithm was specified to identify, between 1970 and 2008, a cohort of newly treated adult (≥18 years) ESRD patients, using routinely collected hospital inpatient datasets. Between 1970 and 1996 patients were identified from Oxford Record Linkage Study with a similar derivation process being expanded into all-England Hospital Episode Statistics (HES) between 2000 and 2008. This included a regional subset of HES, hereafter termed "HES Oxford".[93] HES Oxford

Figure 3-1: Datasets used to identify retrospective cohorts of end-stage renal disease patients



†ORLS=Oxford Record Linkage study. ORLS region includes Oxfordshire, Berkshire, Buckinghamshire and Northamptonshire. ESRD= end-stage renal disease. ESRD cohort includes new treated end-stage renal disease patients surviving 90 days. †HES=Hospital episode statistics. *=Termed HES (Oxford) in figures. All patients had upto three years follow-up; end date for ORLS was 31st Dec 1999 and 31st Dec 2011 for HES.

closely approximated the geographic area covered by ORLS. Full details of the criteria used to identify these patients can be found in Chapter 2 Cohort derivation. A summary flowchart of the available data is provided in Figure 3-1.

To allow mortality rates from the new treated ESRD cohort to be compared to a group of contemporaneous adults, hospital controls who were never recorded as undergoing RRT were selected so as to be reasonably representative of the general population by using admissions for a range of minor conditions, a full list of such conditions can be found in Table 2-4.

Basic demographic data (age, sex, ethnicity and socio-economic status (SES) were taken from the hospital admission records at the start of maintenance RRT. Comorbidities based on the Charlson[102,103] index were also identified from diagnostic and procedure codes on admission records at the time of entry into the cohort and for a 'fixed period' of retrospective follow-up (ie, interrogating admission data over a set number of years which preceded the defined start date of maintenance RRT). Comorbidities were grouped accordingly: (i) diabetes mellitus (including type 1 and 2); (ii) vascular disease, including major coronary disease, heart failure, cerebrovascular disease and peripheral arterial disease; and (iii) non-vascular disease including liver disease, cancer, chronic obstructive pulmonary disease (COPD), peptic ulcer disease, hemi- or paraplegia and connective tissue disease (Table 2-6).

For the derived ESRD cohort in HES, two specific renal characteristics were also derived: a presumed primary renal disease (PRD) and an initial RRT modality. PRD was categorised into polycystic kidney disease, glomerulonephritis, diabetic kidney disease, or other/unknown cause, and an initial RRT modality was dichotomised into either being dialysis or kidney transplant, which by definition indicated a presumed pre-emptive transplant.

Identifying the socio-economic status of the cohort was also only possible in HES and involved deriving the index of multiple deprivation (IMD version 2004) which ranked the

32,482 geographical areas in England by deprivation (rank 1 being the highest deprivation).[104]

3.3.1 Statistical Methods

Number and proportions are presented for categorical variables. The age distribution was not normally distributed and so medians with interquartile cutoffs are presented. To assess whether baseline characteristics changed significantly over time, tests for the differences across the year groups were performed using Chi-squared (χ^2) tests for binary variables and Kruskal-Wallis test for age.

3.4 Results

3.4.1 Demographics of ESRD cohort

The ESRD cohort included 44,922 treated ESRD patients identified over the 40 year period of which 2,192 patients were identified from ORLS and 42,970 from all-England HES, including 2,328 from HES Oxford (Figure 3-1 & Table 3-1).

Age

The median age of patients starting RRT in Oxfordshire rose by 18 years; from 49 years (interquartile cut offs, 36-60) in 1970-1990 to 61 years (46-72) in 2006-2008. If the initial year group were divided, it is apparent that this increase began early; median age increased from 46 years in 1970-1985 to 56 years in 1986-1990, and 59.5 years in 1994-1996 (Figure 3-2). Consequently, in 1970-1990, only 25% of new patients were older than 60 years compared to nearly 50% of patients from 2000 onwards. Similarly, between 1970 and 1990 the proportion of patients commencing RRT who were ≥70 years was 8.2%, increasing to nearly one third by 2006-2008. Similar trends were observed in HES Oxford and in all-England data from 2000 (Table 3-1).

Gender

There has been no significant change in the overall proportion of females across the entire ESRD cohort, contributing approximately 40% across both cohorts (p for trend over time = 0.20 for ORLS/HES Oxford and p=0.50 for all-England-HES) (Figure 3-2 & Table 3-1).

Ethnicity

Ethnicity data were not reliably recorded in ORLS. From 2000-2008 the proportion of HES Oxford patients with any known ethnicity increased from 81.3% to 96.0%. Of those with a

recorded ethnicity the proportion of non-whites increased from 13.2% in 2000-2002 to 15.9% in 2006-2008 but patients of white ethnicity predominated in all year groups at between 84-86%. In all-England HES data, of these patients with known ethnicity, approximately 80% were of white ethnicity. There were, on average, greater proportions of Blacks (6.6% vs 4.0%) and South Asians (8.5% vs. 7.0%) recorded in all-England HES than HES Oxford (Table 3-1).

Socio-economic status

In HES Oxford, the largest proportion of patients was identified from the highest IMD quintile (43-45%) with nearly two thirds of patients consistently being derived from the two most affluent quintiles. The SES structure in HES Oxford remained largely unchanged between 2000 and 2008. The SES structure in all-England stood in contrast where there was a more even distribution of patients across each IMD quintile. The proportions of patients from each IMD quintile were very different in HES Oxford compared to all-England, reflecting that Oxfordshire includes many districts that were classified as 'least deprived'. The distribution of patients from the each IMD quintiles did not appear to change over the decade of all-England HES.

Comorbidity

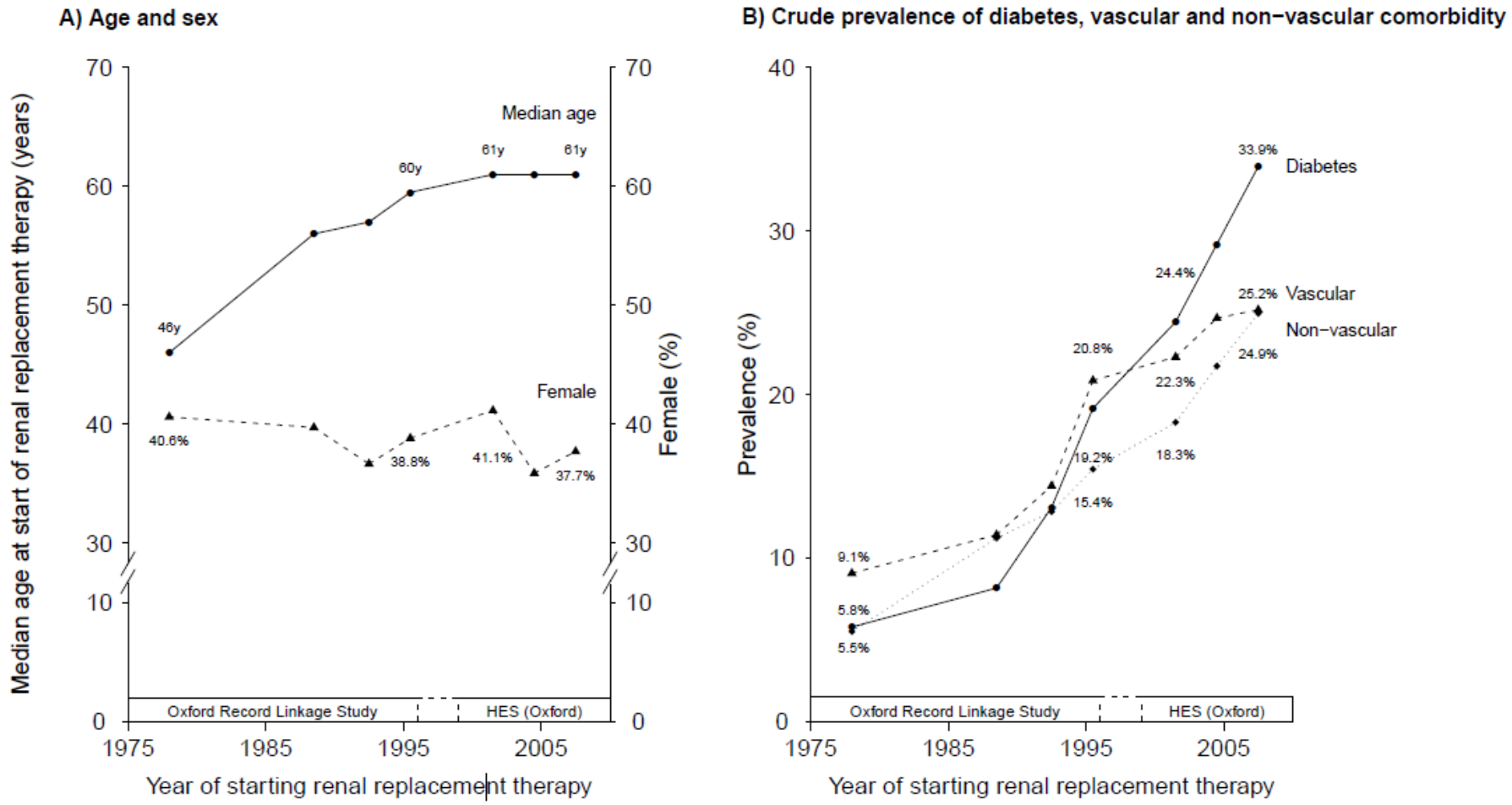
The reported prevalence of baseline major comorbid illness all increased significantly over time across the Oxfordshire cohort over time. The proportion of patients with diabetes was 5.8% between 1970 and 1985, increasing to 8.1% by 1986-1990, then doubling to 16.8% by 1991-1996 and it then doubled again by 2006-2008 (Figure 3-2). Overall the prevalence of diabetes it increased over 4-fold from 6.7% in 1970-1990 to 33.9% in 2006-2008 (Table 3-1).

Prior vascular disease nearly trebled, from 9.1% in 1970-1984 to 25.2% in 2006-2008. This constituted rises in peripheral vascular disease from 3.0% to 12.9%, major coronary disease from 2.6% to 8.3%, congestive heart failure from 5.2% to 10.5% and cerebrovascular disease from 1.4% to 3.5%.

The proportion of new ESRD patients with non-vascular comorbidities increased from 7.8% in 1970-1990 (and even lower at 5.5% in 1970-1985, (Figure 3-2) to 24.9% in 2006-2008 which largely constituted a rise in the prevalence of COPD (1.3% to 10.3%) and smaller increases in the prevalence of all other non-vascular comorbidities: cancer (2.9% to 7.6%), connective tissue disease (2.0% to 4.9%), liver disease (0.5% to 2.3%), peptic ulcer disease (1.6% to 1.9%) and hemi-paraplegia (0.2% to 1.5%).

A summary of baseline comorbidities are presented in Table 3-1 and graphically in Figure 3-2.

Figure 3-2: Baseline characteristics of new treated end-stage renal disease patients, by year



Excludes patients dying within 90 days. HES = Hospital Episode Statistics (Oxford). Results are plotted at midpoint for each year group. For this figure, the Oxford Record Linkage Study includes 4 year groups (1970–85, 1986–90, 1991–93, 1994–96).

Table 3-1: Baseline characteristics of new treated end-stage renal disease patients, by region and year

	Year Groups								P-value for difference across years groups	
Region covered	Oxford, ~40 Years					All-England, ~10 years				
Data Source	Oxford Record Linkage Study		Hospital Episode Statistics (Oxford)			Hospital Episode Statistics (All-England)				
	1970-1990	1991-1996	2000-2002	2003-2005	2006-2008	2000-2002	2003-2005	2006-2008	Oxford‡	England
N=	1,220	972	700	750	878	13,178	13,606	15,946		
Demographics										
Female	40.2%	38.0%	41.1%	35.9%	37.7%	39.5%	37.9%	38.5%	0.197	0.503
Median age (years)	49 (36-60)	59 (44-69)	61 (45-72)	61 (45-72)	61 (46-72)	61 (47-71)	62 (47-72)	63 (49-73)	-	-
18-40	30.2%	18.7%	18.7%	18.7%	15.9%	15.8%	14.8%	13.0%	<0.001	<0.001
40-50	21.2%	15.6%	13.6%	13.1%	14.7%	13.5%	13.4%	12.9%	<0.001	0.001
50-60	23.5%	17.2%	20.7%	20.8%	22.1%	17.8%	16.6%	17.2%	<0.001	<0.001
60-70	16.8%	24.2%	15.4%	16.4%	17.1%	23.1%	22.9%	22.7%	<0.001	<0.001
70-80	7.9%	20.5%	24.4%	23.5%	19.8%	23.6%	24.1%	24.5%	<0.001	<0.001
≥80	0.3%	3.8%	7.1%	7.6%	10.4%	6.1%	8.2%	9.7%	0.010	<0.001
Ethnicity*†										
White	-	-	86.8%	86.4%	84.0%	82.1%	81.2%	79.9%	0.241	<0.001
Black	-	-	3.5%	3.5%	4.7%	6.3%	6.5%	6.9%	<0.001	0.221
South Asian	-	-	7.4%	6.3%	7.2%	8.2%	8.3%	8.7%	0.694	0.202
Other	-	-	2.3%	3.8%	4.0%	3.4%	3.9%	4.4%	0.184	0.000
Unknown (n=)	-	-	131	36	35	1,694	962	745	-	-
Socioeconomic status*										
IMD Q1	-	-	2.9%	3.1%	4.9%	23.4%	23.8%	25.4%	<0.001	<0.001
IMD Q2	-	-	15.9%	13.9%	14.5%	23.1%	23.2%	22.9%	<0.001	0.822
IMD Q3	-	-	17.6%	18.8%	16.7%	19.5%	18.9%	18.8%	<0.001	0.256
IMD Q4	-	-	20.1%	18.9%	20.5%	17.2%	16.7%	17.0%	<0.001	0.643
IMD Q5	-	-	43.6%	45.3%	43.4%	16.9%	17.4%	15.9%	<0.001	0.002
Comorbidities										
Diabetes	6.7%	16.8%	24.4%	29.2%	33.9%	25.7%	29.9%	34.3%	<0.001	<0.001
Vascular	10.0%	18.3%	22.3%	24.7%	25.2%	25.2%	26.5%	28.3%	<0.001	<0.001
Major coronary disease	2.6%	4.2%	5.1%	7.2%	8.3%	6.1%	7.0%	7.7%	<0.001	<0.001
Congestive heart failure	5.2%	8.5%	9.9%	10.8%	10.5%	11.7%	12.3%	12.8%	<0.001	0.012
Cebrovascular disease	1.4%	2.2%	3.1%	2.8%	3.5%	3.3%	3.4%	3.4%	0.067	0.929
Peripheral arterial diseas	3.0%	7.8%	11.3%	11.5%	12.9%	12.0%	12.5%	14.2%	<0.001	<0.001
Non-Vascular	7.8%	14.4%	18.3%	21.7%	24.9%	21.7%	25.0%	27.5%	<0.001	<0.001
Liver disease	0.5%	0.4%	1.7%	1.1%	2.3%	1.6%	2.0%	2.8%	<0.001	<0.001
Cancer	2.9%	4.6%	5.3%	8.9%	7.6%	6.4%	7.8%	8.3%	<0.001	<0.001
Chronic obstrucutve pulr	1.3%	2.9%	6.3%	6.5%	10.3%	8.3%	10.0%	12.1%	<0.001	<0.001
Hemi-, paraplegia	0.2%	0.7%	1.0%	1.3%	1.5%	1.0%	1.2%	1.4%	0.023	<0.001
Peptic ulcer disease	1.6%	2.3%	2.7%	1.9%	1.9%	2.3%	2.3%	2.0%	0.486	0.099
Connective disease	2.0%	4.3%	3.1%	4.4%	4.9%	4.7%	5.0%	4.8%	0.003	0.562
Renal characteristics*										
Initial RRT modality										
Dialysis	94.6%	92.6%	93.7%	92.7%	91.6%	94.5%	94.3%	93.6%	0.076	0.002
Transplant	5.4%	7.4%	6.3%	7.3%	8.4%	5.5%	5.7%	6.4%	-	-
Primary renal diagnosis (presumed)										
Diabetic kidney disease	1.6%	8.4%	20.0%	22.5%	22.1%	19.1%	20.1%	20.4%	<0.001	0.018
Glomeruolonephritis	9.3%	14.1%	9.3%	10.8%	14.5%	10.8%	12.2%	14.1%	<0.001	<0.001
Polycystic kidney diseas	10.5%	8.4%	8.6%	7.5%	10.4%	9.2%	8.6%	8.9%	0.110	0.210
Other known diagnosis/u	78.5%	69.0%	62.1%	59.2%	53.1%	60.9%	59.1%	56.6%	<0.001	<0.001

Excludes patients dying within 90 days. Data are n or % or median (IQR). †Ethnicity only recorded in Hospital Episode Statistics (92% complete) with percentages quoted only for those with a known ethnicity. *Not used for standardization. Baseline characteristics of hospital controls are in Supplemental Table 6.Excludes patients dying within 90 days. Data are n or % or median (IQR). *The index of multiple deprivation (IMD) version 2004 ranks 32,482 geographical areas in England by deprivation (rank 1 has the highest deprivation). ‡Calculated across the 3 or 5 year groups depending on if variable was recorded in ORLS.

Renal Characteristics of the derived ESRD cohort

Initial RRT modality

The data suggested that the proportion of patients identified as commencing maintenance RRT via dialytic therapies has reduced, on absolute scale, by 3.4%: from 94.6% in 1970-1990 to 91.2% in 2006-2008 with a reciprocal increase in the proportions of patients identified as starting with a transplant, from 5.4% to 8.4%. This observed pattern of an increasing proportion of pre-emptive transplantation in HES Oxford was similar to that in all-England, yet the proportions of patients identified as starting maintenance RRT with a transplant in all-England were, on average, lower. The test for trend across the year groups of was non-significant in Oxford, p = 0.08 but in all-England, where there were many more pre-emptive transplants performed, a significant trend was identified, p= 0.002 (Table 3-1).

Presumed primary renal disease

The proportion of patients with an identifiable 'presumed' PRD increased over time, from 21.5% in 1970-1990 to 46.9% in 2006-2008. The proportion of ESRD patients with a presumed PRD of diabetic kidney disease rose from 1.6% in 1970-1990 to 22.1% in 2006-2008. The proportion with presumed glomerulonephritis as the cause of ESRD was 9.3% in 1970-1990, rising to 14.5% by 2006-2008. The proportion of patients with polycystic kidney disease fell slightly from 10.5% in 1970-1990 to 8.4% by 1991-1996, 8.6% by 2000-2002, and 7.5% in 2003-2005 before increasing back to 10.4% by 2006-2008.

All-England data were similar to HES Oxford with roughly one fifth of patients having diabetic kidney disease, 8-10% having polycystic kidney disease with a little over 50% having other known or unknown diagnoses (Table 3-1).

The difficulties in consistently identifying primary renal diagnosis, especially in ORLS with upto three quarters not being able to be identified, limited its use as variable to take forward into the proposed comparative mortality analyses, as there was not a comparative variable in

the general population. ESRD data repositories have substituted knowledge of prior co-morbid illnesses at the start of a RRT career with PRD to use as co-variable in mortality analyses but as 10-15% of patients have an unknown aetiology of ESRD and you cant have more than one PRD (you couldn't have PKD and diabetes) then there are obvious limitations.

3.4.2 Stratified baseline characteristics within ESRD cohorts; by initial RRT modality

In the period covering ORLS, pre-emptive transplants were relatively uncommon with only 66 performed between 1970-1990, equating to 3.3 per annum (p.a.) and then 72 in the subsequent 6 years between 1991-1996, equating to 12/pa. In HES Oxford, the absolute numbers of pre-emptive transplant recipients continued to increase to 44 (14.7/pa) in 2000-2002, to 55 (18.3/pa) in 2003-2005 and 74 in 2006-2008 (24.6/pa). Patients who were identified as receiving a kidney transplant as their initial modality of RRT were more likely to be younger, less morbid than those starting on dialytic therapies (Table 3-2 & Table 3-3). Pre-emptive transplant recipients had a median age at start of RRT of 36, (IQR, 26-45) rising to 45 (from 2000) compared to dialysis patients who had a median age of 50 (37-61) in 1970-1990 rising to 62 (49-73) by 2006-2008 (Table 3-2 & Table 3-3). The proportion of females who were identified as receiving a transplant as their initial mode of RRT was, in general, lower than that those starting via dialysis but remained fairly static over the period of the cohort (Table 3-2 & Table 3-3).

The IMD quintile of patients who received a transplant as their initial RRT modality both in Oxford and all-England were more likely to come from less deprived areas than those starting on dialysis. Of all-England patients identified as receiving a transplant as their initial RRT, the proportions residing from the most deprived (IMD 1) districts fell from 16.4% to 12.6% (Table 3-2 & Table 3-3).

The prevalence of major comorbidities was considerable less in patients identified as having a transplant as opposed to dialysis. Vascular disease among those who received a pre-

emptive transplant had on average, a 5.7% prevalence, compared to 28.1% in patients starting on dialytic therapies. Non-vascular disease was identified in 11.2% of those receiving pre-emptive transplants as opposed to 25.8% in those that started via dialytic therapies (Table 3-2 & Table 3-3).

Table 3-2: Baseline characteristics of new treated end-stage renal disease patients with transplantation being the first recorded modality of renal replacement therapy

	Year Groups							
Region covered	**Oxford, ~40 Years**					**All-England, ~10 years**		
Data Source	**Oxford Record Linkage Study**		**Hospital Episode Statistics (Oxford)**			**Hospital Episode Statistics (All-England)**		
	1970-1990	**1991-1996**	**2000-2002**	**2003-2005**	**2006-2008**	**2000-2002**	**2003-2005**	**2006-2008**
N=	66	72	44	55	74	719	779	1,019
Demographics								
Female	33.3%	47.2%	27.3%	36.4%	35.1%	34.2%	34.8%	36.7%
Median age (years)	36 (26-45)	43 (33-52)	45 (33-53)	41 (33-53)	45 (38-51)	45 (36-55)	44 (34-54)	45 (36-54)
18-40	54.5%	37.5%	40.9%	41.8%	31.1%	34.4%	37.5%	33.0%
40-50	25.8%	29.2%	29.5%	30.9%	39.2%	26.6%	29.4%	31.2%
50-60	15.2%	26.4%	15.9%	18.2%	16.2%	24.8%	20.9%	20.9%
60-70	4.5%	6.9%	9.1%	9.1%	12.2%	12.2%	11.0%	13.0%
70-80	0.0%	0.0%	4.5%	0.0%	1.4%	2.1%	1.2%	1.9%
≥80	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
Ethnicity†								
White	-	-	100%	86.3%	83.6%	81.0%	84.6%	85.8%
Black	-	-	0%	5.9%	2.7%	6.1%	4.8%	4.1%
South Asian	-	-	0%	3.9%	5.5%	8.1%	6.2%	6.2%
Other	-	-	0%	3.9%	8.2%	4.8%	4.4%	3.8%
Unknown (n=)	-	-	10	4	1	76	70	55
Socioeconomic status*								
IMD Q1	-	-	2.3%	0.0%	6.8%	16.4%	13.2%	12.6%
IMD Q2	-	-	6.8%	7.3%	12.2%	19.6%	16.3%	17.4%
IMD Q3	-	-	4.5%	20.0%	10.8%	19.9%	21.1%	18.0%
IMD Q4	-	-	22.7%	18.2%	16.2%	20.3%	21.1%	21.8%
IMD Q5	-	-	63.6%	54.5%	54.1%	23.8%	28.4%	30.3%
Comorbidities								
Diabetes	1.5%	8.3%	13.6%	14.5%	23.0%	9.3%	12.7%	18.9%
Vascular	6.1%	1.4%	2.3%	5.5%	6.8%	4.6%	5.0%	7.0%
Non-Vascular	4.5%	9.7%	18.2%	3.6%	4.1%	9.0%	11.2%	12.9%
Renal characteristics								
Primary renal diagnosis (presumed)								
Diabetic kidney disease	0.0%	4.2%	11.4%	14.5%	21.6%	7.1%	9.2%	13.8%
Glomerulonephritis	4.5%	22.2%	22.7%	21.8%	13.5%	14.7%	18.6%	21.2%
Polycystic kidney disease	16.7%	15.3%	22.7%	16.4%	20.3%	16.4%	18.1%	20.3%
Other known diagnosis/unknown	78.8%	58.3%	43.2%	47.3%	44.6%	61.8%	54.0%	44.7%

Excludes patients dying within 90 days. Data are n or % or median (IQR). †Ethnicity only recorded in Hospital Episode Statistics (92% complete) with percentages quoted only for thise with a known ethnicity. *The index of multiple deprivation (IMD) version 2004 ranks 32,482 geographical areas in England by deprivation (rank 1 has the highest deprivation).

Table 3-3: Baseline characteristics of new treated end-stage renal disease patients in which dialysis was the first recorded modality of renal replacement therapy

	Year Groups							
Region covered	**Oxford, ~40 Years**					**All-England, ~10 years**		
Data Source	**Oxford Record Linkage Study**		**Hospital Episode Statistics (Oxford)**			**Hospital Episode Statistics (All-England)**		
	1970-1990	**1991-1996**	**2000-2002**	**2003-2005**	**2006-2008**	**2000-2002**	**2003-2005**	**2006-2008**
N=	1,154	900	656	695	804	12,459	12,827	14,927
Demographics								
Female	40.2%	38.0%	42.1%	35.8%	37.9%	39.8%	38.1%	38.6%
Median age (years)	50 (37-61)	60 (45-70)	63 (47-72)	63 (47-73)	62 (49-73)	62 (48-72)	63 (49-73)	64 (51-74)
18-40	30.2%	18.7%	17.2%	16.8%	14.6%	14.7%	13.4%	11.6%
40-50	21.2%	15.6%	12.5%	11.7%	12.4%	12.8%	12.5%	11.7%
50-60	23.5%	17.2%	15.4%	16.3%	17.2%	17.4%	16.3%	17.0%
60-70	16.8%	24.2%	21.5%	21.7%	23.0%	23.7%	23.6%	23.4%
70-80	7.9%	20.5%	25.8%	25.3%	21.5%	24.9%	25.5%	26.0%
≥80	0.3%	3.8%	7.6%	8.2%	11.3%	6.5%	8.7%	10.3%
Ethnicity†								
White	-	-	86.0%	86.4%	84.0%	82.1%	81.0%	79.6%
Black	-	-	3.7%	3.3%	4.9%	6.4%	6.6%	7.0%
South Asian	-	-	7.9%	6.5%	7.4%	8.2%	8.5%	8.9%
Other	-	-	2.4%	3.8%	3.6%	3.4%	3.8%	4.5%
Unknown (n=)	-	-	121	32	34	1,618	892	690
Socioeconomic status*								
IMD Q1	-	-	2.9%	3.3%	4.7%	20.1%	20.4%	21.3%
IMD Q2	-	-	16.5%	14.4%	14.7%	21.1%	20.7%	20.1%
IMD Q3	-	-	18.4%	18.7%	17.3%	20.0%	20.4%	19.9%
IMD Q4	-	-	20.0%	19.0%	20.9%	20.0%	19.2%	20.2%
IMD Q5	-	-	42.2%	44.6%	42.4%	18.7%	19.3%	18.5%
Comorbidities								
Diabetes	6.7%	16.8%	25.2%	30.4%	35.0%	26.7%	31.0%	35.3%
Vascular	10.0%	18.3%	23.6%	26.2%	26.9%	26.4%	27.8%	29.8%
Non-Vascular	7.8%	14.4%	18.3%	23.2%	26.9%	22.4%	25.8%	28.5%
Renal characteristics								
Primary renal diagnosis (presumed)								
Diabetic kidney disease	1.6%	8.4%	20.6%	23.2%	22.1%	19.8%	20.8%	20.8%
Glomeruolonephritis	9.3%	14.1%	8.4%	9.9%	14.6%	10.6%	11.8%	13.6%
Polycystic kidney disease	10.5%	8.4%	7.6%	6.8%	9.5%	8.8%	8.0%	8.1%
Other known diagnosis/unknown	78.5%	69.0%	63.4%	60.1%	53.9%	60.8%	59.4%	57.4%

Excludes patients dying within 90 days. Data are n or % or median (IQR). †Ethnicity only recorded in Hospital Episode Statistics (92% complete) with percentages quoted only for thise with a known ethnicity. *The index of multiple deprivation (IMD) version 2004 ranks 32,482 geographical areas in England by deprivation (rank 1 has the highest deprivation).

3.4.3 Demographics of general population hospital controls

The general population hospital control cohort consisted of 5,613,781 patients who entered the cohort at the time of a minor condition or procedure. This 5.6 million included 532,019 patients identified in the ORLS (1970-1996) and 5,081,762 patients from all-England HES between 2000-2008, of which 253,069 patients were from HES Oxford (Figure 3-1 & Table 3-4).

Age

The median age of patients at entry into the Oxfordshire general population cohort rose by seven years from 40 years (29-57) in 1970-1990 to 47 years (33-64) in 2006-2008. Compared to the ESRD cohort, the age structure of the general population controls therefore did not change to the same magnitude. Nevertheless, the proportion of patients over 60 years increased from a quarter to one third between 1970-1990 and 2006-2008, whilst the proportion of patients over 70 years increased by about a half from 12.5% in 1970-1990 to 19.0% in 2006-2008 (Table 3-4).

Gender

The proportion of females who contributed to the general population hospital controls was higher than ESRD cohorts and decreased slightly from the 56.9% in 1970-1990 to 50.0% from 2003 onwards (Table 3-4).

Comorbidity

The general population cohort were much less comorbid than the ESRD population. However even within the general population the prevalence of comorbidities increased substantially.

The prevalence of diabetes rose 4-fold in the hospital controls from 0.8% in 1970-1990 to 4.1% in 2006-2008 (Table 3-4).

The proportion of general population controls identified as having baseline vascular disease increased from 2.0% in 1970-1990 to 3.6% in 2006-2008. This constituted a doubling of the reported prevalence of major coronary disease (0.6% to 1.2%), congestive heart failure (0.6% to 1.2%) and cerebrovascular disease (0.4% to 0.8%) and a more modest increase in peripheral arterial disease, from 0.6% to 1.0%. General population control patients identified from HES Oxford data had, in general, a 20-30% lower proportion than that in all-England patients, but yet there were similar increases were in Oxford and all-England patients over time (Table 3-4).

The prevalence of comorbidities which saw the largest absolute increases were serious non-vascular disease, rising by 6.2% from 3.6% in 1970-1990 to 9.8% in 2006-2008. Increases in prevalence of COPD constituted, by far, the largest portion of this observed increase, rising about six-fold from 0.9% to 6.3% (Table 3-4).

Table 3-4: Baseline characteristics of general population hospital controls, by year

	Year Groups							
	Oxford					All-England		
	Oxford Record Linkage Study		Hospital Episode Statistics (Oxford)			Hospital Episode Statistics (All-England)		
	1970-1990	1991-1996	2000-2002	2003-2005	2006-2008	2000-2002	2003-2005	2006-2008
N	406,897	125,122	86,476	87,000	79,593	1,753,792	1,683,382	1,644,588
Demographics								
Female	56.9%	51.8%	51.0%	49.7%	49.6%	50.3%	49.5%	49.2%
Median age (years)	40 (29-57)	41 (30-63)	47 (33-65)	47 (33-66)	47 (33-64)	49 (34-68)	51 (35-69)	50 (35-68)
18 - 40	49.5%	47.3%	39.3%	37.3%	37.2%	36.4%	33.5%	33.5%
40 - 50	15.4%	13.8%	14.5%	15.4%	16.0%	14.1%	14.7%	15.4%
50 - 60	12.4%	10.3%	13.9%	14.3%	14.7%	13.5%	13.8%	13.9%
60 - 70	10.4%	10.4%	12.1%	12.8%	13.2%	12.7%	13.3%	13.9%
70 - 80	8.5%	10.4%	11.7%	11.6%	10.6%	13.5%	13.9%	13.0%
≥80	4.0%	7.8%	8.4%	8.5%	8.4%	9.8%	10.9%	10.3%
Comorbidities								
Diabetes	0.8%	1.2%	2.2%	3.1%	4.1%	3.1%	4.5%	5.4%
Vascular	2.0%	2.6%	2.9%	3.3%	3.6%	3.9%	4.3%	4.3%
Major coronary disease	0.6%	0.9%	1.0%	1.2%	1.2%	1.3%	1.5%	1.4%
Congestive heart failure	0.6%	0.8%	0.9%	1.0%	1.2%	1.3%	1.4%	1.5%
Cerebrovascular disease	0.4%	0.7%	0.6%	0.8%	0.8%	0.9%	1.0%	1.0%
Peripheral arterial disease	0.6%	0.6%	0.7%	0.8%	1.0%	0.9%	1.0%	1.1%
Non-vascular	3.6%	3.6%	5.7%	6.6%	9.8%	8.1%	9.5%	11.6%
Liver disease	0.1%	0.1%	0.2%	0.4%	0.6%	0.3%	0.5%	0.7%
Cancer	1.5%	1.2%	1.3%	1.4%	1.9%	1.5%	1.8%	2.1%
Chronic obstructive pulmonary disease	0.9%	1.4%	3.2%	3.9%	6.3%	5.0%	6.2%	7.9%
Peptic ulcer disease	0.5%	0.5%	0.4%	0.3%	0.4%	0.5%	0.5%	0.5%
Connective tissue disease	0.6%	0.3%	0.6%	0.7%	0.9%	0.8%	0.9%	1.0%

Excludes patients dying within 90 days. Data are n or % or median (IQR). The 'controls' were individuals who had been admitted to hospital for any one of a wide range of minor medical or surgical conditions. These included admissions with diagnoses of squint, cataracts, otitis externa/media, varicose veins, hemorrhoids, upper respiratory tract infections, nasal polyps, teeth disorders, inguinal hernia, nail diseases, sebaceous cyst, soft tissue knee complaints, bunions, contraceptive advice, limb fractures, dislocations sprains and strains, minor head injury, superficial injuries or contusions and gallbladder disease, and operations included appendiectomy, dilation and curettage, primary lower limb arthoplasties, tonsillectomy and adenoidectomy. For individuals with more than one control condition, the episode of care which was included in the analysis as the control event was selected at random and any patients entering the renal replacement therapy cohort were excluded.

3.5 Discussion

The characteristics of incident RRT patients have changed substantially over the over the past 40 years since 1970, with changes in Oxford since 2000 mirroring trends observed in all-England. In the 1970s, maintenance RRT was a prioritised treatment available to younger and healthier patients contrasting the modern era where the median age at starting RRT has risen to over 60 years with approximately a third of all incident patients having diabetes recorded in prior hospital admissions.

There were substantially less dramatic changes in the characteristics of the large set of hospitalised general population controls. They too have, on average, become older and reportedly more comorbid over time, but the magnitude of these changes, (especially in age and prevalence of comorbid illness) are less than that observed in the derived ESRD cohort. As age, sex and comorbidities are key predictors of mortality[107,112] when comparing mortality trends between these populations these characteristics needs to be appropriately adjusted before any temporal changes can be fairly interpreted. This has not been possible in previous studies using ESRD registry data as any such data either lacked or had incomplete data on comorbid illness and there was no opportunity for comparable data to be drawn from a general population.

The collection and reporting of comorbidity variables to the core database, the UK-Renal Registry, have improved but remain poor. For example, in 2007 only 3 out of 50 English renal centres provided 100% data whilst 20 centres provided <10% including 9 centres reporting no comorbidity data at all.[113] European[10] and US renal registries[114] have generally included the PRD as a surrogate for comorbidity in their adjusted analyses but no other large study has had access to comorbidity data for an ESRD renal population *alongside* those of any comparative population over such a long period of time. Moreover the availability of

the large set of contemporaneously derived general population hospital controls permits analogous standardization.

The large changes in the characteristics of RRT patients principally reflect the increased access and provision of RRT over these 40 years.[3,27,49] Consequently, the selection onto dialysis programs has become less stringent with more comorbid patients being much more commonly offered maintenance RRT including kidney transplantation.[42] The general population are also living longer and as age is among the most significant risk factor for the development of ESRD this has resulted in more patients developing ESRD.[115,116] Similarly, the epidemic of type 2 diabetes and its associated obesity and albuminuria contribute to the increasing prevalence of ESRD as they are all established risk factors for the development of the disease.[117-119] These changes have happened in the context of better survival from cancer[120], cardiovascular disease[121] and increased funding for RRT programmes[49] resulting in older patients, with increasing comorbidity now constituting the majority of patients commencing RRT.[5]

3.5.1 Comorbidity ascertainment from routinely collected hospital inpatients records

Table 3-5: Level of agreement of individual components of pre-dialysis CKD cohort between hospital inpatients records and clinical notes

	Recorded Prevalence				
	Hospital inpatient records		Clinical Notes		
	n	%	n	%	Kappa value
Vascular disease					
Ischaemic Heart disease	1146	35.6	1277	39.7	0.63
Hypertension	928	28.8	1715	53.3	0.28
Ceberovascular disease	282	8.8	248	7.7	0.80
Peripheral vascular disease	250	7.8	379	11.8	0.39
Heart Failure	511	15.9	546	17.0	0.45
Diabetes	501	15.6	805	25.0	0.65
Non-vascular disease					
Dementia	91	2.8	187	5.8	0.38
COPD	255	7.9	283	8.8	0.51
CTD	140	4.3	154	4.8	0.54
Haematological malignancy	39	1.2	78	2.4	0.57
Non-haematological malignanc	300	9.3	454	14.1	0.51
Chronic liver disease	37	1.1	33	1.0	0.51

COPD=chronic obstrucutve pulmonary disease, CTD=connective tissue disease. Adapted from Soo et al. BMC 2014;7:253. A period of 5 years of retrospective follow-up employed in hospital records from the date of registration into the regonal CKD

The identification of prior comorbidity using electronic healthcare records in a CKD population has been tested before in a Scottish, but not-English, CKD cohort.[122] In this analysis the researchers had access to direct linkage to inpatient clinical notes for their comparsion.[122] Electronic records identified comorbidities in a

retrospective period of 5 years whilst there was an unlimited period of prior review in the clinical notes. Agreement between comorbidity derived from administrative data and clinical notes was measured using a kappa statistic. Cerebrovascular disease, ischaemic heart disease and diabetes had good to fair agreement (i.e. $\kappa>0.6$), whilst non-vascular diseases such as cancer, connective tissues and chronic obstructive pulmonary disease all had less agreement, (i.e. >0.5 κ <0.6) (Table 3-5). Subgroup analyses revealed that agreement broadly improved with more advanced renal disease,[122] presumably because of increased number of inpatient episodes. Combining these individual comorbidities, based on the Charlson comorbidity index[102], showed that 73% of patients had comorbidity scores within plus or minus one point of the clinical notes.[123] No other studies have published the validity of utilising derived comorbidity for an English cohort of patients with advanced renal disease, identified from HES or its predecessors, and incorporated them as covariates in mortality analyses.

3.5.2 Duration of retrospective period used to ascertain of major comorbidities

One of the unique features of this thesis is that there was the opportunity to derive baseline comorbidities from a retrospective period before starting RRT. They were extracted using a 'fixed' period of retrospective follow-up prior to the entry date to ensure that patients starting RRT in any given year had a consistent period of retrospective follow-up during which identify comorbidity. Having an *unrestricted* retrospective period would have meant that patients starting RRT in 2008 could have had upto 10 years of *potential* prior follow-up in contrast to patients in 2000 only having a maximum of 2 years (as HES data began in 1998). This would introduce ascertainment bias of prior comorbidities.[124,125] Understanding whether, and how, altering the duration of this retrospective period affected the proportions of comorbid illnesses was therefore investigated. However these efforts came to little as comparing studies from other healthcare systems,[126] perhaps in different medical conditions and pertaining to different coding manuals was not thought to be appropriate.[125,127] However, data from the HES analysed by the Dr. Foster Unit, concluded that differences in hospital

standardized mortality ratios (HSMR) could be from differences in coding practice or a difference of comorbidity between hospitals. Yet the authors did reflect that and commented thankfully that, “gaming of comorbidity via secondary diagnoses is not common in England.” There has been other initiatives that may have contributed to coding practice changes which are particular to the NHS. The introduction of “Payment by Results” (PbR) scheme which saw a phased introduction into the NHS during 2003/2004 provided a financial incentive for hospital trusts in England to improve the coding of comorbidities.[128,129] Furthermore, the instructions given to coders in ORLS and HES on the type of comorbidities that should be recorded in a given admission differed. In ORLS, comorbidity was only recorded if it was *directly relevant* to the admitting diagnosis whilst in HES the recommendation was (and remains) to capture “any condition that affects the management of the patient and contributes to an accurate clinical picture within the current episode of care.”[130]

The impact of clinical coding practices and their effects on the ascertainment of comorbidities were therefore considered separately in each dataset in an attempt to understand whether there was a constant risk fallacy.[131]

3.5.3 Clinical coding practices in all-England Hospital Episode Statistics

Between 2000-2002 the median number of hospital episodes prior to patients index date into the cohort was 3 (IQR 2-6) increasing to 4 (2-8) by 2006-2008. The number of concurrent diagnostic codes per each episode increased from a mean of 3.4 (SD 1.4) in 2000-2002 to 4.5 (2.0) in 2006-2008, an increase of almost one third. When stratified by age this increase in the median number of diagnoses per episodes was more apparent in older patients. The proportion of patients with only one episode to identify of prior comorbid illness increased from 6% in 2000-2002 to 9% in 2006-2008 (Table 3-6).

Table 3-6: Number of episodes available for retrospective follow-up prior to start of RRT to identify comorbidities (with number of diagnoses per episode), by year and by age at start of RRT

Region	Year Groups					Trend p-value for difference across years	
	Oxford Record Linkage Study		all-England HES				
	1970-1990	1991-1996	2000-2002	2003-2005	2006-2008	ORLS	HES
Percentage of incident RRT patients with only one episode	24%	14%	6%	8%	9%	<0.0001	<0.0001
Median number of episodes							
All participants	3 (2-5)	4 (2-8)	3 (2-6)	4 (2-7)	4 (2-7)	<0.0001	<0.0001
18-40 years	2 (1-5)	4 (2-9)	3 (1-5)	3 (2-6)	3 (2-6)	<0.0001	<0.0001
40-50 years	3 (1-5)	4 (2-9)	3 (1-5)	3 (2-6)	3 (2-6)	<0.0001	<0.0001
50-60 years	3 (2-6)	4 (2-8)	3 (2-6)	4 (2-6)	4 (2-7)	0.01	<0.0001
60-70 years	3 (2-5)	5 (2-8)	4 (2-6)	4 (2-7)	4 (2-7)	<0.0001	<0.0001
70-80 years	3 (2-5)	5 (3-9)	4 (2-6)	4 (2-7)	4 (2-7)	0.001	<0.0001
≥80 years	3 (2-8)	5 (4-9)	4 (2-6)	4 (2-7)	4 (2-7)	0.27	<0.0001
Median number of diagnoses per epsiode							
All participants	1.2 (0.8)	1.5 (1.0)	3.4 (1.4)	3.9 (1.8)	4.5 (2.0)	<0.0001	<0.0001
18-40 years	1.1 (0.9)	1.3 (0.9)	3.1 (1.3)	3.3 (1.6)	3.7 (1.8)	0.02	<0.0001
40-50 years	1.2 (0.8)	1.4 (1.1)	3.2 (1.3)	3.6 (1.7)	4.1 (1.9)	0.01	<0.0001
50-60 years	1.2 (0.7)	1.4 (1.0)	3.4 (1.4)	3.9 (1.8)	4.4 (2.0)	0.01	<0.0001
60-70 years	1.2 (0.7)	1.6 (1.0)	3.6 (1.5)	4.0 (1.9)	4.6 (2.0)	<0.0001	<0.0001
70-80 years	1.2 (0.7)	1.5 (0.9)	3.6 (1.4)	4.1 (1.8)	4.9 (2.0)	0.001	<0.0001
≥80 years	1.3 (0.6)	1.3 (0.7)	3.6 (1.5)	4.0 (1.8)	4.6 (1.9)	0.89	<0.0001

Excludes patients dying within 90 days. Data are or median (IQR) or mean (SD). RRT = Renal replacement therapy. ORLS = Oxford Record Linkage Study. HES = Hospital Episode Statistics (all-England). Only diagnoses in the episodes starting in the 5 years in ORLS or the 2 years in HES prior to the start of RRT were used when identifying comorbidities at baseline.

3.5.4 Effect of different durations of retrospective periods in HES

In all-England HES, data were available from 1998. The median duration of *potential* (i.e. unrestricted) retrospective follow-up accrued by patients before their start date of maintenance RRT increased from 1.3 years (IQR 0.1-2.4) in 2000-2002 to 3.3 (0.9-5.1) in 2003-2005, to 5.4 (2.0-7.8) by 2006-2008 (Table 3-7).

For the 2003-2005 group of incident patients, the effect of lengthening the retrospective follow-up period from two to five years would have had only a small increase in the capture of prior diabetes from 30% to 31%, for prior vascular disease the proportions would have increased from 27% to 31% and for prior non-vascular disease from 25% to 29% (Table 3-7). On a relative scale, this represented increases of 3.3%, 12.9% and 16.0% respectively. Had an unrestricted period been used then this relative change would have been 3.3%, 18.5% and 20%.

For the 2006-2008 year group, increases from two to five year period of retrospective follow-up would have resulted in absolute increases in prevalence of baseline diabetes by 1% (34% to 35%), vascular disease 5% (28% to 35%) and serious non-vascular disease by 4% (28%

Table 3-7: Baseline comorbidities by different durations of retrospective follow-up prior to start of RRT, by year

Region	Year Groups				
	Oxford Record Linkage Study		all-England HES		
	1970-1990	1991-1996	2000-2002	2003-2005	2006-2008
Median duration (years) from first record to start of RRT	1.9 (0.0-8.2)	5.6 (0.2-14.8)	1.3 (0.1-2.4)	3.3 (0.9-5.1)	5.4 (2.0-7.8)
Diabetes					
2 years	5.7%	15%	**26%**	**30%**	**34%**
5 years	**6.7%**	**17%**	-*	31%	35%
Unrestricted	7.3%	17%	-*	31%	35%
Vascular					
2 years	8%	15%	**25%**	**27%**	**28%**
5 years	**10%**	**18%**	-*	31%	33%
Unrestricted	12%	22%	-*	32%	36%
Non-vascular					
2 years	5.7%	13%	**22%**	**25%**	**28%**
5 years	**7.8%**	**14%**	-*	29%	32%
Unrestricted	11%	18%	-*	30%	35%

Data are median (IQR) or %. RRT = Renal replacement therapy. ORLS = Oxford Record Linkage Study. HES = Hospital Episode Statistics (all-England). *Not possible as 5 year retrospective follow-up precedes start of cohort (01/01/1998). Bold percentages represent the prevalences quoted in the baseline characteristics and used subsequently.

to 32%; Table 3-7). On a relative scale, this represented increases of 2.9%, 17.9% and 14.2% respectively. Had an unrestricted period of retrospective follow-up been used then relative increases, from 2 years, would have been 2.9%, 28.6% and 25% respectively.

3.5.5 Clinical coding practices in Oxford Record Linkage Study

The median number of prior hospital episodes captured in ORLS/all-England HES increased by about one third, from 3 (2-5) in 1970-1990 to 4 (2-7) by 1991-1996, and a significant trend was observed overall across nearly all the separate age groups (Table 3-6). The median number of codes recorded per hospital episode also increased from 1.2 (SD 0.8) in 1970-1990 to 1.5 (1.0) in 1991-1996, an increase of about one-quarter. There were also reductions in the proportion of ESRD patients recorded as having only one hospital episode prior to their index date: decreasing from 24% to 14% between 1970-1990 and 2006-2008 (Table 3-6).

3.5.6 Effect of different durations of retrospective periods in ORLS

In ORLS, data were available from 1965. The median duration of *potential* (i.e. unrestricted) retrospective follow-up accrued by patients before their start date of maintenance RRT increased from 1.9 years (IQR 0.0-8.2) in 1970-1990 to 5.6 (0.2-14.8) in 1991-1996, (Table 3-7). To ensure patients in each year group were afforded the same opportunity to ascertain comorbidity, the effect of different durations of retrospective follow-up prior to start of RRT were again explored. In ORLS, 2 years provided substantially less ascertainment of major comorbidities compared to 5 years and an unrestricted period.

Taking the 1970-1990 year group, if a 2 year period of retrospective follow-up, as oppose to 5 years (see below for reasons), was chosen then the prevalence of diabetes, would have fallen from 6.7% to 5.7%, vascular disease from 10% to 8.0% and vascular disease 7.8% to 5.7% respectively. On a relative scale, this represented decreases of 14.9%, 20.0% and 26.9% respectively. If an unrestricted period of retrospective follow-up had been applied to the 1970 to 1996 year groups then the absolute decrease in the ascertainment of major comorbidity would have been greater: 2.6% for diabetes, 4% for vascular disease and 5.3% for non-vascular disease. On a relative scale, this would have represented a potential under-ascertainment of the prevalence of baseline co-morbidity of 45.6% for diabetes, 50% for vascular disease and 93.0% for non-vascular disease (Table 3-7).

For the 2003-2005 group of incident patients, the effect of lengthening the retrospective follow-up period from two to five years would have had only a small increase in the capture of prior diabetes from 30% to 31%, for prior vascular disease the proportions would have increased from 27% to 31% and for prior non-vascular disease from 25% to 29% (Table 3-7). On a relative scale, this represented increases of 3.3%, 12.9% and 16.0% respectively. Had an unrestricted period been used then this relative change would have been 3.3%, 18.5% and 20%.

For the 2006-2008 year group, increases from two to five year period of retrospective follow-up would have resulted in absolute increases in prevalence of baseline diabetes by 1% (34%

to 35%), vascular disease 5% (28% to 35%) and serious non-vascular disease by 4% (28% to 32%; Table 3-7). On a relative scale, this represented increases of 2.9%, 17.9% and 14.2% respectively. Had an unrestricted period of retrospective follow-up been used then relative increases, from 2 years, would have been 2.9%, 28.6% and 25% respectively.

3.5.7 Rationale for the final decision on the duration of retrospective period used to ascertain major comorbidities

The 'fixed' period of retrospective follow-up in this cohort – 5 years in ORLS and 2 years in HES – was decided based on the four points:

1. It maximised the use of available data (as it allowed the derivation to go back to 1965 in ORLS and 1998 in HES);

2. It offered suitable timeframes in which the vast majority of comorbid illness could be identified;

3. It accommodated the different coding practices and data structures between ORLS and HES.

4. Allowing external validation to other data reposities who hold data on mortality of ESRD patients.

3.5.8 Limitations

Some limitations in the cohorts are noteworthy. First, ORLS and HES do not hold other variables (e.g. smoking status) which are known to affect mortality, as well as some other important clinical and laboratory metrics (e.g. blood pressure, LDL-cholesterol and body-mass index).[132-138] It will therefore not possible to adjust for all baseline differences in subsequent longitudinal analyses and the lack of ethnicity or SES data in ORLS also precluded its inclusion into regression models. Secondly, pragmatic but informed decisions were made on the durations of retrospective follow-period used in the ascertainment of

comorbidities which means there is loss of some information about comorbidity in each year of the cohort. Using an unrestricted period would though, result introducing a bias when mortality rates are adjusted as the degree of under-ascertainment of comorbidity would have progressively decreased over time. Lastly, the cohort is dependent on NHS admissions and would not include those admitted for privately funded care. However, private RRT is rare.[61]

3.6 Conclusions

The types of patient receiving maintenance RRT has changed significantly across the 40-year from 1970 with patients becoming significantly older and more comorbid. The magnitude of this secular change in the ESRD population is larger than that observed in a large set of general population controls. As comorbidities are key determinants of survival in both populations the benefit of having a uniform approach to identifying these comorbidities was applied and should provide an opportunity to perform more reliable standardization of mortality rates from descriptive analyses.

3.7 Bullet points of Chapter 3

- 44,922 incident ESRD patients were identified between 1970-2008

- Over almost 40 years in Oxford, the age at start of RRT increased 15 years, from 46 (IQR 36-60) in 1970-1985 to 61 (46-72) years by 2006-2008

- The crude prevalence of major comorbid illness identified in patients prior to them starting maintenance RRT between the first (1970-1990) and last (2006-2008) year groups were as follows:
    - Diabetes increased from 6.7% to 33.9%
    - Vascular disease increased from 10.0% to 25.2%
    - Non-vascular disease increased from 7.8% to 24.9%

- The magnitude of these proportion changes was not mirrored in the a large set of general population hospital controls

Chapter 4 Validation

“Validation” of treated end-stage renal disease cohorts derived from routinely collected English hospital inpatient data (1970-2008)

4.1 Abstract

Background

Whether it is possible to derive cohorts of maintenance renal replacement therapy patients from English routinely collected hospital inpatients datasets is unknown.

Methods

A set of clinical definitions, mapped through versions of clinical coding manuals and incorporated into a specifically designed derivation algorithm was applied to two datasets: the Oxford Record Study Linkage (ORLS; between 1970-1996) and all-England Hospital Episode Statistics (HES; between 2000-2008). This identified a retrospective cohort of 44,922 English ESRD patients who had commenced maintenance RRT and survived at least 90 days. Indirect and direct validation techniques were employed using summary data from the UK-Renal Registry (UK-RR) 2007-2010, UK-Transplant Registry (UK-TR) 2000-2011 and Oxford Kidney Unit's (OKU) electronic patient records 1970-2008 (i.e. reference datasets) and data from randomised trials of patients with renal disease (SHARP 2003-2010) and 3C (2010-2013) and linkage to HES, respectively.

Results

a) HES-based cohort: Between 2007-2010, which covered the period when the UK-RR had full coverage of English renal centres, demographics of the derived all-English ESRD cohorts were similar to that reported in the UK-RR. In 2010, for example, both datasets had a median age of 64 years, near equivalent proportions were female patients (UK-RR: 38% vs. HES: 37%) and broadly similar ethnicity structure (White ethnicity 77% vs. 78%; Black 6% vs. 7%). Between 2000-2011, 20,248 kidney transplants were identified from HES compared to 20,248 reported to the UK-TR (a relative difference of 1.6%).

b) ORLS-based cohort: In Oxfordshire between 1970-2008, a similar numbers of patients with comparable demographic structures were recorded in OKU data compared to those identified from ORLS. The age and sex standardized three-year mortality rates between

OKU and the derived Oxfordshire ESRD cohort also mirrored each other: between 1970-1990 OKU had a 3-year mortality rate of 33.7% (95% CI, 29.5-37.8%) compared to 35.6% (31.4-39.9%) in ORLS with rates falling to 22.9% (19.8-25.9%) and 22.4% (18.8-26.0%) by 2006-2008, respectively.

c) Direct validation using data from SHARP with its linkage to HES demonstrated that the algorithm identified 321 out of 346 (92.8%) participants whom had been adjudicated as having maintenance RRT, corresponding to a kappa statistic of 0.84 (0.81-0.88) (ie excellent agreement) and using similar methods even greater agreement on the fact of transplantation, 0.92 (0.89-0.96).

Conclusions

Direct validation using HES-linked trial data suggested that a clinical algorithm could be used to derive a cohort of maintenance renal replacement therapy patients from HES. Summary statistics of patient numbers and basic demographics from the cohorts of treated ESRD patients *derived* exclusively from routinely collected hospital inpatient data are similar to those in summary statistics from the UK-RR, UK-TR, and OKU. The data used in this thesis, although not free from error, therefore appears to be sufficiently reliable to identify a cohort of treated ESRD patients to allow broad-brush descriptions of long-term changes in mortality rates.

4.2 Introduction

"Validation" of cohorts derived from routinely-collected healthcare data is recommended in the RECORD reporting guidelines (**RE**cording of studies **C**onducted using **O**bservational **R**outinely-collected health **D**ata)[139] as it can provide reassurances that any data used are reliable and representative of the condition being studied.[140] This chapter details the methods and results of analyses that were performed to help "validate" whether a retrospective cohort of treated ESRD patients could be reliably derived from mortality-linked English routinely collected hospital inpatient data between 1970-2008.

Coding of inpatient activity is mandated for all patients admitted to English NHS hospitals. A systematic review in 2012, performed by the Dr Foster Unit, claimed that discharge coding accuracy was, "robust enough to support its use in research", although the authors did note that there was variation in the accuracy of coding depending on which condition or procedure is being studied[128] but showed evidence that the quality of coding has improved over time.[141] Operations and procedures are generally more accurately captured than diagnoses as they are typically distinct entities occurring on a specific date whilst the start of a diagnosis can be uncertain.[128,142] Procedural codes may also be easier for coders to identify in hospital notes as they frequently have separate documentation and are not intertwined into the often evolving clinical narrative of a medical admission and the process of making a secure diagnosis.[143]

Identification of a treated ESRD cohort in routinely collected hospital admission data (i.e. dialysis-dependent ESRD patients or those with a functioning kidney transplant) posed an substantial challenge as ESRD is a heterogeneous condition without a simple set of unique diagnostic or procedural codes. Nevertheless, there is precedent, but not for English patients. Electronic healthcare data have been used to identify treated ESRD patients in

Canadian hospital admission data yet they also combined inpatient data with corresponding reimbursement data.[144] This Canadian study found that two 'outpatient claims of dialysis' identified over 97.5% of maintenance dialysis patients, with a positive predictive value (PPV) of 0.81 (95% CI 79-82). In the UK, HES data have been used to identify retrospective cohorts of transplant patients but not maintenance dialysis patients.[145] This body of work aimed to identify treated ESRD patients, ie dialysis *and* kidney transplant population in England over the 40 years since 1970. Validation of this endeavour is uncertain. I aimed to use summary data from the UK-Renal Registry (UK-RR) 2007-2010,[113,146-148] UK-Transplant Registry (UK-TR) 2000-2011,[149] Oxford Kidney Unit's (OKU) electronic patient records 1970-2008 (i.e. reference datasets) to assess the reliability of the ORLS & HES derived cohorts. Validation studies using data from UK participants of a kidney transplantation and separately a CKD randomised-controlled trials, both with direct linkage to HES data (the 3C study (**C**AMPATH, **C**alcineurin inhibitor reduction and **C**hronic allograft nephropathy, 2010-2013) and SHARP (**S**tudy of **H**eart **a**nd **R**enal **P**rotection, 2003-2010] respectively) were also undertaken.[150-153]

4.3 Methods/Procedures

The methodology and baseline characteristic of the ESRD cohort are described in Chapter 2 Chapter 2 ‘Cohort derivation’ and Chapter 3 ‘Baseline characteristics’. Briefly, a large retrospective cohort of incident ESRD patients was derived from routinely collected hospital inpatient datasets: Oxford Record Linkage Study (1970-1996) and all-England Hospital Episode Statistics (HES) 2000-2008 which included a regional subset, termed HES (Oxford) which closely approximated to the area previously covered by ORLS.

Indirect “validation” of these treated ESRD cohorts was performed using summary data extracted from other repositories that hold data on treated ESRD patients: UK-Renal Registry’s (UK-RR) annual reports,[113,147,154] UK-Transplant Registry database[149] and the Oxford Kidney Unit’s electronic patient database.

Direct validation using HES-linked trial data was also utilised using data from English participants in randomised controlled trials. In SHARP, there was a pre-specified trial outcome of the start of maintenance RRT. The linked-HES data for these patients was processed as per the derived algorithm used to identify this anonymised cohort and compared. Direct validation of patients’ primary renal diagnosis was performed among patients with kidney transplants, recruited to the 3C clinical trial.[150,155] In 3C, the nurse-reported primary renal diseases were grouped into either diabetic kidney disease, polycystic kidney disease and glomerulonephritidies which were then compared to what was identified in linked hospital admissions using a kappa statistic of agreement. Full details of the methodology used to define identify presumed PRD from HES is found in Chapter 2 subsection 2.11.1.

4.3.1 Cohort comparisons with UK-Renal Registry data 2007-2011

The UK-Renal Registry, which was founded in 1996, records demographic, clinical and laboratory information on all patients commencing on RRT in England and Wales and has published annual reports since 1998.[156] Before this, cross-sectional (and usually voluntary) surveys of RRT patients were reported to the European Renal Association/European Dialysis and Transplant Association (ERA/EDTA).[157] HES obtained complete coverage of NHS hospitals in England from 1998, whilst the UK-RR achieved *complete* coverage of English renal centres from 2007. This means comparisons with the derived all-England HES ESRD cohort were restricted to between 2007 and 2010.[113,146-148] Summary statistics including the number of patients, demographics (age, sex and ethnicity), initial RRT modality and PRD were manually extracted from UK-RR annual reports and compared to those identified from HES using standard statistical terms. See Chapter 2 for full details of these definitions with note that the seventeen codes for ethnicity in HES were mapped to the UK-RR format.[88,158]

4.3.2 Cohort comparisons with UK-Transplant Registry data 2000-2011

The National Health Service Blood and Transplant (NHSBT) service curates the UK National Transplant Database (UK-TR) which records details of all organ transplant recipients in the UK. The Human Organ Transplants Act in 1989[159] makes it a statutory requirement that all transplants operations performed in the United Kingdom be recorded centrally. A data request was placed with the statistical team at NHSBT asking for the number of, by month and year, isolated kidney transplants (excluding multi-organ allografts) performed in England between 2000 and 2011. Kidney transplants from other countries within the United Kingdom were excluded as this activity would not be captured by all-England HES. The counts of kidneys transplants provided by the UK-TR were compared against this. Kidney transplantation was identified in all-England HES using Classification of Interventions and

Procedures version 4 (OPCS-4) codes M01.2, M01.3, M01.4, M01.5 M01.8 and M01.9 mentioned in any hospital episode over the 12 year comparison period, 2000 and 2011.

4.3.3 Cohort comparisons with OKU-derived treated ESRD cohort 1970-1996

The Oxford Kidney Unit (OKU) was founded in 1967 and all patients living in the wider Oxfordshire area would have been principally managed by the OKU. The Royal Berkshire Hospital started its RRT program in 1987 but Oxford remained the tertiary renal unit for transplantation and any dialysis access invasive surgery. The clinical notes of early ESRD patients in Oxfordshire were kept in paper form in OKU offices and clinical coders from ORLS had full access to these paper records (personal communication with the retired curator of the ORLS dataset: Professor Michael Goldacre). From 1986, the OKU introduced a computerised system, called “PROTON” which was one the first electronic patient record systems.[160] When adopted, all OKU patients who had previously received maintenance RRT were retrospectively added, thereby providing an electronic record of all treated ESRD patients (importantly though *without any* reliable record of comorbidity) in the wider Oxfordshire region (communication with Associate Professor C.G.Winearls, co-director of OKU 1988-2000). Anonymised data were extracted from PROTON on all the incident maintenance RRT adults who had survived 90 days from their documented start date of maintenance RRT. The number of new patients and their basic demographics (age and sex) were then compared to treated ESRD patients identified in ORLS and HES (Oxford). The geographic areas served by OKU expanded differently to the area covered by ORLS, and so, whilst the datasets cannot cover exactly the same region there was considerable geographical overlap.

In addition to comparing the number of patients and their demographics, a Poisson regression model was used to calculate and then compare the age and sex adjusted three-year mortality rates of the OKU (1970-2008) RRT patients and the Oxfordshire derived

ESRD cohort (ie ORLS and HES Oxford), standardised to the age and sex of an 'average' 1970-2008 RRT population. See Table 5-2 for full details of the characteristics of the reference population used for this and the appendix for a more detailed description of statistical methods used.

4.3.4 Cohort comparisons with directly linked data from the SHARP study

The SHARP study (**S**tudy of **H**eart **a**nd **R**enal **P**rotection) was a prospective randomised controlled trial conducted by the University of Oxford. 9,270 eligible patients with established CKD from 18 countries were randomised and allocated to take either daily cholesterol-lowering therapy with a combination tablet containing simvastatin 20mg plus ezetimibe 10mg, or matching dummy "placebo" tablets for an average of 5 years.[153] The SHARP study completed follow-up in 2010,[152] and the 1,622 English participants (of which 1,139 were pre-dialysis at randomisation) had signed informed consent permitting long-term linkage to routinely collected hospital admission data from HES. The fact, date and modality of first RRT for these pre-dialysis patients was confirmed by trained (and blinded) clinical adjudicators using clinical documents collected from study centres. Kappa statistics were used to compare adjudicated trial outcomes to what the derivation algorithm proposed.

4.3.5 Cohort comparisons with directly linked data from 3C Study

The 3C (**C**AMPATH, **C**alcineurin inhibitor reduction and **C**hronic allograft nephropathy) Study was a prospective randomised controlled trial conducted by the University of Oxford.[150,151,161,162] Eligible patients, at the time of receiving a renal transplant (and therefore by definition having treated ESRD) signed informed consent which included expressed permission to previous and subsequent hospital admissions, the national death register (ONS) and cancer registries. These linked data were used to *directly* validate some of 3C's participants' baseline characteristics.

4.4 Results

4.4.1 Cohort comparisons with UK-RR data 2007-2011

Basic demographics

Between 2007 and 2010, 22,340 incident RRT patients were reported to the UK Renal Registry, compared to 21,905 patients which had been identified, via the algorithm, in all-England HES, a difference of 435 or 1.9% (Table 4-1). The median age of patients who started maintenance RRT between was between 63 years and 64 years in both HES and UK-RR. The proportion of females was also approximately equivalent in both datasets at between 38 and 40% Table 4-1).

The ethnicity field was more incomplete in the UK-RR, with “unknown” reported in a quarter of patients in contrast to HES which captured between 94-95% of patients’ ethnicity. In 2010, when UK-RR ethnicity data were more complete, the proportions of patients reported to be of White and Black ethnicity were 77% and 6% in all-England HES vs. 78% and 7% in UK-RR, respectively (Table 4-1).

Renal characteristics

Initial RRT modality

Between 2007 and 2010, the proportion of incident patients recorded by the UK-RR as receiving a pre-emptive transplant rose by 2%, from 5% in 2007 to 7% in 2010. This was a lower proportion than that captured in HES which identified 8% in 2007 rising to 10% by 2010 (Table 4-1).

Presumed primary renal disease

Between 2007 and 2010, diabetes nephropathy was assigned as the primary renal disease (PRD) in 20-21% of incident patients were reported to the UK-RR. This compares to 17-20%

among those that were identified in all-England HES data over the same period. Polycystic kidney disease was recorded as the PRD in 6-7% in the UK-RR compared to 8-9% across all years in HES. The proportions of PRD ascribed to ‘glomerulonephritis’ varied more; the UK-RR recorded steady rates of 10%, 11%, 11% and 11% compared to proportions of 14% in 2007 in HES, increasing to 23% by 2010. Both datasets suffered from incomplete information with over 50% of PRD being grouped into a category which included unknown and unavailable (Table 4-1).

Table 4-1: Baseline characteristics of all-England adults being treated for end-stage renal disease, recorded in all-England Hospital Episode Statistics and the UK Renal Registry, by year

	Year Groups							
	2007		2008		2009		2010	
	HES	UK-RR	HES	UK-RR	HES	UK-RR	HES	UK-RR
Number of incident RRT patients*	5,412	5,483	5,420	5,626	5,572	5,690	5,501	5,541
Demographics								
Female	38%	38%	39%	39%	39%	38%	38%	37%
Median age† (years)	63	64	63	64	63	64	64	64
Ethnicity‡								
Proportion with ethnicity reported	*94%*	*75%*	*94%*	*74%*	*95%*	*78%*	*95%*	*94%*
White	76%	78%	76%	78%	76%	80%	77%	78%
Black	7%	8%	7%	7%	7%	8%	6%	7%
Asian	8%	11%	9%	11%	9%	10%	8%	12%
Others	4%	3%	4%	3%	4%	3%	4%	2%
Renal characteristics								
Initial renal replacement therapy modality								
Dialysis	92%	95%	91%	94%	91%	94%	90%	93%
Transplant	8%	5%	9%	6%	9%	6%	10%	7%
Primary renal diagnosis								
Diabetic kidney disease	20%	20%	20%	21%	19%	22%	17%	21%
Glomerulonephritis	14%	10%	15%	11%	17%	11%	23%	11%
Polycystic kidney disease	9%	6%	9%	7%	8%	6%	8%	6%
Other known diagnosis/unknown/unavailable	57%	64%	56%	61%	56%	61%	52%	62%

Data are n or % or median. HES = Hospital Episode Statistics (all-England). UK-RR = UK Renal Registry. Only years with >99% of renal units providing data to UK-RR presented [https://www.renalreg.org/publications-reports/]. *Most recently reported data are presented. †UK-RR 2007 data were derived from England and Wales only. UK-RR 2008-2010 data were from England only. ‡Ethnicity derived from Hospital Episode Statistics used more categories.

4.4.2 Cohort comparisons with UK-Transplant Registry data 2000-2011

Between 2000 and 2011 the number of isolated kidney transplant operations in England recorded to the UK Transplant Registry was 20,579 compared to 20,248 identified in all England-HES, a difference of 331 grafts or 1.6%. Between 2000 and 2005 HES captured *less* transplant activity than the UK-TR by an average difference of 86 (0.42% of the total transplants) transplants per year. By 2006-2011, these differences were qualitatively different with HES identifying *more* kidneys transplants than the UK-TR. HES captured, on average 30 more transplants per year (1.6% of total transplants) than the UK-TR over this period (Table 4-2).

Table 4-2: Number of kidney transplant operations in England recorded in all-England Hospital Episode Statistics and the UK Transplant Registry, by month and year

	2000		2001		2002		2003		2004		2005		2006		2007		2008		2009		2010		2011		2000-2011	
Month	**HES**	**UKTR**	**HES**	**UKTR**	**HES**	**UKTR**	**HES**	**UKTR**	**HES**	**UKTR**	**HES**	**UKTR**	**HES**	**UKTR**	**HES**	**UKTR**	**HES**	**UKTR**	**HES**	**UKTR**	**HES**	**UKTR**	**HES**	**UKTR**	**HES**	**UKTR**
Jan	99	104	100	119	120	129	140	145	130	147	100	104	109	108	145	136	164	157	178	169	213	208	191	185		
Feb	93	102	89	95	70	81	99	103	144	155	97	101	136	145	133	131	145	145	161	153	176	166	182	178		
Mar	134	154	120	128	87	99	104	113	130	145	114	118	118	132	143	146	152	150	173	170	183	197	170	174		
Apr	99	106	88	96	94	97	97	100	119	127	141	140	126	123	129	126	165	166	166	157	175	171	161	154		
May	102	109	130	144	107	107	105	117	126	129	139	143	152	150	159	153	166	161	180	178	167	171	191	185		
Jun	113	124	102	105	112	124	111	125	109	107	138	138	143	149	149	143	144	142	178	171	191	186	171	166		
Jul	99	104	120	136	110	113	105	112	113	121	141	143	140	137	158	156	183	186	186	182	181	172	203	204		
Aug	104	114	112	124	104	112	98	113	115	108	115	111	136	133	145	137	149	148	169	168	162	155	175	170		
Sep	81	88	98	104	124	129	151	147	111	122	126	131	159	157	131	133	176	178	169	167	162	166	194	197		
Oct	100	120	125	137	149	156	111	121	145	145	132	127	142	138	154	144	211	208	210	206	193	193	194	187		
Nov	121	129	107	117	152	158	119	127	114	119	109	114	161	156	165	167	171	176	194	196	221	217	199	195		
Dec	113	127	98	108	113	121	98	109	141	141	138	139	158	148	157	151	168	166	187	178	186	186	200	192		
Total	1258	1381	1289	1413	1342	1426	1338	1432	1497	1566	1490	1509	1680	1676	1768	1723	1994	1983	2151	2095	2210	2188	2231	2187	**20248**	**20579**
Absolute	-123		-124		-84		-94		-69		-19		4		45		11		56		22		44		**-331**	
%	-8.9%		-8.8%		-5.9%		-6.6%		-4.4%		-1.3%		0.2%		2.6%		0.6%		2.7%		1.0%		2.0%		**-1.6%**	

HES = Hospital Episode Statistics. UKTR = UK Transplant Registry. Multi-visceral organ transplants excluded. †Incorporated into National Health Service Blood and Transplant (NHSBT) [http://www.nhsbt.nhs.uk/]. The OPCS-4 codes used to identify kidneys transplants in all-England Hospital Episode Statistics were M01.2, M01.3, M01.4, M01.5, M01.8 and M01.9.

4.4.3 Cohort comparisons between ORLS and OKU-derived ESRD cohorts 1970-2008

Basic demographics: ORLS period

Between 1970-1990, OKU recorded 1,347 patients compared to the 1,220 new treated ESRD patients that were identified in ORLS, a difference of 127 patients (9.4% of the total). Despite the slightly different geographical boundaries of the two resources, the median age at the start of RRT in the 1970-1990 was 49 years with near equal proportions of female patients at between 40% and 41%. The age structures were also comparable with half of all patients being under 50 years and a quarter being over than 60 years in both databases (Table 4-3).

Between 1991 and 1996, ORLS identified 972 new maintenance ESRD patients whilst OKU recorded 967 patients, a difference of 5 (0.5% of the total). There were similar proportions of female patients (38% in ORLS vs. 39% in OKU). ORLS patients, during this period, had a median age that was 4 years older: median age 59 years (IQR, 44-69) vs. 55 years (42-67) in OKU.

Basic demographics: HES (Oxford) period

Data from OKU were then compared to the regional subset of all-England HES covering wider Oxfordshire, so-called HES (Oxford), during the period from 2000 to 2008. During this time, HES (Oxford) identified 448 more incident ESRD patients than OKU. These patients were, on average older than those patients recorded by OKU: 61 years vs. 59 years in 2000-2002, 61 years vs. 58 years in 2003-2005 and 61 years vs. 56 years in 2006-2008 respectively. Aligned to the difference in median age, the age structure of two datasets showed HES (Oxford) had consistently larger proportions of patients aged 70 years and a smaller proportion of patients under 50 years (Table 4-3).

Table 4-3: Demographic of treated end-stage renal disease patients in Oxfordshire, by dataset

	Year Groups				
	1970-1990	1991-1996	2000-2002	2003-2005	2006-2008
ORLS* 1970-1996, HES (Oxford) 2000-2008					
Number of incident RRT patients	1220	972	700	750	878
Female	40	38	41	36	38
Age (years)	49 (36-60)	59 (44-69)	61 (45-72)	61 (45-72)	61 (46-72)
18-40	30%	19%	19%	19%	16%
40-50	21%	16%	14%	13%	15%
50-60	24%	17%	15%	16%	17%
60-70	17%	24%	21%	21%	22%
70-80	7.9%	20%	24%	23%	20%
≥80	0.3%	3.8%	7.1%	7.6%	10%
Oxford Kidney Unit**					
Number of incident RRT patients	1347	967	597	640	646
Female	41%	39%	39%	35%	39%
Age (years)	49 (35-60)	55 (42-67)	59 (43-70)	58 (42-71)	56 (42-69)
18-40	32%	22%	21%	21%	21%
40-50	20%	18%	16%	16%	20%
50-60	22%	18%	15%	16%	16%
60-70	17%	22%	21%	20%	18%
70-80	8.8%	16%	19%	20%	16%
≥80	0.2%	4.3%	7.9%	6.7%	9.0%

Excludes patients dying within 90 days. Data are n or % or median (IQR). RRT = Renal replacement therapy. ORLS=Oxford Record Linkage Study. HES= Hospital Episode Statistics. *Restricted to residency within the Oxford Record Linkage region of Oxfordshire, Berkshire, Buckinghamshire and Northamptonshire. **Data source is a retrospectively entered database of RRT patients cared for by the Oxford Kidney Unit which does not contain information on comorbidity. Differences in cohort size between data sources are due to the different catchment areas of ORLS and OKU.

Three-year standardized mortality rates in Oxfordshire 1970-2008

The three-year age and sex standardized mortality rates for patients identified from ORLS and HES (Oxford) mirror those calculated from OKU. In OKU the three-year age and sex standardized mortality rate in 1970-1990 was 33.7% (95% CI 29.5–37.8%) compared to 35.6% (95% CI, 31.4–39.9%) in OKU, reducing to 22.9% (19.8–25.9%) in ORLS/HES (Oxford) and 23% (18.8–22.4%) in OKU by 2006-2008 (Table 4-5).

Table 4-5: Age and sex standardized three-year mortality rates in new treated end-stage renal disease patients, by dataset

Year Group	Oxford Kidney Unit (%) (95% CI)	Oxford Record Linkage Study (%) (95% CI)
1970-1990	35.6% (31.4-39.9)	33.7% (29.5-37.8)
1991-1996	26.9% (23.2-30.7)	30.9% (27.4-34.5)
2000-2002	24.7% (20.7-28.8)	26.5% (22.8-30.3)
2003-2005	22.4% (18.9-25.9)	25.4% (21.9-28.8)
2006-2008	22.4% (18.8-26.0)	22.9% (19.8-25.9)

Standardized to the age and sex structure of an 'average' 1970−2008 RRT population. See Table 5-2 for details

4.4.4 Cohort comparisons with directly linked data from the SHARP study

There were 1,622 patients, from England, randomised in SHARP. Of these 1,139 (70.2%) were pre-dialysis patients at randomisation. When the number of adjudicated events of maintenance dialysis were compared to those in all-England HES using derivation algorithm (and definition of maintenance as described in Chapter 2) there was excellent agreement with a kappa statistic of 0.84 (95% CI, 0.81-0.88), see Table 4-6. Absolute differences in the start date of these events showed in the 274 out of the 321 (85.4%) mutually identified cases of maintenance RRT in HES had a start date within three months of that reported in SHARP.

Direct comparison of adjudication confirmed site-reported maintenance dialysis vs Hospital Episode Statistics in SHARP Study

Table 4-6: Direct comparison of adjudication confirmed site-reported maintenance dialysis vs Hospital Episode Statistics in SHARP Study

SHARP pre-dialysis English participants who satisfied criteria of incident ESRD using HES algorithm	Pre-dialysis SHARP participants with an adjudiucated event of incident ESRD: YES	Pre-dialysis SHARP participants with an adjudiucated event of incident ESRD: NO	
YES	321 (28%)	52 (5%)	373
NO	25 (2%)	741 (65%)	766
Total	346	793	1139

Kappa statistic 0.84 (95% CI, 0.81-0.88)

Direct comparison was also made looking at the level of agreement on whether these pre-dialysis SHARP participants had received a kidney transplant as identified in HES. The level of agreement was again excellent, kappa statistic 0.92 (0.89-0.96) (Table 4-7). In 129/132 (97.7%) mutually identified transplants, the date of the implantation, identified in HES was within one month of its respective trials' adjudicated date, which improved to 99.2% (131/132) for dates within two months.

Table 4-7: Direct comparison of adjudicated-confirmed kidney transplant in randomised trial vs Hospital Episode Statistics identified kidney transplantation in SHARP participants

SHARP patients with a an adjudication confirmed site report of kidney transplant	SHARP English participants who staisfied as having a kidney transpant in HES: Yes	No	Total
Yes	132 (12%)	9 (1%)	141
No	10 (1%)	988 (87%)	998
Total	142	997	1139

Kappa statistic 0.92 (95% CI, 0.89-0.96)

4.4.5 Cohort comparisons of primary renal disease with directly linked data from 3C Study

All-England HES had excellent agreement with a kappa statistic of 0.92 (95% CI, 0.88-0.96) when compared to the PRD of polycystic kidney disease which was recorded by study nurses on the electronic case report forms. The 2 x 2 is shown in Table 4-8.[162]

Table 4-8: 2 x 2 table of agreement of the recording of polycystic kidney disease. Comparison from 3C database and all-England HES

		Polycystic kidney disease recorded as a diagnosis in all-England HES†		
		Yes	**No**	**Totals**
Cystic Kdiney disease recorded as primary cause of ESRD* in 3C	**Yes**	108	1	**109**
	No	15	529	**544**
	Totals	**123**	**530**	**653**

Kappa Statistic = 0.92 (95% CI, 0.88-0.96)

*ESRD=end-stage renal disease †ICD-10 terms Q61.2 and Q61.3 mentioned in any position in any hospital spell

4.5 Discussion

This chapter describes various methods used to assess the reliability of using routine healthcare data to derive a representative cohort of English treated ESRD patients between 1970 and 2008. The excellent level of agreement between the clinically adjudicated SHARP trial ESRD outcomes and maintenance RRT derived from HES using the clinical algorithm demonstrates the reliability of the identification rules used to derive the final ESRD cohort. Comparisons of the number of incident patients, their basic demographics and renal characteristics with the UK-RR, UK-TR and OKU data suggest that the derived cohorts, although unlikely to be completely free from error, are broadly representative of patients receiving RRT across this whole period.

In particular, the number of kidney transplants identified in HES closely approximated the number reported by UK-TR and validation work in 3C confirmed that HES accurately records this procedure.[157]

Cohort comparisons with UK-Renal Registry data 2007-2011

The UK-RR annual reports provided data from which the counts, demographics and renal characteristics of the derived all-England ESRD cohort could be compared. These results suggested that the number of new treated ESRD patients that were identified was within 2% of the UK-RR number, and there was a broadly comparable sex and age structure which are proposed covariates for subsequent mortality analyses.

Comparisons with UK-Transplant Registry, 2000-2011

In particular, the number of kidney transplants identified in HES closely approximated the number reported by UK-TR confirming that HES can accurately this seminal procedure performed exclusively in ESRD patients. A successful transplant remains the optimal treatment for patient with ESRD and it was important that these events were validated to

ensure that any analyses where the fact of transplantation is an important variable were possible.[42] The high accuracy of HES data in recording transplantation may be a result of the fact that procedure and operation notes are easily identifiable in hospital records and therefore may be well coded.[128] The small differences in the absolute counts may reflect coding errors or geographic differences, including the possibility that an ESRD patient who lives in Wales or Scotland may have been a recipient of a kidney transplant from an English Transplant centre. Such a patient would have been excluded by the HES algorithm but would have been included in the UK-TR summary statistics. Similarly if a non-UK citizen living abroad came to the UK and received a kidney transplant then this would be recorded by UK-TR but not HES. The under-counting of kidney transplants in HES relative to UK-TR between 2000-2005 is in contrast to some over-counting between 2005-2011. Without direct validation techniques, the precise reasons for this are not known yet it is possible that coders may have erred when patients are called in for a transplant but do not go on to receive it.

Comparisons with Oxford Kidney Unit data, 1970-2008

The electronic records kept by the Oxford Kidney Unit provided an opportunity to indirectly "validate" the characteristics of ESRD patients in the early decades of this study, a period when there was no UK-RR data. From 2000 onwards, the discrepancy in counts may be explained by the slightly different geographic areas that were being covered and that referral patterns from primary care will not be bound by ORLS's geographic landscape. The extremely similar age and sex adjusted mortality rates though do provide important reassurance that this older dataset still can reliably identify maintenance RRT patients.

Comparisons using directly linked data from SHARP study

Directly linked data confirmed that the HES derived algorithm reliably identified the fact of and date of kidney transplantation. This built on the indirect validation which compared

counts of transplantation, using data from UK-TR and are outlined in section 4.4.2 *and* internal validation in section 2.9 which described the proportion of patients identified by the proscribed 'rules of maintenance RRT' who latter went on to fulfil other such rules including transplantation.

It was crucial that transplantation, which is known to reduce the mortality of ESRD patients was captured accurately.[42] Any slight differences may have represented cross-border issues whereby residents in North Wales may receive a transplant in North West English hospitals (in Merseyside) or the perhaps when potential transplant recipients are called for a transplant but it never took place and the coders mis-attributed the true nature of the admission.

The direct comparison of SHARP data in regards to commencement of maintenance dialysis demonstrated similarly provided reassuring results. It suggested that the iterative process used to confirm RRT was being provided as a *maintenance* therapy, as opposed to it being provided for potential recoverable renal failure was a necessary step.

Comparisons of primary renal disease using directly linked data from 3C Study

This very high level of agreement for the most common inherited cause of ESRD was the impetus to explore other uses of the dataset, with analyses of a disease association study in patients with polycystic kidneys being described in Chapter 6 and published in Supplemenal Appendix 1.3.[163-167] This level of agreement is manifestly different from patients whom have *presumed* diabetic nephropathy in combination with hypertension and ischaemic changes where a nurse-recorded primary renal disease is more likely to differ from the patients' understanding on the complex (and often multiplicative) nature of their primary cause of renal disease. As there was uncertainty about the reliability of primary renal diagnosis derived from routine healthcare data, it was not used as a variable in the prospective mortality analyses in the subsequent results chapter.

Limitations

The main limitation of using any routinely collected hospital inpatient data are its anonymised nature, preventing wholescale direct validation of the whole derived cohort on an individual patient-level basis with another data resource. This prevents direct confirmation of the fact and date of starting maintenance RRT. Between 2000 and 2006, validation of the numbers of patients, their demographics and renal characteristics were also not possible for the all-England derived HES ESRD population, because lack of nationwide coverage by the UK-RR. Validation work of patients identified in the early epoch relied on electronic data entered manually by clinicians in OKU.

The start date of RRT is an important variable and may be subject to some error, when derived from hospital inpatient data, as although many hospitals appeared to record each haemodialysis sessions as day-admission, others may not. Therefore among those centres not recording *every* dialysis session there may be some uncertainty and this may partly explain the overestimation of pre-emptive transplants in HES; reflecting difficulties in identifying patients who began dialytic therapies and particularly PD as an outpatient.[168]

Lastly, assessment of the reliability of comorbidity data for the early patients was not possible as it was not reliably recorded on PROTON or by the UK-RR. The UK-RR has proposed that they link their data to HES in order to improve reporting of comorbidity and they have been able to do this for incident patients identified between 2002 and 2006 and permission to these data were only temporary.[88]

4.6 Conclusions

A retrospective cohort of treated ESRD adults can be identified using data exclusively from routinely collected hospital inpatients data. Indirect validation techniques were principally used to compare summary statistics of counts and demographics details of the ESRD cohort as the anonymous nature of the data precluded comprehensive direct validation. Nevertheless direct validation of the algorithm was possible for a subset of English patients who reached ESRD during follow-up of a randomised trial in which permissions had been sought to use linked hospital data for research purposes. This provided further evidence that the ESRD cohort derivation procedures were sufficiently reliable to proceed with prospective analyses. The various analyses described in this chapter suggest that the derived ESRD cohort is indeed representative of a contemporaneous ESRD population and that any errors are not in a specific age, sex or ethnic group. Moreover, the similarity of ORLS/HES Oxford and OKU mortality rates over the 40-year period are particularly reassuring.

4.7 Bullet points of Chapter 4

- Direct and indirect techniques of validation were used as recommended by the RECORD Statement.

- The indirect methods included comparisons of the derived data to summary statistics taken from other data repositories.

- Comparisons with the UK Renal Registry, between 2007-2010, showed the same median age at 64 years, near equivalent proportions of female patients (UK-RR: 38% vs. HES: 37%) and broadly similar ethnicity structure (White ethnicity 77% vs. 78%; Black 6% vs. 7%).

- Comparison with NHSBT, between 2000-2011, showed that the number of renal transplants identified in HES was within 2%.

- Direct validation techniques were undertaken using linked HES data from SHARP participants. This provided excellent levels of agreement: kappa 0.84 (0.81-0.88) for identification of maintenance RRT and even better for the fact of transplantation.

Chapter 5 Main results; mortality trends

Mortality trends in 45,000 English End-stage renal disease patients, 1970-2010

This chapter largely contains the material that has been published in the peer-reviewed journal. Impact factor 8.306 (2018) See **Appendix section 1.2** or the links below

Main Article:
Declining comorbidity-adjusted mortality rates in English patients receiving maintenance renal replacement therapy. **Storey, Benjamin C**. et al. *Kidney International*, Vol **93 (5)**,1165-1174

Online supplementary materials:
Supplementary materials

5.1 Abstract

Background

To compare long-term mortality trends in end-stage renal disease (ESRD) populations versus the general population after accounting for differences in age, sex and comorbidity.

Methods

Cohorts of 45,000 ESRD patients starting maintenance renal replacement therapy (RRT, ie, dialysis or transplantation) and 5.6 million controls selected to represent the general population were identified from two large electronic hospital inpatient datasets: the Oxford Record Linkage Study (1965-1999) and all-England Hospital Episode Statistics (2000-2011). All-cause and cause-specific 3-year mortality rates for both populations were calculated using Poisson regression and standardized to the age, sex, diabetes and other comorbidity structure of an 'average' 1970-2008 RRT population.

Results

The median age at initiation of RRT in 1970-1990 was 49y (interquartile cutoffs 36–60y) and 63y (49–73y) by 2006-2008. Over that period, there were increases in the prevalence of vascular disease (from 10.0 to 28.3%) and diabetes (from 6.7 to 34.3%). After accounting for these age, sex and comorbidity differences, standardized 3-year all-cause mortality rates in treated ESRD patients between 1970 and 2011 fell by about one-half (relative decline 51%, 95%CI 41–60%; absolute decline from 40.7% to 20.0%), steeper than the one-third decline (34%, 95%CI 31–36%; absolute decline from 8.6% to 5.7%) observed in the general population. Declines in 3-year mortality rates were evident among those who received a kidney transplant and those who remained on dialysis. In both the ESRD and the general population, mortality rates among people with diabetes have declined more steeply than those without.

Discussion

Since 1970, all-cause mortality rates among those on maintenance RRT have declined more steeply than rates in the general population. Similarly, mortality among people with diabetes have also declined more rapidly than those without diabetes, both among those on RRT and in the general population. Nevertheless, mortality rates for those with diabetes and particularly those with ESRD remain high.

5.2 Introduction

Maintenance dialysis programmes for end-stage renal disease (ESRD) began in the United Kingdom in the 1960s.[1-3] Until the 1980s, renal replacement therapy (RRT, ie, dialysis or kidney transplantation) was restricted to ESRD patients who were considered the most economically active and those with diabetes or other comorbidities were often not referred or treated.[4] This contrasts with the situation 50 years later when the median age of patients starting maintenance RRT is 65 years and diabetes is the leading cause of ESRD.[5]

Examining long-term temporal mortality trends helps describe past and current serious health risks. Their interpretation is difficult in RRT populations as comparisons between treated ESRD and other populations need to take account of the substantial secular changes in the prevalence of comorbid illnesses which influence both mortality[6-8] and the likelihood of receiving RRT. To date, no large study has standardized mortality rates in treated ESRD and general population cohorts to the same comorbidity as well as age/sex structure. Therefore, although data from ESRD registries in the United States 1977-2007,[9] Europe 1998-2007,[10] Australasia 1992-2005,[11] and UK 2002-2011[5] have all shown modest improvements in mortality for people with treated ESRD, it is unclear whether the magnitude of this change is comparable to that those observed in the general population during the same period.[12]

The Oxford Record Linkage Study (ORLS) was established in 1963 and recorded information about all hospital inpatient admissions in Oxfordshire and the surrounding counties.[13] Hospital Episode Statistics (HES) succeeded ORLS and established nationwide coverage from 1998. Mortality trends among new maintenance RRT patients and a set of general population controls, extracted from these two datasets are presented.

5.3 Methods

The Central and South Bristol Multi-Centre Research Ethics Committee (04/Q2006/176) has granted ethical approval for these analyses of linked hospital inpatient data. Retrospective cohorts of new maintenance RRT patients ('new treated ESRD') and general population hospital controls were derived from two routinely collected hospital inpatient datasets with linkage to national mortality data. The ORLS collected information on hospital admissions in Oxfordshire from 1963, expanding to surrounding counties to cover a population of 2.5 million.[169] Nationwide individual patient linked HES data replaced ORLS in 1998 recording information about admissions from all National Health Service hospitals in England. Analyses include a period from 1st January 1965 to 31st December 2011 (with cohort follow-up starting from 1st January 1970).

Both ORLS and HES record detailed information about hospital admissions including: patient demographics, dates of admission and discharge, admitting speciality, the primary diagnosis and relevant secondary diagnoses (all coded using the International Statistical Classification of Diseases and Related Health Problems [ICD] versions 7 to 10), and all inpatient procedures accompanied by their dates (coded using the Office of Population Censuses and Surveys [OPCS] Classification of Surgical Operations and Procedures versions 2 to 4).

Algorithms incorporating diagnostic, procedural and speciality codes relevant to renal disease, dialysis and transplantation to identify adults aged ≥18 years in ORLS who started RRT between 1970-1996, and in HES between 2000-2008 were developed. Those patients whose records indicated dialysis was for acute kidney injury or who died within 90 days of starting RRT were excluded (as is standard in the study of incident ESRD cohorts). For full details of cohort derivations see Chapter 2 or the summary derivation flowchart in Figure 2-4 and Figure 2-5). To allow mortality rates from the new treated ESRD cohort to be compared

to a group of contemporaneous adults, hospital controls who were never recorded as undergoing RRT were selected so as to be reasonably representative of the general population by using admissions for a range of minor conditions including inguinal hernias, soft tissue knee complaints, tonsillectomy, etc. (full list of conditions in Table 2-4). Hospital controls provided the advantage that comorbidity could be identified from admission records (information that is incompletely recorded in vital statistics). Baseline information on age, sex and ethnicity (categorised into White, Black, South Asian, other and unknown, and only reported in HES) was extracted.[170] A presumed primary renal diagnosis (polycystic kidney disease, glomerulonephritis, diabetic kidney disease, or other/unknown cause), initial RRT modality (dialysis or transplant) and co-morbidities based on the Charlson index[88,102] were identified from diagnostic and procedural codes on admission records at the time of entry into the cohort and for a fixed period of retrospective follow-up beforehand. For the purpose of adjustment, comorbid illnesses were classified as (i) diabetes mellitus (combining type 1 and 2); (ii) vascular disease, including major coronary disease, heart failure, cerebrovascular disease and peripheral arterial disease; and (iii) serious non-vascular disease including liver disease, cancer, chronic obstructive pulmonary disease (COPD), peptic ulcer disease, hemi- or paraplegia and connective tissue disease (definitions in Table 2-6).

The reliability of routine hospital admission data for the identification of new treated ESRD by comparing the number of transplants in ORLS and HES with the UK-Transplant Registry (Table 4-2)[149], the cohort sizes and characteristics with UK-Renal Registry (Table 4-4) annual reports,[113,146-148] and data (including mortality rates) collected from Oxford Kidney Unit databases compiled prospectively since 1967 (Table 4-4, & Table 4-5) were assessed. Subsequent mortality was identified from linked national mortality data. The primary outcome was all-cause mortality, and secondary outcomes were cause-specific mortality identified from the Underlying Causes of Death and separated into vascular (cardiac and non-cardiac)

and non-vascular mortality (renal disease [ie, death from renal failure or its causes], cancer, infection, and other/unspecified; definitions in Figure 2-6).

5.3.1 Condensed statistical analyses

Patient follow-up was separated by year of cohort entry into five groups: 1970-1990, 1991-1996, 2000-2002, 2003-2005, and 2006-2008 (ie, there was a gap between the two cohorts between 1997-1999). The different number of years covered by each group ensured similar numbers of patients in the two ORLS groups (1970-1996) and, separately, in the three HES groups (2000-2008). All-cause and cause-specific mortality rates for each group were estimated using Poisson regression adjusted for age, sex and comorbidities. Three-year mortality rates are presented as it ensured data from those starting dialysis as late as 2008 could be included. Age was included as a continuous variable using linear and quadratic terms. To account for the Poisson regression assumption that the mean and variance of the rates are equal, robust standard errors were calculated.[171] Marginal standardization[172] was used to adjust mortality rates to the characteristics of an 'average' 1970-2008 RRT population, defined using the entire ORLS RRT cohort and a random sample from each of the HES year groups such that the standard population had approximately equal numbers of RRT patients from each decade (characteristics in Table 5-2). To allow for comparisons of change in mortality over time between the ESRD and general population cohorts, percentage change in 3-year mortality rates between the 1970-1990 and 2006-2008 groups (ie, over approximately 25 years) were presented with 95% confidence intervals (CI) for the ORLS and a HES cohort which closely matched the ORLS catchment area (referred to as "HES Oxford" in Figures). For the all-England HES and the "HES Oxford" cohorts, percentage changes in 3-year mortality rates between the 2000-2002 and 2006-2008 groups (ie, over about 10 years) are presented so mortality trends from Oxfordshire and surrounding counties can be compared to all-England data.

To explore mortality rates among those who received a transplant and those who did not, subsequent analyses were stratified by including an interaction term between year group and transplantation status by three years. This allowed estimation of separate rates for transplant recipients and those who remained on dialysis. Subgroup analyses by prior diabetes were performed using a similar method.

In sensitivity analyses, 1-year, 2-year, 4-year and 5-year mortality rates were also calculated for comparison. Three-year mortality rates standardized to a 2006-2008 English RRT population were also provided. All analyses used SAS v9.3 (SAS Institute, Cary NY, USA) and R v3.2.1.

5.4 Expanded statistical methods

Firstly, it was considered whether it would be appropriate to study a mortality rate or a mortality risk. A rate was decided upon as it is more clinically informative and appropriate for in temporal trend analyses. To calculate rates there were two standard regression models that could have taken into account time to event: Cox or Poisson. Cox models the hazard of an outcome without specifying the form of the baseline hazard function. Estimation of the underlying baseline hazard would be required to obtain absolute rates from this model. However, it is possible to generate absolute rates directly from Poisson regression parameter estimates so it was decided to use this model for this study.

5.4.1 Data processing before proceeding to regression model

For each patient identified in the ESRD study population covariates and outcome variables were generated including fact of and date of death (including a 'time to event' variable) and binary variables for the presence or not of individual comorbid illnesses identified prior to start of maintenance RRT.

Patient follow-up was separated by year of cohort entry into five groups: 1970-1990, 1991-1996, 2000-2002, 2003-2005, and 2006-2008. The different number of years covered by each group ensured similar numbers of patients in the two ORLS groups (1970-1996) and, separately, in the three HES groups (2000-2008). Three-year mortality rates were presented as it ensured data from those starting dialysis as late as 2008 could be included as they were followed-up until 31st December 2011.

In baseline data, proportions were presented for the categorical variables. As age was not normally distributed, medians with interquartile cutoffs were presented. To assess whether baseline characteristics changed significantly over time, tests for the differences across the year groups were performed using Chi-squared (χ^2) tests for binary variables and Kruskal-Wallis test for age.

5.4.2 Choice of regression model; Poisson

The outcome of interest was decided to be a 3 year mortality *rate* to be calculated using Poisson regression with the addition of an offset variable. Poisson regression models the natural log of the expected count as a linear function of the selected independent variables.[173] A rate is just the expected count for an outcome (i.e. death) per a given unit of time. The offset takes into account that individual patients were followed up for different lengths of time.

Before its adoption, the assumptions that underlie a Poisson distribution were explored:

1. It excludes negative numbers

   A 3 year mortality rate cannot be <0%

2. The occurrence of an event does not affect the probability that a second event can occur, i.e. the events are random and therefore independent of each other.

   You cannot die twice so the first part of this assumption is not violated. Similarly when any given ESRD patient dies this does not generally affect the chances of other patients dying.

3. The variance is equal to the mean

   This was mitigated by usage of robust standard errors, see below.

It became apparent that the variance was not equal to the mean, which violated one of the main assumptions of Poisson regression. In light of this, in conjunction with statistical colleagues, a negative binomial method was proposed and trialled but felt not to be appropriate. The problem encountered with the negative binomial model was that the estimated means were markedly different from those obtained using Poisson regression and gave values that were implausible, such as 3 year mortality rates >100%. In this scenario, the mean rate from Poisson was deemed more reliable as the assumption of the mean and variance being equal does not influence the maximum likelihood estimates of parameters in a Poisson regression. The negative binomial was therefore abandoned with a Poisson model

incorporating robust standard errors used thereafter.[171] Robust standard errors have been shown to be an appropriate method of dealing with the violation of the assumption of equidispersion.[174]

Likelihood ratio tests were conducted to select appropriate variables to be included into the model. A stepwise selection technique was used with both forward and backward steps. Age was included as a continuous variable using linear and quadratic terms. Various other polynomials of age were explored and deemed unnecessary whilst grouping age into age bands (i.e. 30-34, 35-39 etc…) was considered but rejected principally as there was not sufficient statistical power in the ORLS dataset with very few patients aged over 80 years identified in earlier year groups. Sex was included in the model as it is accepted that it influences survival in the general population and is typically incorporated into mortality statistics reported in renal registries. Thereafter each individual comorbid illness was entered and it became apparent that diabetes made a significant difference, tested by calculating the difference in twice the log-likelihood statistic before and after its inclusion with a significance threshold of $p<0.05$. Other individual comorbidities were similarly assessed and offered little improvement yet when grouped into broader categories of vascular and serious non-vascular (as tabulated in Table 2-6) they reached statistical significance and were thus included.

IMD and ethnicity were not explored as there was no data collected in ORLS.

5.4.3 Final covariates used for analyses.

Age was included as continuous variable using linear and quadratic terms;

Sex was dichotomised (male and female);

Baseline major comorbidity which was treated as a binary variable and grouped into; diabetes, vascular disease or serious non-vascular.

5.4.4 Standardization techniques

Indirect standardization calculates the strata specific observed/expected death rates within a reference population and then apply these rates to a given study population. Then one would ordinarily calculate an observed/expected ratio (the standard mortality ratio; SMR) multiplying it by the crude rate in the reference population to provide adjusted mortality rates.[175] This traditional indirect standardization was not felt to be flexible enough (for example it would have been necessitated age groupings and other strata of comorbidities). Marginal standardization is a regression equivalent whereby the regression coefficients estimated using the study population are applied to each of the individuals in the reference population giving a probability of the interest outcome (i.e. death within three years) for each patient.[172,173] These individuals' probabilities were then summed to get a total expected death 'count'. This total was then divided by total person years follow-up to give the 3-year *standardized* mortality rate. This is the mortality rate that would have been observed had the study population been forced to be in a particular year group; standard errors for these rates were also generated. The detailed statistical plan was published in the associated manuscript, see Appendix section 1.2.

The key advantage of marginal standardization is that it gave rates that were applicable to the population being studied. For example, a common alternative approach is to set confounding variables to the overall mean values and then base standardized rates on these. But no real patient has these values (as you can get the sex variable as being, 0.4, referring to a patient being 40% female and 60% male). This makes the rates less applicable and tangible for practicing nephrologists.

5.4.5 Reference population

Due to the large change in baseline characteristics in the incident ESRD population an 'average RRT' population was selected as the most appropriate reference population. This was defined using the entire ORLS RRT cohort and a random sample from each of the HES year groups such that the standard population had approximately equal numbers of RRT patients from each decade. Changing the reference population to be more reflective of a modern incident ESRD population was studied as a sensitivity analyses and indeed increased the absolute mortality rates reductions but not the proportional decline from 1970-1990 to the 2006-2008 year groups (see Table 5-2 for baseline characteristics of an average RRT population and Figure 5-7 for the effect on mortality rates that changing the reference population used for the purposes of standardization).

5.4.6 Further analyses, use of an interaction term

To explore mortality rates among those who received a transplant and those who did not, subsequent analyses were stratified by including an interaction term between year group and transplantation status by three years. An interaction effect is when the outcome variable is differentially affected by the presence (or not) of another variable, in this case kidney transplantation. Including an interaction term of kidney transplantation allowed estimation of separate rates for transplant recipients and those who remained on dialysis.

Subgroup analyses by prior diabetes, age (<60, ≥60) and sex were performed using a similar method, and are accompanied by standard heterogeneity tests which compared the proportional reductions in mortality over time between the subgroups.

5.4.7 Sensitivity analyses

1-year, 2-year, 4-year and 5-year mortality rates were also calculated for comparison and presented as survival probabilities which were calculated by subtracting the adjusted mortality rates from 100.

All analyses used SAS v9·3 (SAS Institute, Cary NY, USA) and R v3·2·1 and were conceived in conjunction with the units' dedicated team medical statisticians.

Analogous statistical methods were performed to calculate standardized rates for the general population hospital control cohorts in ORLS and HES Oxford and separately for the both the ESRD and control population in all-England HES.

5.4.8 Missing data

Missing data is common in observational data of this kind. In this thesis only patients that had age and sex recorded at their index admission were included. Missing data for baseline comorbidities could not be assessed as it was unknown as to whether the absence of a comorbidity code meant the patient actually had *no* comorbid illness or whether the clinical coders missed any relevant codes. Attempting to incorporate multiple imputation models into the ESRD cohort and then also the very large general population would require significant computing power and time and was not deemed practicable or feasible. If any presumed missing data occurred at random then the results and analyses would be the same. Analyses were performed looking at the effect of changing the period of retrospective look-back period on the prevalence of baseline co-morbidity and justification of the period finally used can be found in Chapter 3.5.2. Other determinants of all-cause mortality that were recorded included socio-economic status and ethnicity yet these were not included in ORLS

database and so could not be incorporated into the analyses across the whole period. They were, though, utilised and included in the disease association study of PKD in chapter 6.

5.5 Results

5.5.1 Summarized baseline characteristics

Full discussion on the baseline characteristics of the ESRD cohort can be found in Chapter 3

ESRD cohort

Between 1970-2008, 44,922 new ESRD patients started maintenance RRT (2192 in ORLS 1970-1996 and 42,730 from all-England HES 2000-2008) and 5,613,781 general population controls (532,019 from ORLS and 5,081,762 from HES) were identified. Indirect validation included observing closely matched numbers of kidney transplant operations recorded in HES and the UK-Transplant Registry[149] (Table 4-2); closely matched cohort sizes, demographics and renal characteristics when HES data were compared to summary English data from the UK-Renal Registry (Table 4-1);[113,146-148] and similar age and sex adjusted 3-year mortality rates for ORLS/"HES Oxford" and for Oxford Kidney Unit (Table 4-4, Table 4-5). For fuller details on the validation of the cohort, see Chapter 4

In Oxfordshire, the median age at start of maintenance RRT increased from 49y (interquartile cutoffs 36-60y) in 1970-1990 to 61y (46-72y) by 2006-2008. Consequently, while only one-quarter of patients starting RRT from 1970-1990 were aged ≥60y, by 2006-2008 this proportion was more than one half (Figure 3-2 & Table 3-1). Of those starting RRT, the proportion that were female remained at about 40% across all time periods (Figure 3-2) but the proportion with any major comorbidity rose steeply from 1970 to 2008. In particular, diabetes prevalence among those starting RRT increased from 5.5% during 1970-1985 to 33.9% in 2006-2008, whilst prior vascular disease increased from 9.1% to 25.2% (Table 3-1 & Figure 3-2), constituting increases in peripheral arterial disease from 3.0% to 12.9%, major coronary disease from 2.6% to 8.3%, and admission for heart failure from 5.2% to 10.5% (Table 3-1). Prior cancer was recorded in 2.9% of RRT patients during 1970-1990 and 7.6% of patients during 2006-2008. The demographics and comorbidity of treated ESRD patients

in Oxfordshire who started RRT between 2000-2008 were broadly similar to those observed in the rest of England (Table 3-1).

General population cohort

Compared to new ESRD patients, general population controls were on average younger and more likely to be female. General population controls in the later time periods were older and had more comorbidity than general population controls from the earlier periods (Table 3-4).

5.5.2 All-cause mortality; <u>unadjusted</u>

ESRD cohort

Of the 1,220 new ESRD patients starting RRT in 1970-1990, 267 (crude 3-year mortality rate 24.8%) died within the first three years. For the 878 Oxfordshire patients and 15,946 all-England patients starting RRT in 2006-2008, 221 (28.7%) and 4,482 (38.2%) died within three years, respectively. Crude mortality rates – which do not take account of secular changes in age, sex or comorbidity of those who received maintenance RRT – showed an average increase in mortality between 1970-1996, followed by the beginnings of a decline (Table 5-3A & Figure 5-7A) from 2000 onwards.

General population cohort

Since 1980, crude three-year mortality increased in the general population hospital controls by 32%, from 3.8% (3.7-3.9%) in 1970-1990 to 5.0% (4.8-5.2%) in 2006-2008 (Figure 5-7A).

5.5.3 All-cause mortality; age and sex standardized

ESRD cohort

After standardization by age and sex, a continuous decline in 3-year mortality rates from 1970 became evident: from 33.7% (30-38%) in 1970-1990 to 22.9% (20-26%) by 2006-2008; a 32% proportional reduction (Table 5-3B & Figure 5-1).

General population cohort

Similarly in the general population following age and sex adjustment mortality rates declined smoothly by 20%, from 5.5% in 1970-4.4% in 2006-2008 (Figure 5-1 & Table 5-3B).

5.5.4 All-cause mortality; age, sex and comorbidity standardized

ESRD cohort

The addition of comorbidity as a covariate resulted in the mortality rates steepening (Figure 5-7C & Table 5-3D). When standardized to an average RRT population, 3-year mortality rates fell on an absolute scale by 20.7% (from 40.7% in 1970-1990 to 20.0% in 2006-2008), and relatively by 51% (95% CI, 41%–60%) over this period (Figure 5-1 & Table 5-3C). Had a more modern RRT population been chosen as the reference population for standardization then the absolute decline would have increased to 31%, with no change in the proportional reduction (Table 5-3D).

All-England data from 2000 mirrored findings in Oxfordshire data from the same period (Figure 5-1).

General population cohort

Comorbidity adjustment also steepened the declines mortality rates in the general population. On an absolute scale this caused rates to fall by 2.9% (from 8.6% in 1970-1990

to 5.7% in 2006-2008), corresponding a 34% (95% CI, 31%–36%) proportional decline (Figure 5-1).

5.5.5 Sensitivity analyses, one to five year standardized mortality rates

ESRD

Examination of 1-year, 2-year, 3-year and 5-year mortality rates were performed as sensitivity analyses and showed steep, and relatively linear, declines in mortality rate, no matter what duration of prospective follow-up was applied (Figure 5-8).

5.5.6 Impact of transplantation on mortality in ESRD patients

Kidney transplantation was introduced in Oxfordshire in 1975. The 3-year standardized mortality rate among these early transplant recipients was substantially lower than for those who remained on dialysis (15.3% versus 41.8% during 1970-1990), and fell over time such that the 2000-2008 3-year standardized mortality rates for transplanted patients were 4.6% (Figure 5-2). Three-year mortality also substantially and continually declined among ESRD patients who remained on dialysis. The trend in declines in three-year mortality rates were similar in both the Oxfordshire and all-England data over the period 2000-2008.

5.5.7 All-cause mortality, stratified by baseline characteristics

By prior diabetes

In the general population, there were steeper reductions in mortality over time in people with diabetes or not (heterogeneity p<0·0001 for Oxfordshire and p<0·0001 for all-England). The same was not observed among treated ESRD patients in Oxfordshire over 25 years (heterogeneity p=0·41), but there was evidence of steeper declines in mortality rates among people with diabetes from 2000 in England (heterogeneity p=0·01). Although the absolute

difference in mortality rates between those with and without diabetes has become substantially smaller between 1970-2011 (Figure 5-3 & Table 5-4).

By sex

In the general population hospital controls there were significantly steeper reductions in standardized mortality rates in males than females, p<0.0001 in Oxfordshire (since ~1980) and since 2000, in all-England, p<0.0001. The same was not observed in the ESRD population where the proportional declines in all-cause mortality rates, since 1980 were similar in male and females, 52% (36-61%) and 54% (41-67%) respectively, p=0.56 respectively with similar non-significant changes found in Oxfordshire (p=0.98) and England (p=0.91) since the turn of the century (Figure 5-4 & Table 5-5).

By age

Patients aged <60 years in the general population and ESRD cohorts had similar proportional declines to respective patients aged ≥60 years although the absolute magnitude of these reductions was greater in the ESRD cohort. In the general population patients <60 years had a 32% (25-39%) proportional decline whilst patients ≥60 years had a 34% (31-36%), p=0.63. Over the same period, patients aged <60 years in the ESRD population had a 52% (36-68%) reduction in mortality rates whilst patients ≥60 years were observed to have a 53% (41-64%) reduction (Figure 5-5 & Table 5-6), p=0.98.

This pattern was different in more recent analyses from all-England ESRD patients, where those <60 years saw significantly greater proportional declines than those ≥60 years, 32% (26-38%) vs 24% (20-28%), p=0.03 (Figure 5-5); likely due to higher survival rates in younger patients who more frequently received kidney transplants.

5.5.8 Cause specific mortality analyses

Vascular mortality

Among new ESRD patients, 3-year mortality rates from vascular causes fell from 12.2% between 1970-1990 to 7.4% by 2006-2008, representing a 25-year relative reduction of about 40% (95% CI 19%–60%) since 1980, which included about a 31% (95% CI 2–60%) reduction in cardiac mortality and 55% (95% CI 28–82%) reduction in non-cardiac vascular mortality (Figure 5-6).

In general population controls, 3-year mortality from vascular mortality declined from 4.1% in the 1970-1990 group to 1.9% by 2006-2008. This represented a relative 25-year decline in 3-year vascular mortality of 53% (95% CI 50–56%), which included a 58% (95% CI 55–61%) decline in cardiac and 45% (95% CI 40–50%) decline in non-cardiac vascular mortality (Figure 5-6). Between 1970-2011, declines in cardiac mortality have therefore been steeper in the general population than new ESRD patients. Again, all-England data from 2000-2011 mirrored findings from Oxfordshire 2000-2011.

Non-vascular mortality

In new ESRD patients, 3-year mortality from non-vascular causes declined steeply and continuously since 1970 from 28.4% in the 1970-1990 group to 12.6% by 2006-2008 (Figure 5-6). On a relative scale this represented is a 25-year decline of 56% (95% CI 45–66%) since 1980. The commonest underlying non-vascular causes of death were from renal failure or its causes (eg, chronic, diabetic, hypertensive and polycystic kidney diseases). Such mortality fell from 16.8% to 4.9% between the 1970-1990 and 2006-2008 groups, a relative decline of 71% (95% CI 61–81%). Declines in other common non-vascular causes were more modest. These included a reduction of 27% in infectious mortality (95% CI -14–68%;

absolute decline from 3.3% to 2.4%) and a reduction of 50% in cancer mortality (95% CI 21%–80%; absolute rates 4.2% and 2.1%) (Figure 5-6).

In general population controls, the declines in 3-year non-vascular mortality were more modest than the corresponding declines in new ESRD patients. Three-year standardized mortality rates fell from 4.6% in 1970-1990 to 3.8% by 2006-2008, which on a relative scale represents a 25-year 17% (95% CI 13–21%) decline since 1980. This included a 25-year 26% relative reduction in death from cancer (95% CI 20–31%; absolute decline from 2.1% to 1.6%), and 30% relative reduction in infection-related mortality (95% CI 22–37%; absolute decline from 0.7% to 0.5%) (Figure 5-6).

In treated ESRD patients, the steeper proportional declines in non-vascular mortality compared to those in the general population (56% vs. 17%, Figure 5), and shallower declines in vascular mortality (17% vs. 40% respectively) resulted in the proportion of all deaths ascribed to vascular disease rising from 29.9% in 1970-1990 to 36.8% in 2006-2008, whilst the proportion of all deaths ascribed to vascular disease in the general population fell from 47.5% to 33.3% over the same period (Figure 5-9).

5.6 Discussion

A large cohort of newly-treated ESRD patients and contemporaneous general population controls, extracted from routine hospital admission datasets established before the start of maintenance RRT programs began in the UK, were used to compare changes in cause-specific mortality, taking account of the major changes in age and comorbid illnesses of those selected to start RRT. Three-year absolute mortality rates from many causes have remained high among people on maintenance RRT, but on a relative scale, overall mortality has halved. This decline is substantially steeper than the one-third decline observed in the general population. As those on RRT are at much higher mortality risk than the general population, this translates into substantially larger reductions in absolute mortality rates. Nevertheless, on average, those with ESRD currently still experience mortality rates 4-5-times higher than the general population.

An important finding from this study is that the reported reductions in mortality rates have declined faster than reported by ESRD registries from the United States 1977-2007,[9] Europe 1998-2007,[10] Australasia 1992-2005,[11] and UK 2002-2011.[5] These registry studies may have underestimated improvements in mortality by virtue of not being able to adjust for temporal changes in serious vascular and non-vascular comorbidities. The presented age, sex and comorbidity-adjusted estimates suggest relative mortality declines of perhaps 30% over the 10 years from the mid-1990s, which is larger than the approximately 20% declines evident from contemporaneous European registry data *without* such comorbidity adjustment.[176,177] Our results from HES data were, however, almost identical to the relative declines in comorbidity-adjusted mortality rates reported by a 2002-2006 study which used UK-Renal Registry HES-linked data.[88]

Over the last 40 years, there has been a progressive and steep increase in the proportion of people with diabetes who start RRT treatment for ESRD. There was evidence that mortality rates have fallen faster among people with diabetes both in the general population and in those on maintenance RRT, meaning the absolute gap in mortality rates between those with and without diabetes has progressively closed over the last few decades. Nevertheless, our most recent data suggest that those with diabetes are on average at about 40-50% higher risk than those without, irrespective of ESRD.

This study includes data in the 25 years before RRT registries had complete nationwide coverage in England. Over the early period, the numbers of people on RRT progressively increased and short-to-medium mortality was still attributed, in large part, to renal failure or its causes. This renal mortality rate has fallen by more than a half over the last 40 years. Kidney transplantation may have been a key intervention in reducing such mortality.[42] By 2000, 25 years after the first kidney transplant in Oxford,[178] standardized 3-year mortality rates among those selected to receive a kidney transplant were as low as 4-5%. However, those remaining on dialysis have also experienced substantial improvements in mortality rates over time which could be attributable to multiple incremental improvements in the way renal care has been delivered in dialysis units, and/or improvements in the way patients are prepared for RRT.[57,179]

In contrast to the early improvements in renal mortality, reductions in mortality rates from infections were more delayed, beginning from the late 1990s. Focus on infection control measures including hand hygiene protocols, flushed connection systems for peritoneal dialysis catheters,[180] emphasis on natural arteriovenous haemodialysis access,[31,181] the introduction of antibiotic haemodialysis catheter locks,[182,183]and proactive vaccination programs[184] may all have contributed.

In the stratified analyses, the proportional reductions in 3-year mortality rates in ESRD patients were not observed to be different between the sexes in contrast to that seen in the general population controls. The general population men have benefited more than women from the advances in the treatments of occlusive atherosclerotic vascular disease (as it is more prevalent in men) whilst in treated ESRD patients, irrespective of sex, there is a higher proportion risk of non-atherosclerotic disease such as heart failure where there are fewer proven therapies.

The differences in the proportional reduction in 3-year all-cause mortality rates between those with and without diabetes suggests that there has been steeper proportional declines in the non-diabetic ESRD population than those observed in the general population without diabetes. This has contributed to the overall narrowing of all-cause mortality rates as the proportional declines in diabetic patients (either ESRD or general population) has been similar. The reasons for this cannot be explored further as residual confounding would distort assumptions.

The finding that mortality from vascular disease has declined less steeply among treated ESRD populations than general populations corroborates similar observations made in Australasia between 1992 and 2005.[11] These English results now demonstrate that this lesser decline in vascular mortality appears to result from slow declines in cardiac mortality. The reasons why improvements in cardiac mortality rates in treated ESRD populations have been slower than the rapid declines observed in general populations (both in this study and in other national representative data[185]) cannot be tested in the present study. Other studies have found effective interventions to reduce vascular mortality in high-risk people[133,186,187] may be less effective in ESRD populations (eg, lowering low-density lipoprotein cholesterol[188]), and interventions for renal-specific risk factors (eg, renal anaemia,[189] low dialysis dose,[190] and hyperparathyroidism[191]) do not have clear cardiovascular benefits. Studies also suggest there has been underuse of coronary intervention in people with chronic kidney disease.[192] As vascular disease was found to be the underlying cause of 1-in-

3 deaths within three years of starting renal replacement therapy (RRT), identification of the causes of high vascular mortality rates in ESRD patients should remain a research priority.

Using and comparing data from registries of UK RRT activity and the Oxford Kidney Unit, data derived from routinely collected hospital admission data, although not completely free from error (see Chapter 4 Validation), can provide representative and reliable descriptions of changes in mortality rates, with our results mirroring recent HES-linked UK-Renal Registry.[88] One limitation of these data is that the general population controls were selected for having been hospitalized for minor conditions. This was necessary as it enabled adjustment for comorbidity and therefore reliable comparisons between the different populations. It cannot be guaranteed that the mortality rates in hospital controls were completely representative of mortality rates in an unselected Oxfordshire and English populations. Another limitation was the lack of information on certain exposures which may have changed substantially over time and influenced mortality, such as cigarette smoking. Finally, completion of death certificates may have varied with time, and in particular, that some deaths due to vascular causes may have been attributed to renal disease, infection or other non-vascular causes (and vice versa). However, a key strength of this study is that cause-specific mortality data from all the cohorts share the same certification and coding principles in any given year, making comparisons between ESRD and general populations more reliable.[193-195]

5.7 Conclusion

In summary, the full extent of mortality declines among RRT patients since 1980 is only apparent when changes in comorbidity are taken in to account. This approach suggests mortality rates in RRT patient have halved since 1970, faster than declines in the mortality in the general population. Declines in 3-year mortality rates were evident among those who received a kidney transplant and those who remained on dialysis. However, among those on RRT with or without diabetes, high residual mortality risk from both vascular and non-vascular causes remains.

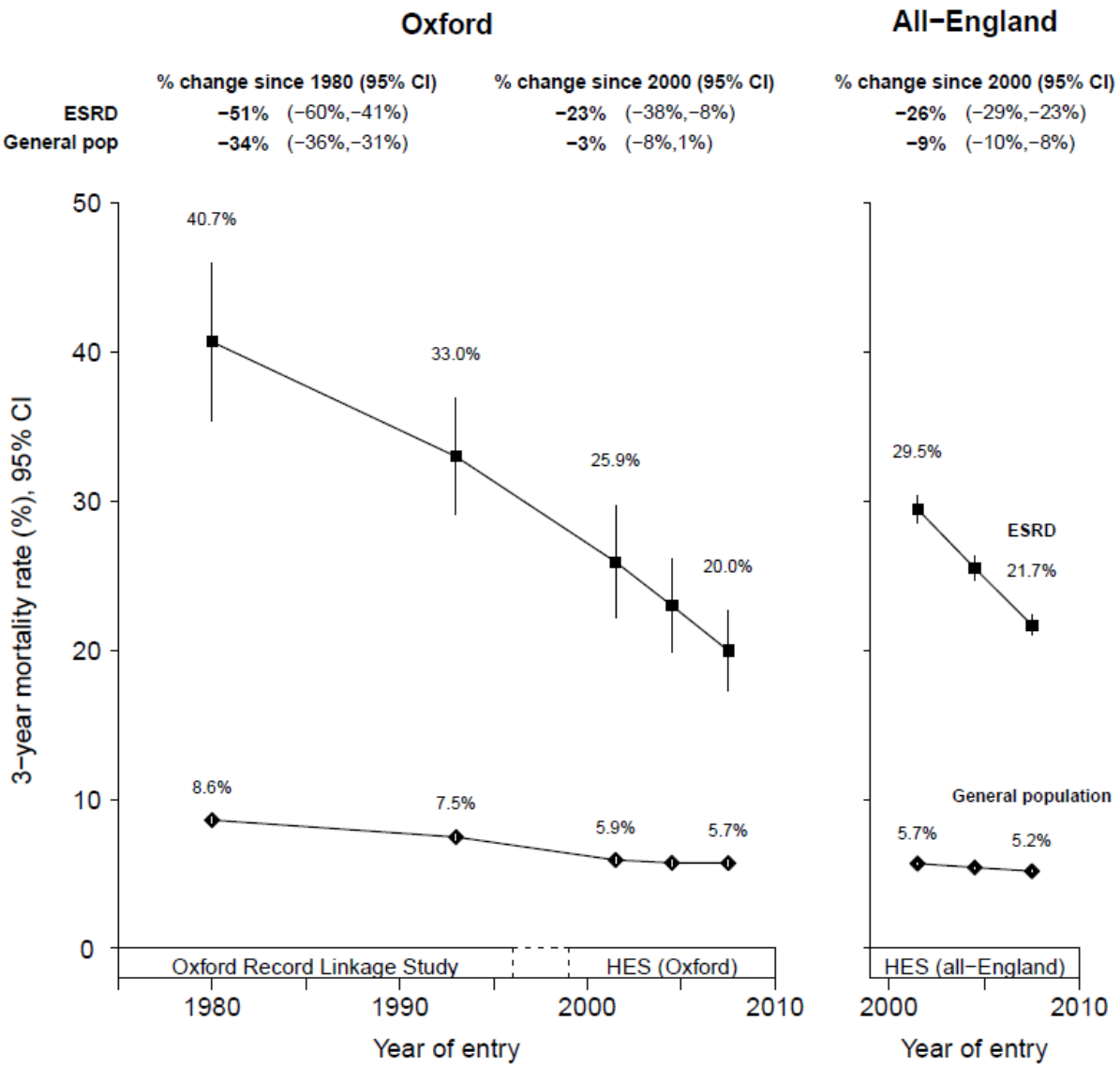
5.8 Main illustrative materials for results

Table 5-1: Baseline characteristics of new treated new treated end-stage renal disease patients, by year

	Year Groups							
	Oxford					All-England		
	Oxford Record Linkage Study		Hospital Episode Statistics (Oxford)			Hospital Episode Statistics (All-England)		
	1970-1990	1991-1996	2000-2002	2003-2005	2006-2008	2000-2002	2003-2005	2006-2008
N	1,220	972	700	750	878	13,178	13,606	15,946
Demographics								
Female	40.2%	38.0%	41.1%	35.9%	37.7%	39.5%	37.9%	38.5%
Median age (years)	49 (36-60)	59 (44-69)	61 (45-72)	61 (45-72)	61 (46-72)	61 (47-71)	62 (47-72)	63 (49-73)
18 - 40	30.2%	18.7%	18.7%	18.7%	15.9%	15.8%	14.8%	13.0%
40 - 50	21.2%	15.6%	13.6%	13.1%	14.7%	13.5%	13.4%	12.9%
50 - 60	23.5%	17.2%	15.4%	16.4%	17.1%	17.8%	16.6%	17.2%
60 - 70	16.8%	24.2%	20.7%	20.8%	22.1%	23.1%	22.9%	22.7%
70 - 80	7.9%	20.5%	24.4%	23.5%	19.8%	23.6%	24.1%	24.5%
≥80	0.3%	3.8%	7.1%	7.6%	10.4%	6.1%	8.2%	9.7%
Ethnicity†*								
White	-	-	86.8%	86.4%	84.0%	82.1%	81.2%	79.9%
Black	-	-	3.5%	3.5%	4.7%	6.3%	6.5%	6.9%
South Asian	-	-	7.4%	6.3%	7.2%	8.2%	8.3%	8.7%
Other	-	-	2.3%	3.8%	4.0%	3.4%	3.9%	4.4%
Unknown	-	-	131	36	35	1,694	962	745
Comorbidities								
Diabetes	6.7%	16.8%	24.4%	29.2%	33.9%	25.7%	29.9%	34.3%
Vascular	10.0%	18.3%	22.3%	24.7%	25.2%	25.2%	26.5%	28.3%
Major coronary disease	2.6%	4.2%	5.1%	7.2%	8.3%	6.1%	7.0%	7.7%
Congestive heart failure	5.2%	8.5%	9.9%	10.8%	10.5%	11.7%	12.3%	12.8%
Cerebrovascular disease	1.4%	2.2%	3.1%	2.8%	3.5%	3.3%	3.4%	3.4%
Peripheral arterial disease	3.0%	7.8%	11.3%	11.5%	12.9%	12.0%	12.5%	14.2%
Non-vascular‡	7.8%	14.4%	18.3%	21.7%	24.9%	21.7%	25.0%	27.5%
Liver disease	0.5%	0.4%	1.7%	1.1%	2.3%	1.6%	2.0%	2.8%
Cancer	2.9%	4.6%	5.3%	8.9%	7.6%	6.4%	7.8%	8.3%
Chronic obstructive pulmonary disease	1.3%	2.9%	6.3%	6.5%	10.3%	8.3%	10.0%	12.1%
Peptic ulcer disease	1.6%	2.3%	2.7%	1.9%	1.9%	2.3%	2.3%	2.0%
Connective tissue disease	2.0%	4.3%	3.1%	4.4%	4.9%	4.7%	5.0%	4.8%
Renal characteristics*								
Initial renal replacement therapy modality								
Dialysis	94.6%	92.6%	93.7%	92.7%	91.6%	94.5%	94.3%	93.6%
Transplant	5.4%	7.4%	6.3%	7.3%	8.4%	5.5%	5.7%	6.4%
Primary renal diagnosis (presumed)								
Diabetic kidney disease	1.6%	8.4%	20.0%	22.5%	22.1%	19.1%	20.1%	20.4%
Glomerulonephritis	9.3%	14.1%	9.3%	10.8%	14.5%	10.8%	12.2%	14.1%
Polycystic kidney disease	10.5%	8.4%	8.6%	7.5%	10.4%	9.2%	8.6%	8.9%
Other known diagnosis/unknown	78.5%	69.0%	62.1%	59.2%	53.1%	60.9%	59.1%	56.6%

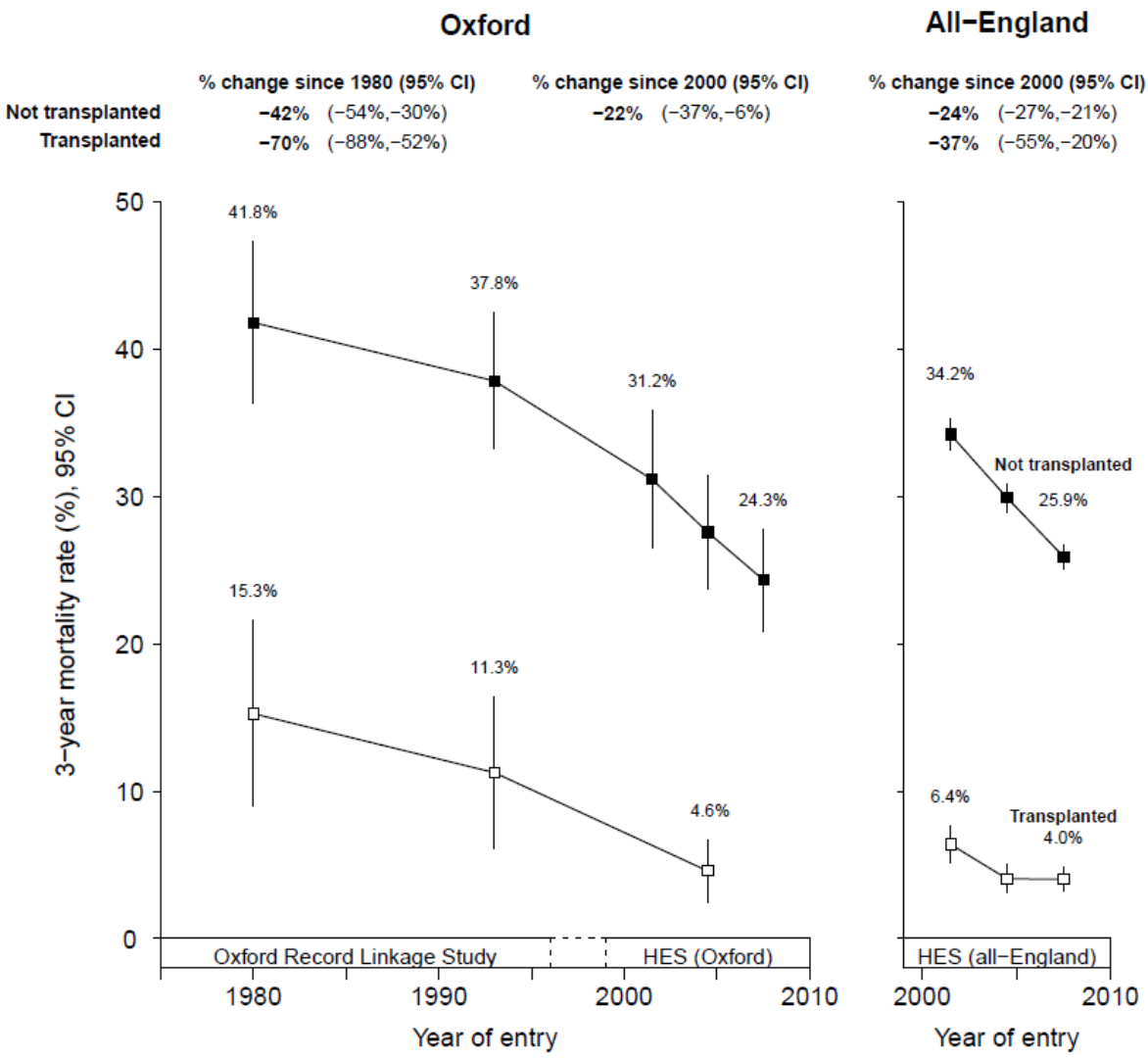
Excludes patients dying within 90 days. Data are n or % or median (IQR). †Ethnicity only recorded in Hospital Episode Statistics (92% complete) with percentages quoted only for thise with a known ethnicity. ‡Also includes hemi or paraplegia. *Not used for standardization.

Figure 5-1: Standardized three−year mortality rates in new treated end−stage renal disease patients and general population controls



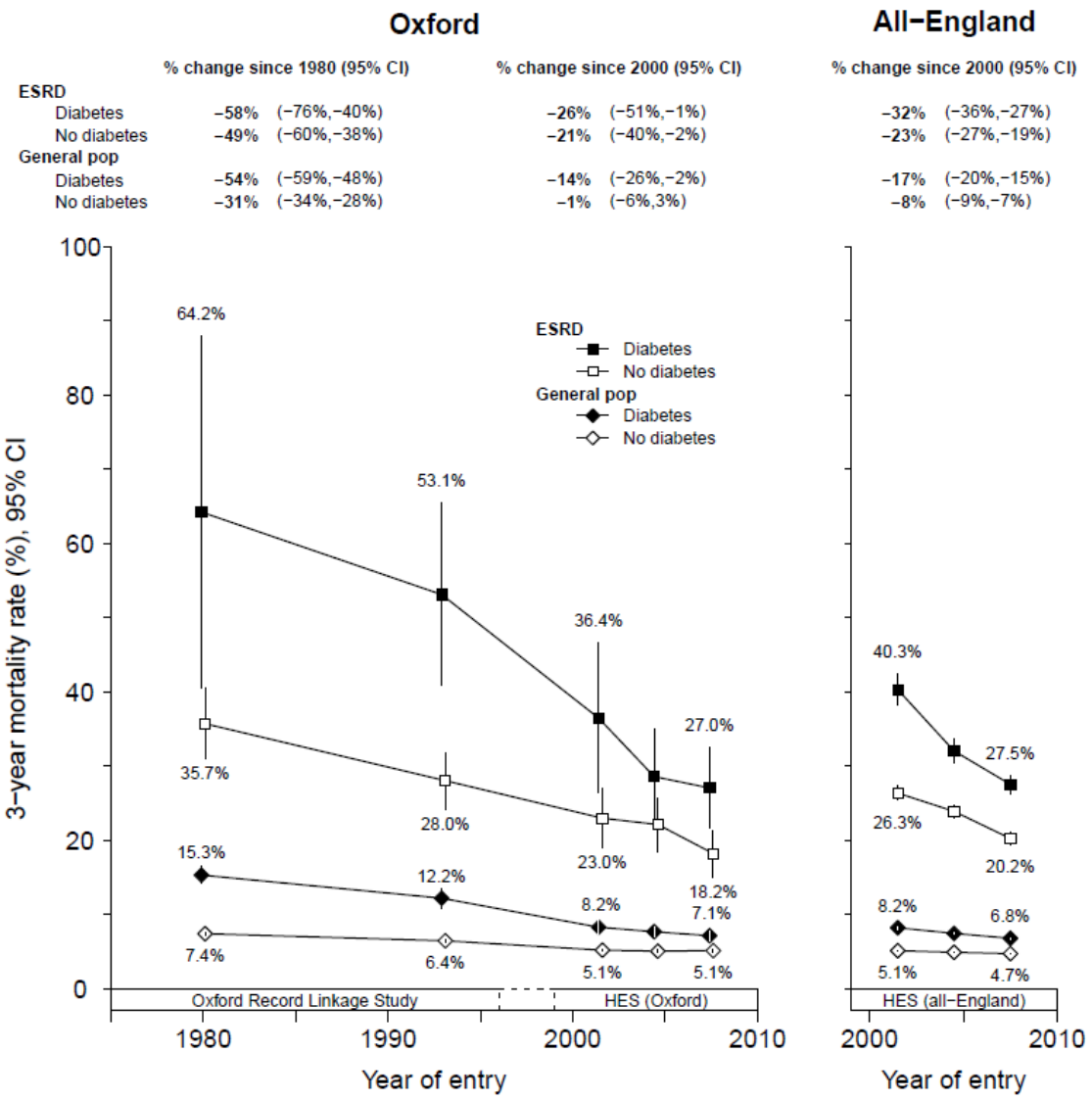
Standardized to the age, sex and comorbidity structure of an 'average' 1970−2008 renal replacement therapy population (see Supplemental Table 5 for characteristics). Excludes patients dying within 90 days. CI = Confidence interval. ESRD = End−stage renal disease. HES = Hospital Episode Statistics. Year of entry is year of starting renal replacement therapy or year of relevant general population controls admission. Rates plotted at midpoint of each year group.

Figure 5-2: Standardized three−year mortality rates in new treated end−stage renal disease patients, stratified by whether patient is transplanted within 3 years of starting renal replacement therapy



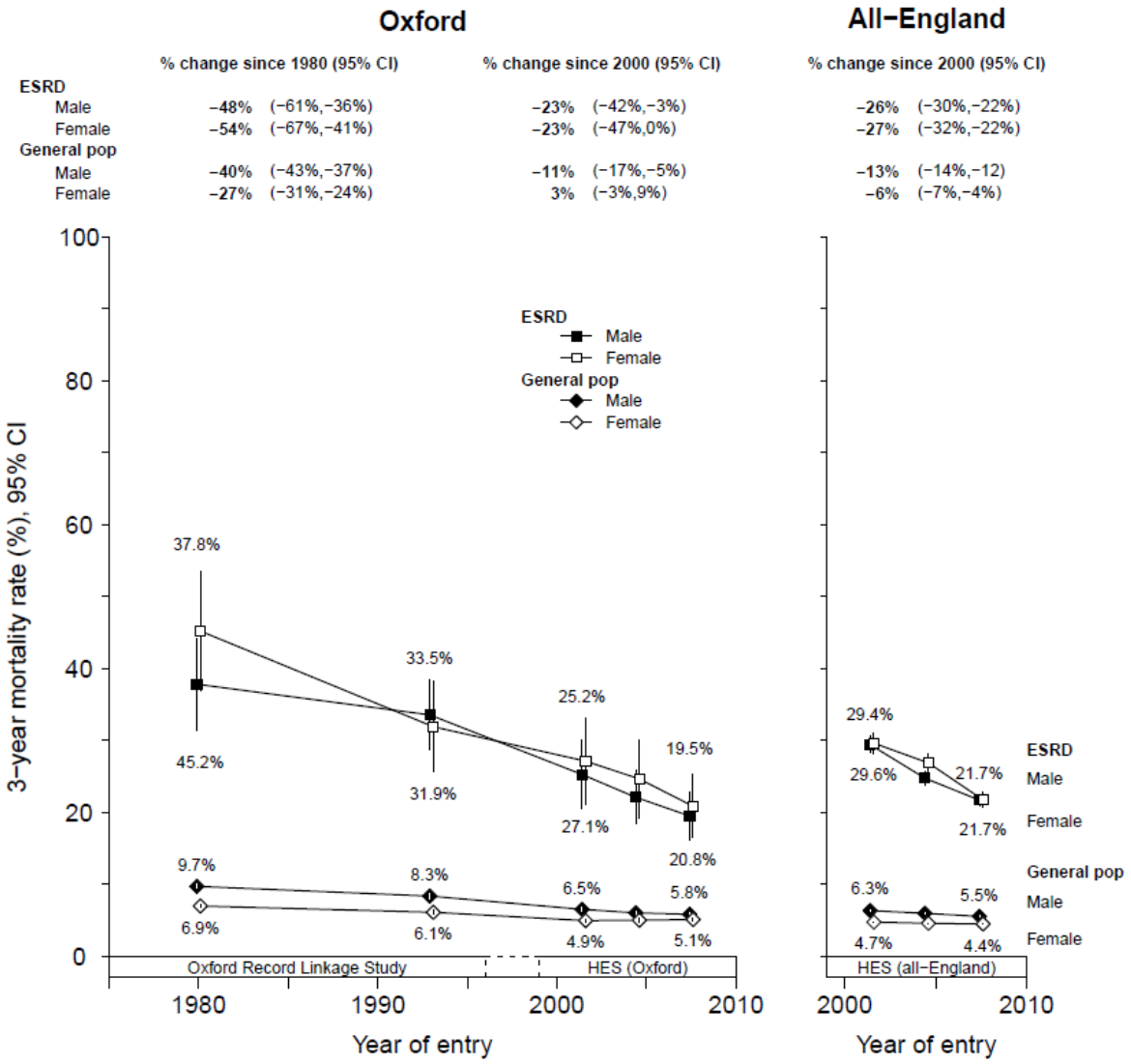
Standardized to the age, sex and comorbidity structure of an 'average' 1970−2008 renal replacement therapy population (see Supplemental Table 5 for characteristics). Excludes patients dying within 90 days. CI = Confidence interval. ESRD = End−stage renal disease. HES = Hospital Episode Statistics. Year of entry is year of starting renal replacement therapy or year of relevant general population controls admission. Rates plotted at midpoint of each year group.

Figure 5-3: Standardized three−year mortality rates in new treated end−stage renal disease patients and general population controls, stratified by prior diabetes



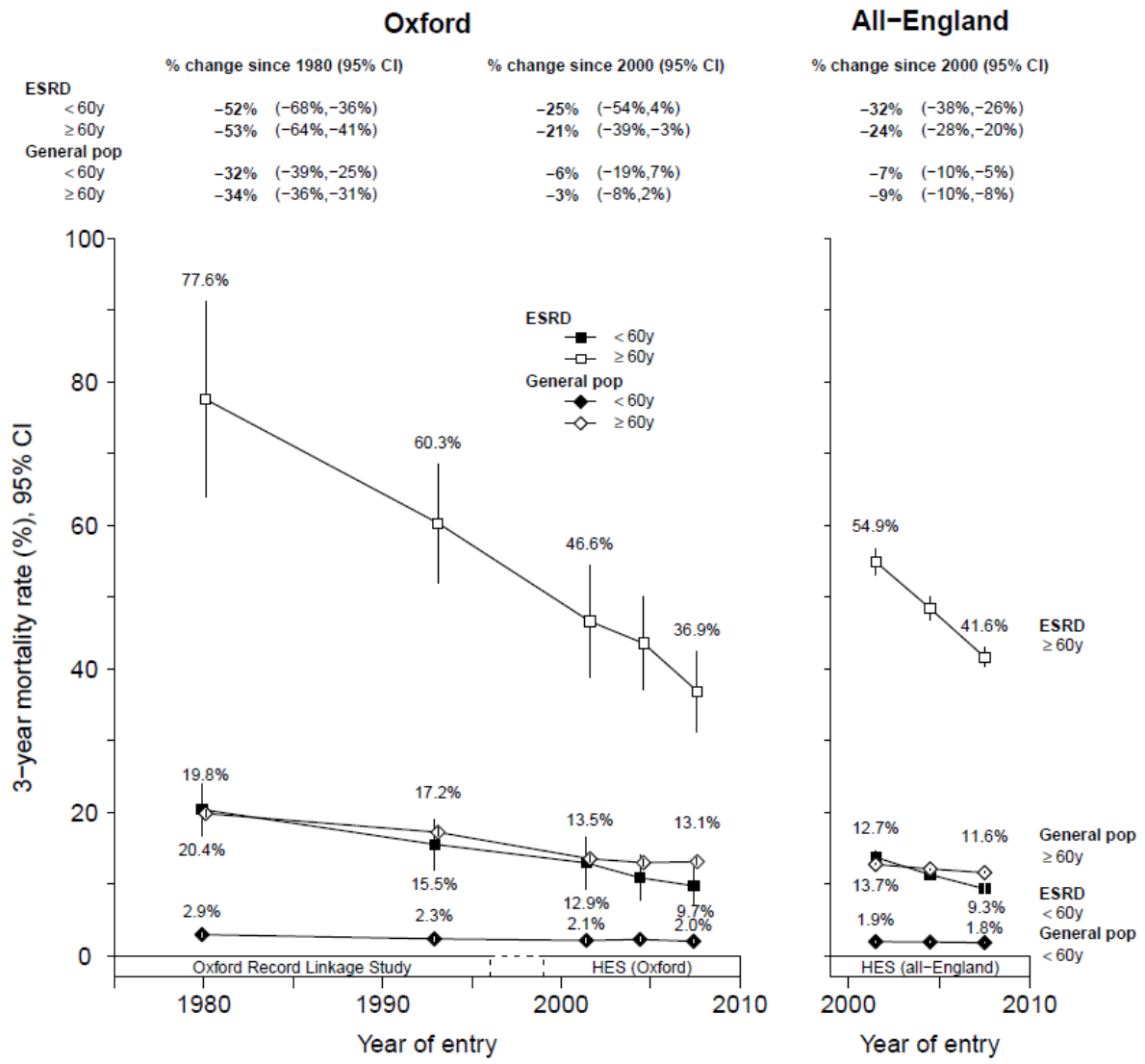
Standardized to the age, sex and comorbidity structure of an 'average' 1970−2008 RRT population (see Supplemental Table 5 for characteristics). Excludes patients dying within 90 days. CI = Confidence interval. ESRD = End−stage renal disease. HES = Hospital Episode Statistics. Year of entry is year of starting renal replacement therapy or year of relevant general population controls admission. Rates plotted at midpoint of each year group.

Figure 5-4: Standardized three−year mortality rates in new treated end−stage renal disease patients and general population controls, stratified by sex



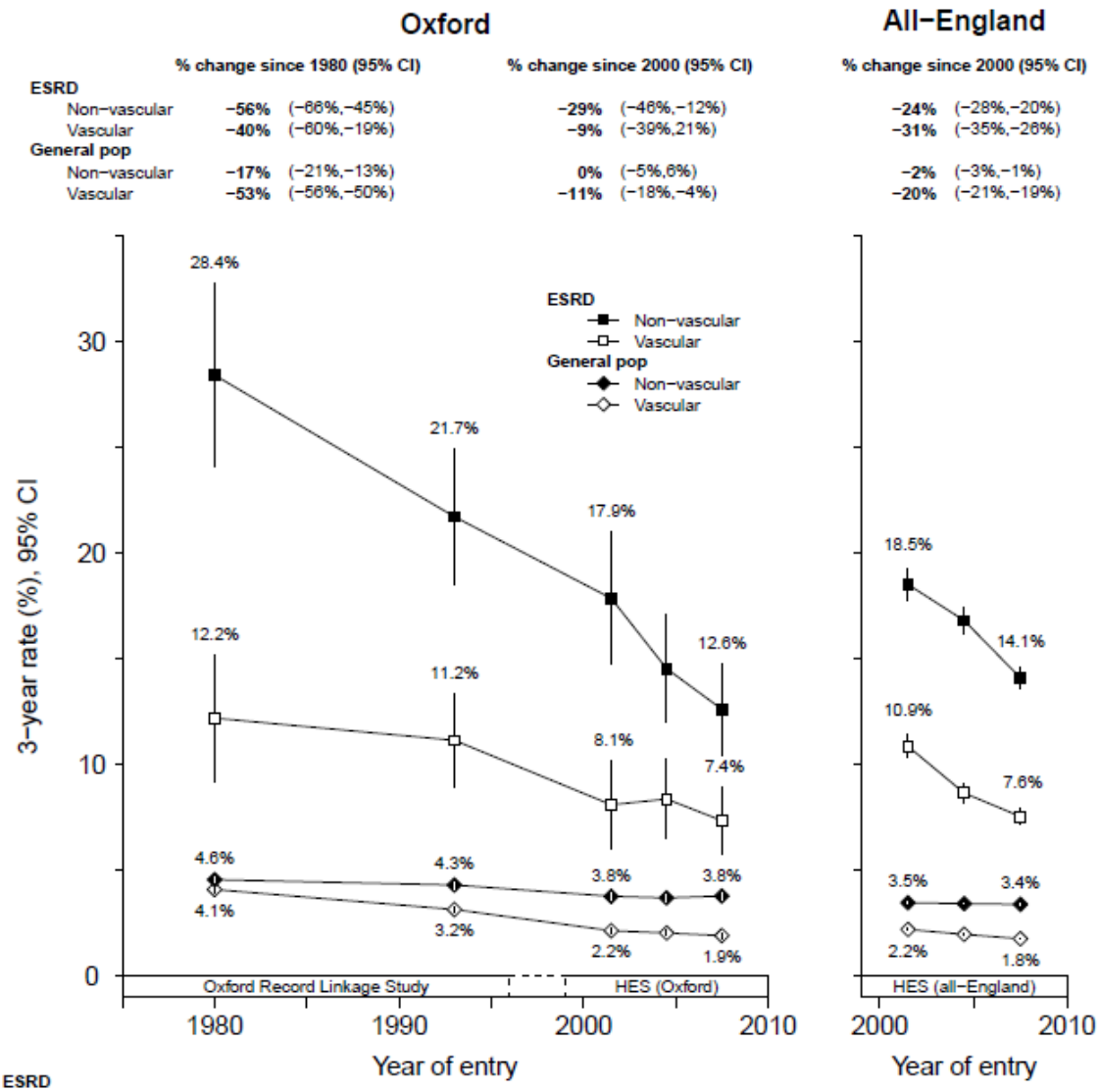
Standardized to the age and comorbidity structure of an 'average' 1970−2008 RRT population (see Supplemental Table 5 for characteristics). Excludes patients dying within 90 days. CI = Confidence interval. ESRD = End−stage renal disease. HES = Hospital Episode Statistics. Year of entry is year of starting renal replacement therapy or year of relevant general population controls admission. Rates plotted at midpoint of each year group.

Figure 5-5: Standardized three−year mortality rates in new treated end−stage renal disease patients and general population controls, stratified by age



Standardized to the age, sex and comorbidity structure of an 'average' 1970−2008 RRT population (see Supplemental Table 5 for characteristics). Excludes patients dying within 90 days. CI = Confidence interval. ESRD = End−stage renal disease. HES = Hospital Episode Statistics. Year of entry is year of starting renal replacement therapy or year of relevant general population controls admission. Rates plotted at midpoint of each year group.

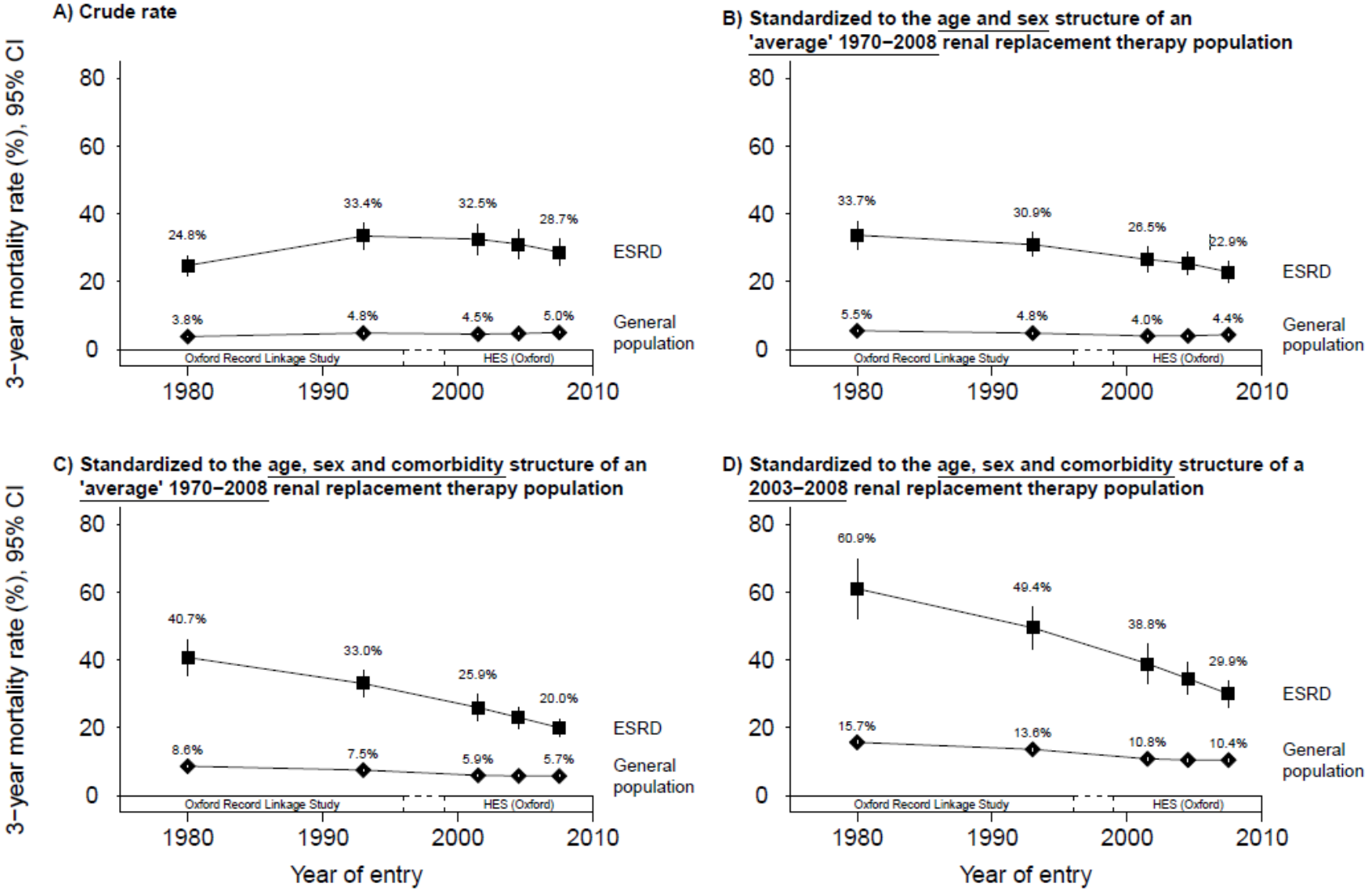
Figure 5-6: Standardized three−year vascular and non−vascular mortality rates in new treated end−stage renal disease patients and general population controls



ESRD						
Vascular death						
Cardiac	7.6%	7.7%	5.3%	5.3%	7.4%	5.4%
Non−cardiac	4.7%	3.5%	2.8%	2.1%	3.5%	2.2%
Non−vascular death						
Renal	16.8%	7.8%	5.9%	4.9%	7.2%	4.6%
Cancer	4.2%	4.5%	3.4%	2.1%	3.3%	3.4%
Infection	3.3%	3.5%	3.9%	2.4%	3.0%	2.3%
Other/unspecified	4.5%	5.7%	4.4%	3.3%	4.8%	3.7%
General population						
Vascular death						
Cardiac	2.9%	2.2%	1.5%	1.2%	1.5%	1.2%
Non−cardiac	1.3%	0.9%	0.7%	0.7%	0.7%	0.6%
Non−vascular death						
Renal	0.2%	0.1%	0.1%	0.1%	0.1%	0.1%
Cancer	2.1%	1.9%	1.6%	1.6%	1.5%	1.4%
Infection	0.7%	0.7%	0.4%	0.5%	0.4%	0.4%
Other/unspecified	1.6%	1.6%	1.7%	1.7%	1.5%	1.5%

Standardized to the age, sex and comorbidity structure of an 'average' 1970−2008 RRT population (see Supplemental Table 5 for characteristics). Excludes patients dying within 90 days. CI = Confidence interval. ESRD = End−stage renal disease. HES = Hospital Episode Statistics. Year of entry is year of starting renal replacement therapy or year of relevant general population controls admission. Rates plotted at midpoint of each year group.

Figure 5-7: Crude and standardized three−year mortality rates in new treated end−stage renal disease patients



See Supplemental Table 5 for characteristics of reference populations. Excludes patients dying within 90 days. ESRD = End−stage renal disease. HES = Hospital Episode Statistics (Oxford). ORLS = Oxford Record Linkage Study. Year of entry is year of starting renal replacement therapy or year of relevant general population controls admission. Rates plotted at midpoint of each year group.

Table 5-2: Baseline characteristics of end-stage renal disease populations used for standardization

	1970 - 2008 'average' RRT population	2003 - 2008 RRT population
N	3,242	29,552
Demographics		
Female	39.1%	38.2%
Median age (years)	55 (42-68)	62 (48-73)
18 - 40	22.0%	13.8%
40 - 50	16.9%	13.2%
50 - 60	19.9%	16.9%
60 - 70	20.4%	22.8%
70 - 80	17.0%	24.3%
≥80	3.9%	9.0%
Comorbidities		
Diabetes	17.8%	32.3%
Vascular	17.8%	27.5%
Non-vascular	15.7%	26.3%

Excludes patients dying within 90 days. Data are n or % or median (IQR). RRT = Renal replacement therapy.

Table 5-3: Crude and different levels of adjusted three−year mortality rates in new treated end−stage disease patients and renal general population controls, by year and reference population

A) Crude

	ORLS/HES Oxford	
	ESRD	General population
1970-1990	24.8% (22-28%)	3.8% (3.7-3.9%)
1991-1996	33.4% (30-37%)	4.8% (4.7-5.0%)
2000-2002	32.5% (28-37%)	4.5% (4.4-4.7%)
2003-2005	31.0% (27-35%)	4.7% (4.5-4.8%)
2006-2008	28.7% (25-32%)	5.0% (4.8-5.2%)
Proportional change from ~1980	16% rise	32% rise

B) Standardized to the age and sex structure of an 'average' 1970−2008 renal replacement therapy population

	ORLS/HES Oxford	
	ESRD	General population
1970-1990	33.7% (30-38%)	5.5% (5.4-5.6%)
1991-1996	30.9% (27-35%)	4.8% (4.7-4.9%)
2000-2002	26.5% (23-30%)	4.0% (3.9-4.1%)
2003-2005	25.4% (22-29%)	4.0% (3.9-4.1%)
2006-2008	22.9% (20-26%)	4.4% (4.2-4.5%)
Proportional change from ~1980	32% decline	9% decline

C) Standardized to the age, sex and comorbidity structure of an 'average' 1970−2008 renal replacement therapy population

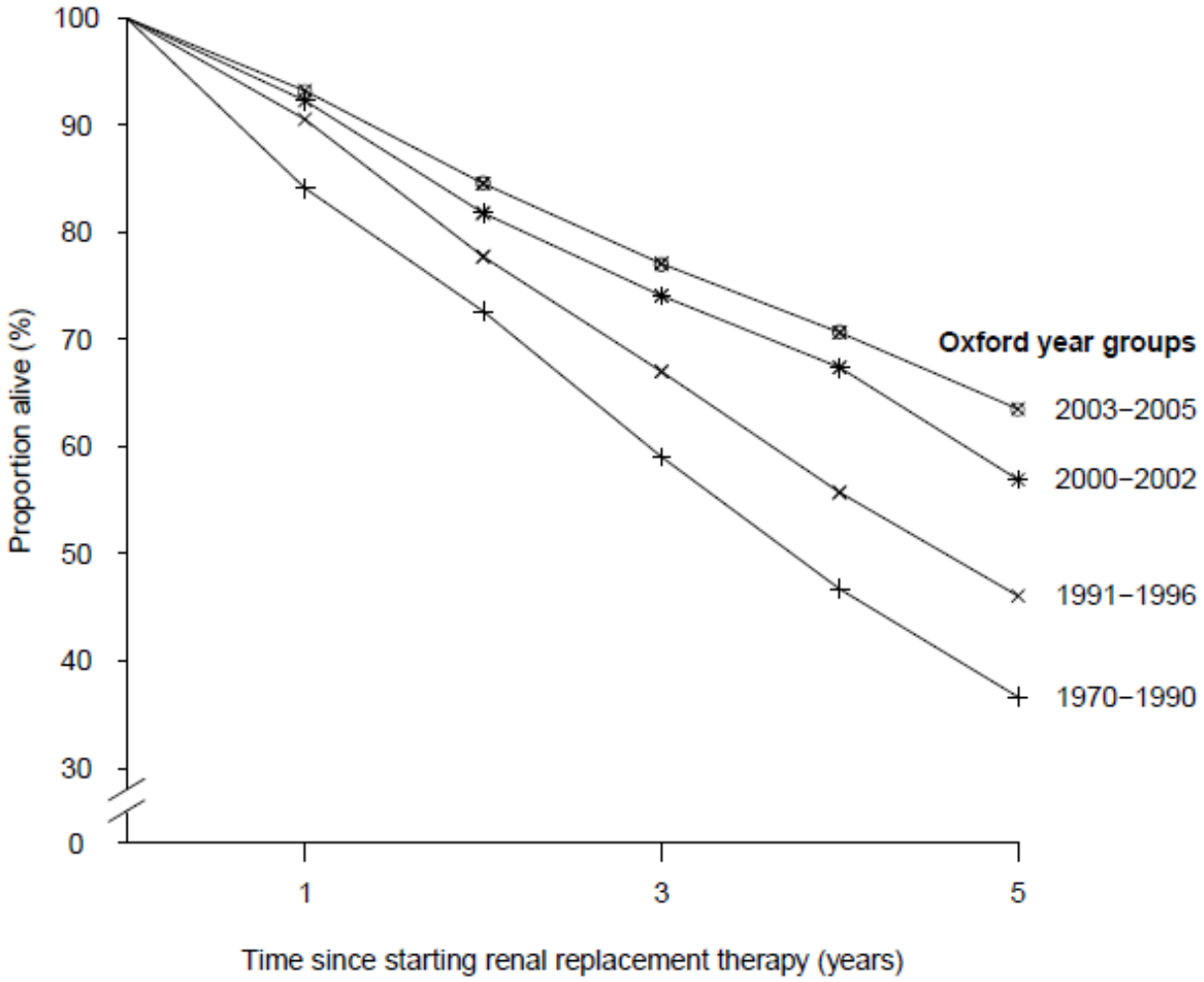
	ORLS/HES Oxford	
	ESRD	General population
1970-1990	40.7% (35-46%)	8.6% (8.4-8.8%)
1991-1996	33.0% (29-37%)	7.5% (7.2-7.7%)
2000-2002	25.9% (22-30%)	5.9% (5.7-6.1%)
2003-2005	23.0% (20-26%)	5.7% (5.5-5.9%)
2006-2008	20.0% (17-23%)	5.7% (5.5-5.9%)
Proportional change from ~1980	51% decline	34%decline

D) Standardized to the age, sex and comorbidity structure of a 2003−2008 renal replacement therapy population

	ORLS/HES Oxford	
	ESRD	General population
1970-1990	60.9% (52-70%)	15.7% (15-16%)
1991-1996	49.4% (43-56%)	13.6% (13-14%)
2000-2002	38.8% (33-45%)	10.8% (10-11%)
2003-2005	34.4% (30-39%)	10.4% (10-11%)
2006-2008	29.9% (26-34%)	10.4% (10-11%)
Proportional change from ~1980	51% decline	34% decline

See Supplemental Table 5 for characteristics of reference populations. Excludes patients dying within 90 days. ESRD = End−stage renal disease. HES = Hospital Episode Statistics

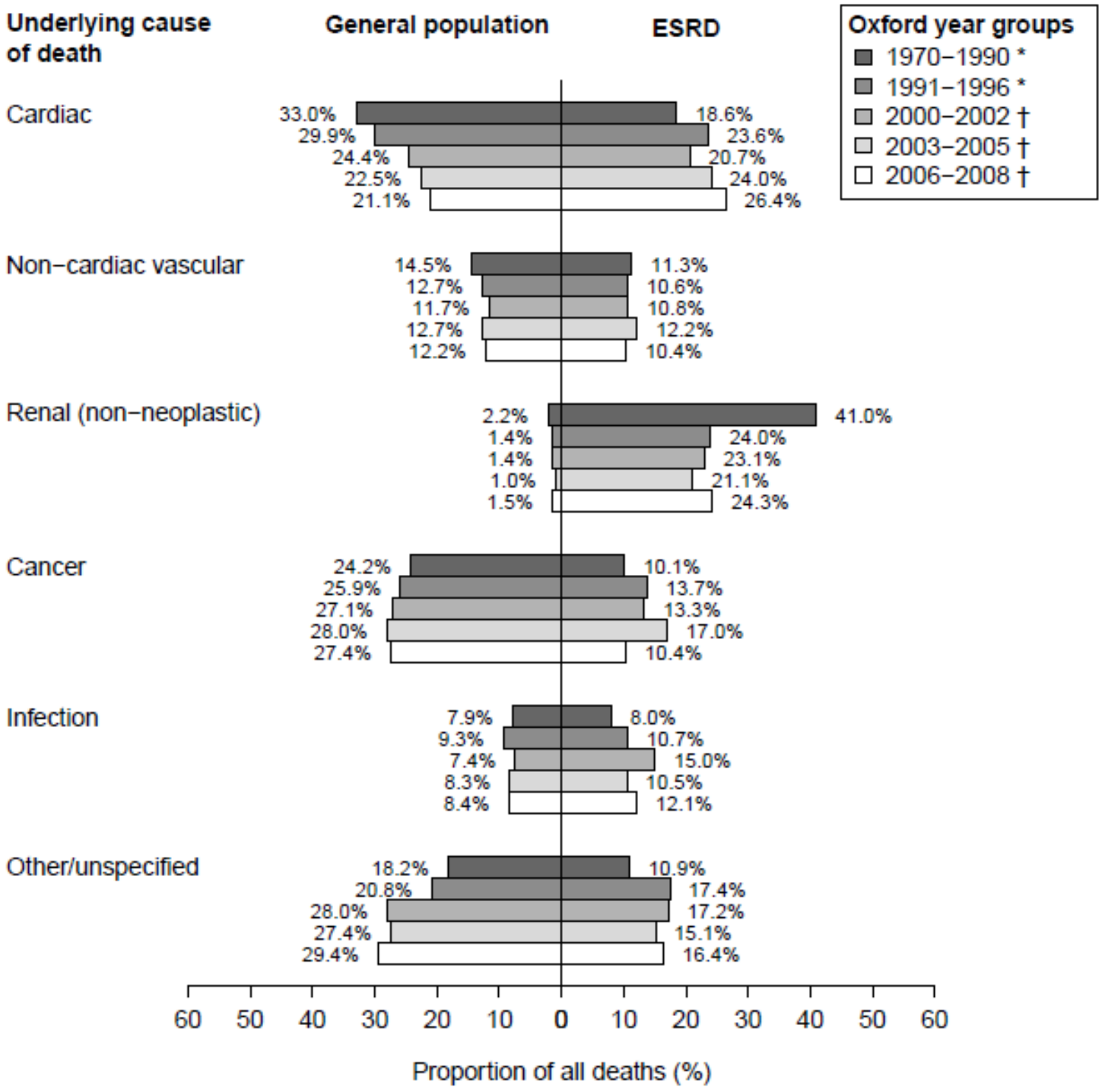
Figure 5-8: Standardized one− to five−year survival probabilities in new treated end−stage renal disease patients



Oxford year groups			
2003−2005 †	93.2% (91.6%−94.9%)	77.1% (73.9%−80.2%)	63.5% (59.4%−67.7%)
2000−2002 †	92.3% (90.4%−94.2%)	74.1% (70.3%−77.9%)	56.9% (51.9%−61.9%)
1991−1996 *	90.6% (88.6%−92.5%)	67.0% (63.1%−70.9%)	46.1% (40.9%−51.2%)
1970−1990 *	84.1% (80.9%−87.4%)	59.1% (53.6%−64.5%)	36.6% (29.8%−43.5%)

Survival probabilities are 100 minus the adjusted mortality rates, standardized by age, sex and comorbidities to an 'average' 1970−2006 renal replacement therapy population (see Supplemental Table 5 for characteristics). Excludes patients dying within 90 days. 95% confidence intervals included in parentheses. *Oxford Record Linkage Study. † Hospital Episode Statistics Oxford.

Figure 5-9: Three−year cause specific deaths as a proportion of all deaths



5.9 Supplementary material for results chapter, not in published manuscript

Table 5-4: Standardized three−year mortality rates in new treated end−stage renal disease patients and general population controls, stratified by cohort and prior diabetes status

ORLS/HES Oxford 1970-2011	ESRD population			General Population		
	Prior diabetes	No prior diabetes	Heterogeneity test	Prior diabetes	No prior diabetes	Heterogeneity test
1970-1990	64.2% (41-88%)	35.7% (31-40%)		15.3% (14-16%)	7.4% (7-8%)	
1991-1996	53.1% (41-65%)	28.0% (24-32%)		12.2% (11-13%)	6.4% (6-7%)	
2000-2002	36.4% (26-47%)	23.0% (19-27%)		8.2% (7-9%)	5.1% (5-5%)	
2003-2005	28.6% (22-35%)	22.1% (18-26%)		7.6% (7-8%)	5.0% (5-5%)	
2006-2008	27.0% (22-32%)	18.2% (15-21%)		7.1% (6-8%)	5.1% (5-5%)	
Percentage change from ~1980	-58% (-76%,-40%)	-49% (-60%,-38%)	p=0.41	-54% (-59%,-48%)	−31% (−34%,−28%)	p<0.0001
Percentage change from ~2000	-26% (-51,-1%)	-21% (-40%,-2%)	p=0.75	-14% (-26%,-2%)	-1% (−6%,3%)	p=0.06

All-England HES 2000-2011	ESRD population			General Population		
	Prior diabetes	No prior diabetes	Heterogeneity test	Prior diabetes	No prior diabetes	Heterogeneity test
2000-2002	40.3% (38-42%)	26.3% (25-27%)		8.2% (8-8%)	5.1% (5-5%)	
2003-2005	32.0% (30-34%)	23.9% (23-25%)		7.4% (7-8%)	4.9% (5-5%)	
2006-2008	27.5% (26-29%)	20.2% (19-21%)		6.8% (7-7%)	4.7% (5-5%)	
Percentage change from ~2000	-32% (-36%,-27%)	-23.9% (-27%,-19%)	p=0.01	-17% (-20%,-15%)	-8% (-9%,-7%)	p<0.0001

Table 5-5: Standardized three−year mortality rates in new treated end−stage renal disease patients and general population controls, stratified by cohort and sex

ORLS/HES Oxford 1970-2011	ESRD population			General Population		
	Male	Female	Heterogeneity test	Male	Female	Heterogeneity test
1970-1990	37.8% (31.4-44.2%)	45.2% (36.9-53.4%)		9.7% (9.4-9.9%)	6.9% (6.7-7.1%)	
1991-1996	33.5% (28.6-38.4%)	31.9% (25.6-38.2%)		8.3% (8-8.7%)	6.1% (5.8-6.3%)	
2000-2002	25.2% (20.4-30%)	27.1% (21-33.2%)		6.5% (6.2-6.8%)	4.9% (4.7-5.1%)	
2003-2005	22.1% (18.3-25.8%)	24.6% (19.2-30.1%)		6% (5.7-6.3%)	5% (4.7-5.2%)	
2006-2008	19.5% (16.2-22.8%)	20.8% (16.4-25.2%)		5.8% (5.5-6.1%)	5.1% (4.8-5.3%)	
Percentage change from ~1980	−48% (−61%,−36%)	−54% (−67%,−41%)	p=0.56	−40% (−43%,−37%)	−27% (−31%,−24%)	p<0.0001
Percentage change from ~2000	−23% (−42%,−3%)	−23% (−47%,0%)	p=0.98	−11% (−17%,−5%)	3% (−3%,9%)	p=0.0018

All-England HES 2000-2011	ESRD population			General Population		
	Male	Female	Heterogeneity test	Male	Female	Heterogeneity test
2000-2002	29.6% (28.2-31%)	29.4% (28.3-30.5%)		6.3% (6.2-6.4%)	4.7% (4.7-4.7%)	
2003-2005	26.8% (25.5-28.2%)	24.7% (23.8-25.7%)		5.9% (5.9-6%)	4.5% (4.5-4.6%)	
2006-2008	21.7% (20.7-22.8%)	21.7% (20.9-22.5%)		5.5% (5.4-5.5%)	4.4% (4.4-4.5%)	
Percentage change from ~2000	−26% (−30%,−22%)	−27% (−32%,−22%)	p=0.91	−13% (−14%,−12)	−6% (−7%,−4%)	p<0.0001

Table 5-6: Standardized three−year mortality rates in new treated end−stage renal disease patients and general population controls, stratified by cohort and age group

ORLS/HES Oxford	ESRD population			General Population		
1970-2011	18-60 years	≥60years	Heterogeneity test	18-60 years	≥60years	Heterogeneity test
1970-1990	20.4% (16.7-24%)	77.6% (63.9-91.3%)		2.9% (2.7-3.2%)	19.8% (19.3-20.3%)	
1991-1996	15.5% (11.9-19.1%)	60.3% (52-68.6%)		2.3% (2-2.6%)	17.2% (16.6-17.7%)	
2000-2002	12.9% (9.3-16.5%)	46.6% (38.9-54.3%)		2.1% (1.8-2.4%)	13.5% (13-14%)	
2003-2005	10.8% (7.6-14%)	43.6% (37-50.1%)		2.2% (2-2.5%)	13% (12.5-13.4%)	
2006-2008	9.7% (7.1-12.3%)	36.9% (31.2-42.5%)		2% (1.8-2.2%)	13.1% (12.6-13.6%)	
Percentage change from ~1980	-52% (-68%,36%)	-53% (-64%,-41%)	p=0.98	-32% (-39%,-25%)	-34% (-36%,-31%)	p=0.63
Percentage change from ~2000	-25% (-54%,4%)	-21% (-39%,-3%)	p=0.82	-6% (-19%,7%)	-3% (-8%,2%)	p=0.70

All-England HES	ESRD population			General Population		
2000-2011	18-60 years	≥60years	Heterogeneity test	18-60 years	≥60years	Heterogeneity test
2000-2002	13.7% (12.8-14.6%)	54.9% (53.1-56.8%)		1.9% (1.9-2%)	12.7% (12.6-12.8%)	
2003-2005	11.3% (10.5-12%)	48.4% (46.8-50.1%)		1.9% (1.8-1.9%)	12.1% (12-12.2%)	
2006-2008	9.3% (8.7-9.9%)	41.6% (40.2-43%)		1.8% (1.7-1.8%)	11.6% (11.5-11.6%)	
Percentage change from ~2000	-32% (-38%,-26%)	-24% (-28%,-20%)	p=0.03	-7% (-10%,-5%)	-9% (-10%,-8%)	p=0.27

5.10 Bullet points of Chapter 5

- RRT patients from Oxfordshire, derived from ORLS and HES (Oxford) have seen a halving of their three-year mortality since 1970, compared a third reduction in a comparative general population

- Stratified analyses showed that patients with diabetes (in both ESRD and the general population) had larger absolute reductions and the difference in mortality between those with and without diabetes has become smaller

- There were steeper reductions in mortality in males compared to females in the general population, which were not apparent in the ESRD population

- In treated ESRD patients, there were steeper proportional declines in non-vascular mortality compared to those in the general population (56% vs. 17%), and shallower overall proportional declines in vascular mortality (17% vs. 40%)

- The proportion of all deaths ascribed to vascular disease in ESRD rose from 29.9% in 1970-1990 to 36.8% in 2006-2008, qualitatively different from the comparable general population where the proportions of vascular deaths fell from 47.5% to 33.3%

Chapter 6 Other uses of the dataset

Disease Association Study — Biliary tract and liver complications in polycystic kidney disease: a 23,000 patient disease-association study

This chapter largely contains the material that has been published in the peer-reviewed journal. Impact factor 8.655 (2017) or See **Appendix section 1.3** or the links below

Main Article:
Biliary Tract and Liver Complications in Polycystic Kidney Disease. Judge PK, Harper CHS, **Storey BC**, et al. *JASN* 2017, 28(9) 2738-2748

Online supplementary materials:
Supplemental material

6.1 Abstract

Background

Polycystic liver disease is a well-described manifestation of autosomal dominant polycystic kidney disease (PKD). Biliary tract complications are less well-recognised. The local kidney unit reported a 50-year experience of 1,007 patients, which raised a hypothesis that PKD is associated with biliary tract disease.

Methods

All-England Hospital Episode Statistics data (1998-2012) within which 23,454 people recorded as having PKD and 6,412,754 hospital controls were identified. Hospitalisation rates for biliary tract disease, serious liver complications and a range of other known PKD manifestations were adjusted for potential confounders and then compared. Compared to non-PKD hospital controls, the rates of admission for biliary tract disease were calculated.

Results

All-England Hospital Episode Statistics data (1998-2012) within which 23,454 people recorded as having PKD and 6,412,754 hospital controls were identified. Hospitalisation rates for biliary tract disease, serious liver complications and a range of other known PKD manifestations were adjusted for potential confounders and then compared. Compared to non-PKD hospital controls, the rates of admission for biliary tract disease were 2.2-times higher in those with PKD (rate ratio [RR] 2.24, 95% confidence interval 2.16-2.33) and 4.7-times higher for serious liver complications (RR 4.67, 4.35-5.02). When analyses were restricted to those on maintenance dialysis or with a kidney transplant, RRs attenuated substantially, but PKD remained positively associated with both biliary tract disease (RR 1.19, 1.08-1.31) and with serious liver complications (RR 1.15, 0.98-1.33). The PKD versus non-PKD hospital control RRs for biliary tract disease were larger for men than women (heterogeneity $p<0.001$), but RRs for serious liver complications appeared higher in women (heterogeneity $p<0.001$). The absolute excess risk of biliary tract disease associated with PKD (0.73%/year) was larger than for serious liver disease (0.24%/year), cerebral

aneurysms (0.11%/year), or inguinal hernias (0.11%/year), but less than for urinary tract infections (2.20%/year).

Discussion

Biliary tract disease appears to be a distinct and important extra-renal complication of PKD.

6.2 Introduction

Autosomal dominant polycystic kidney disease (PKD) is the most common inherited kidney disease.[196,197] It is characterised by progressive enlargement of the kidneys with multiple bilateral cysts and eventual loss of kidney function, often causing end-stage renal disease (ESRD) in middle age.[196,198] Ten percent of the 60,000 patients receiving renal replacement therapy (RRT) in the UK and 5% of the 680,000 in the US have a primary renal diagnosis of PKD.[199,200] PKD is a multi-system disorder with polycystic liver, a common extra-renal manifestation.[201-203] The prevalence of liver cysts in people with PKD increases with age, with >90% of patients aged >40 years having at least one cyst.[204] Unlike renal cysts (which are unaffected by sex), liver cysts are more common and numerous in pre-menopausal women with PKD than in men.[202,204,205] Autosomal dominant PKD is also associated with other abdominal manifestations, including colonic diverticular disease, abdominal wall hernias and pancreatic cysts.[203,205,206] Mild common bile duct dilatation has also been reported,[207] but unlike the much rarer autosomal recessive form of PKD which is associated with non-obstructive intra-hepatic duct dilation (Caroli's disease) and recurrent cholangitis,[208] clinically significant biliary tract complications are less well recognized in autosomal dominant PKD.

An observation was made at the local tertiary renal centre by a senior renal clinician that, in addition to the infective and compressive complications caused by polycystic livers, several patients with autosomal dominant PKD had repeated hospitalisations for biliary tract disease.[209] In order to explore whether their clinical observations reflected a previously undescribed feature of autosomal dominant PKD, the hypothesis that biliary tract disease is more common in PKD using routinely collected English hospital inpatient data 1998-2012 was tested by comparing hospitalisation rates for biliary tract disease among people with PKD versus rates in non-PKD control populations.

6.3 Methods

6.3.1 Disease-association study using routine hospital admission data (1998-2012)

Ethical approval for analysis of the record linkage study data was obtained from the Central and South Bristol Multi-Centre Research Ethics Committee (04/Q2006/176, Figure 8-2) was already in place. Anonymised linked all-England Hospital Episode Statistics (HES) inpatient records with additional linkage to national mortality records were used.[210] Since 1998, HES has recorded information on all hospital inpatient activity in England, including: dates of admission and discharge; demographics (including age, sex, ethnicity); measures of social deprivation; the primary diagnostic reason for admission with relevant secondary diagnoses, coded using the International Statistical Classification of Diseases and Related Health Problems Revision 10 (ICD-10);[211] and all procedures, coded using the Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS) version 4.

6.3.2 Identification of polycystic kidney disease cases

A patient with any mention of ICD-10 codes Q61.2 or Q61.3 in HES was presumed to have a diagnosis of PKD. The validity of using these codes has been directly demonstrated previously as part of a clinical trial among kidney transplant patients, in which there was an excellent level of agreement (kappa statistic >0.9) between nurse-reported primary renal diagnosis of cystic kidney disease and PKD coded in HES[162,212], (see also Chapter 2 Cohort derivation and Chapter 4 Validation, section 4.4.5).To reduce the chances of including autosomal recessive PKD in analyses, people hospitalised or starting RRT before 20 years of age were excluded.

6.3.3 Identification of control populations

Two control populations with no mention of PKD codes in any admission were derived from HES records. The first was a large group of patients admitted for minor diagnoses or procedures (see Table 6-1 footnote for complete list with a very similar derivation process what is detailed in subsection 2.10). The second was any patient who was treated with maintenance RRT (ie, long-term dialysis or kidney transplant) for ESRD and survived for at least 90 days from the start of RRT.

6.3.4 Outcomes

Outcomes for relevant diseases were identified using both information encoded in any diagnostic position (primary or secondary) or any recorded procedure. These included: (i) treated ESRD; (ii) a group of other positive control diseases which have previously been reported to be extra-renal manifestations of PKD[203,213] (including complications or treatment of cerebral aneurysms, abdominal wall hernias [separated into inguinal and other], urinary tract infections, serious cardiac valve disease, and diverticular disease); (iii) a group of liver diagnoses and procedures associated with PKD, including liver abscess and liver de-roofing, resection and transplantation; (iv) and biliary tract diagnoses and procedures, including cholecystitis, biliary tract stones, and cholecystectomy (see Table 6-2 for full list of ICD and OPCS codes used to define outcomes); and (v) a negative control disease (breast cancer) which has previously been reported as not associated with PKD.[214] In addition, sensitivity analyses were performed excluding diagnostic information recorded as secondary diagnoses, and after excluding people who ever had a serious liver complication.

6.3.5 Covariates

The following patient characteristics were extracted from HES: age; sex; ethnicity (white, non-white, and not recorded); region of residence; English Index of Multiple Deprivation

Score (IMD);[215] and comorbidity (diabetes, vascular or cancer considered separately). For hospital control analyses, comorbidity was derived from diagnoses and procedures recorded on the first admission. For the ESRD cohort, comorbidity was derived from the date of the start of RRT and any admission in the preceding two years.

6.3.6 Statistical methods

Baseline characteristics for each derived cohort were expressed as numbers (%) or median (interquartile range) and compared by standard chi-square or Kruskal-Wallis tests respectively. The follow-up time for each outcome began from the index date (defined as the date of the first admission) and ended at the earliest of date of a relevant outcome, death or end of the cohort follow-up (31/03/2012). Rates for each outcome were then calculated using Poisson regression adjusted for age as a continuous variable (using both linear and quadratic terms), sex, ethnicity (3 groups as above), quintiles of IMD score, region of residence (9 groups), prior reported diabetes, vascular disease (excluding subarachnoid haemorrhage) or cancer (excluding breast cancer). Changes in coding practice over time were controlled for by adjustment for calendar year of first admission (or, where relevant, year of start of maintenance RRT).

To assess how much renal function may affect PKD versus non-PKD RRs, analyses were repeated restricted to those PKD and non-PKD controls who had already started maintenance RRT for ESRD, with the index date increased to the date of start of maintenance RRT.

RRs and their 95% CIs were calculated using standard statistical methods. Separate PKD versus non-PKD RRs for men and women and by age groups were calculated and

compared using standard tests for heterogeneity and trend respectively. Analyses used SAS version 9.3 (SAS Institute, Cary, NY) and the R version 3.2.1 (www.r-project.org).

6.4 Results

To test the hypothesis that biliary tract disease might be more common in PKD than would be expected compared to the general population or people with other causes of ESRD, data on 43.2 million people aged over 20 years with at least one hospital admission recorded in linked and anonymised all-England HES between 1998 and 2012 were utilized in a disease association study.

From this resource, 23,454 people were admitted to hospital with a diagnostic code for PKD and who were deemed unlikely to have autosomal recessive form. The median age at the start of follow-up was 58 years (44-70), 10,789 (46%) were female and 20,011 (85%) were white (Table 6-1). A history of prior diabetes or vascular disease was recorded in 906 (4%) and 1,747 (7%) respectively.

In comparison, 6,412,754 hospital controls were identified from an admission for one of a variety of minor conditions (with no mention of PKD in any admission). Hospital controls were on average younger (median age 48 [34-67] years) and less likely to have diabetes (189,858, 3.0%) or vascular disease (181,832, 2.8%; Table 6-1).

6.4.1 Disease-association study of all patients (PKD vs. non PKD)

After adjustment for age, sex, ethnicity, social deprivation, region, prior diabetes, prior vascular disease or cancer, and year of first admission, the rates of admission for a series of disease outcomes were compared among people with PKD versus without PKD (referred to as ‘PKD versus non-PKD rate ratios’, RRs).

Compared to non-PKD hospital controls, adjusted rates of ESRD were 112-times higher in people with PKD (2.82% versus 0.03%/year; rate ratio [RR] 112, 95% CI 109-116; Figure 6-1A).

All patients: Rate ratios for known/typical manifestations of PKD

Figure 6-1 provides adjusted rates and PKD versus non-PKD RRs for a range of other known manifestations of PKD. These include cerebral aneurysms, inguinal and other abdominal wall hernias, urinary tract infections, cardiac valve disease, and diverticular disease (Table 6-2 provides outcome definitions), all of which were positively associated with PKD.

All patients: Rate ratios for 'biliary tract disease' and 'serious liver complication'

Compared to non-PKD hospital controls, the rates of admission for biliary tract disease were 2.2-times higher in people with PKD (1.31% versus 0.59%/year; RR 2.24, 95% CI 2.16-2.33) and 4.7-times higher for serious liver complications (0.31% versus 0.07%/year; RR 4.67, 4.35-5.02; Figure 6-1A). These equate to an absolute excess risk of biliary tract disease associated with PKD of 0.73%/year (95% CI 0.68-0.78%/year), which was larger than the absolute excess risk for serious liver disease (0.24%/year, 0.21-0.28%/year), cerebral aneurysms (0.11%/year, 0.09-0.14%/year), inguinal hernias (0.11%/year, 0.08-0.14%/year), or abdominal wall hernias (0.35%, 0.32-0.38%/year); similar to the excess risk for colonic diverticular disease (0.73%/year, 0.67-0.79%/year); but much less than for urinary tract infections (2.20%/year, 2.10-2.31%/year), Figure 6-1A.

6.4.2 Sub-study of rate ratios in those with ESRD (PKD vs other PRD)

HES does not record laboratory data, so comparisons between people with PKD and general population hospital controls are unable to adjust for any differences in estimated glomerular filtration rate between those with PKD and those without. Repeated analyses, including just the 68,332 people who had started maintenance RRT to adjust for any effect of advanced chronic kidney disease were therefore undertaken.

Within the treated ESRD population, 9% (5,813/68,332) were recorded as having PKD. People with ESRD due to PKD were on average younger (57 versus 62 years), more likely to be female (46% versus 38%), and less likely to have a history of prior diabetes (8% versus 32%) or vascular disease (13% versus 27%) than those with ESRD due to other causes (Table 6-1).

ESRD only: Rate ratios for known/typical manifestations of PKD

After restricting analyses to those with treated ESRD, PKD versus non-PKD RRs for the positive control diseases were attenuated (Figure 6-1B). Nevertheless, compared to those with other causes of ESRD, rates of hospitalisation among people with PKD were 2.2-times higher for cerebral aneurysms (0.13% versus 0.06%/year, RR 2.23, 1.53-3.26), 2.5 times higher for other abdominal wall hernias (1.23% versus 0.50%/year, RR 2.47, 2.19-2.80), and about 60 to 70% higher for both inguinal hernias (1.00% versus 0.59%/year, RR 1.70, 1.49-1.95), and colonic diverticular disease (2.70% versus 1.64%/year, RR 1.65, 1.52-1.79; Figure 6-1B). Rates for serious cardiac valve disease, however, were similar among people with ESRD and PKD and people with other causes of ESRD (1.47% versus 1.63%/year, RR 0.90, 0.81-1.00).

ESRD only: Rate ratios for 'biliary tract disease' and 'serious liver complication'

The RRs for biliary tract disease and serious liver complications were also substantially attenuated when analyses were restricted to those with treated ESRD, but PKD remained positively associated with both conditions. Compared to those with other causes of ESRD, rates of biliary tract disease were 19% higher among people with PKD (1.92% versus

1.61%/year, RR 1.19, 1.08-1.31) and 15% higher for serious liver complications (0.70% versus 0.62%/year; RR 1.15, 0.98-1.33; Figure 6-1B).

Among people on maintenance RRT, the absolute excess risk of biliary tract complications (0.31%/year, 0.13-0.49%/year) in people with PKD remained larger than for serious liver complications (0.09%/year, -0.02-0.2%/year) and for cerebral aneurysms (0.07%/year, 0.03-0.12%/year); became similar to the absolute excess risk for inguinal hernias (0.41%/year, 0.29-0.54%/year); but was somewhat smaller than for other abdominal wall hernias (0.73%/year, 0.59-0.87%/year), colonic diverticular disease (1.06%/year, 0.85-1.27%/year) and urinary tract infections (1.36%/year, 1.01-1.72%/year), Figure 6-1B.

6.4.3 Stratified analyses by age and sex

All patients: Rate ratios for 'biliary tract disease' and 'serious liver complication' (PKD vs. non PKD)

In analyses performed separately for different age groups and by sex, compared with hospital controls, PKD versus non-PKD RRs for serious liver complications were higher in women than in men (heterogeneity $p<0.001$), confirming the observation from the accompanying case series reported in the manuscript, found at Appendix 1.3. However, the reverse was observed for biliary tract disease (heterogeneity $p<0.001$; Figure 6-2). RRs for serious liver disease were larger among younger people with PKD (trend $p<0.001$), but the reverse was also true for biliary tract disease (trend $p<0.001$; Figure 6-2A).

<u>ESRD only:</u> Rate ratios for 'biliary tract disease' and 'serious liver complication'

In analyses restricted to people with treated ESRD, PKD versus non-PKD RRs for biliary tract disease became similar in both sexes (heterogeneity p=0.22), but RRs for serious liver complications remained higher in women than in men (heterogeneity p<0.001; Figure 6-2B). There was no difference in RRs for either complication by age in people with treated ESRD (Figure 6-2).

6.4.4 Sensitivity analyses

In sensitivity analyses, results were similar when repeated with the exclusion of secondary diagnoses to define disease outcomes (Figure 6-3 & Figure 6-4), or with exclusion of people with a serious liver complication (which reduces any over-ascertainment of biliary tract disease identified incidentally during any liver investigations, data not shown).

6.4.5 Cause-specific mortality among people with PKD

Biliary tract or liver disease are an uncommon underlying cause of death among people with PKD, except among those that were hospitalised in the cohort for either biliary tract disease or serious liver complications, in whom it accounted for 8% of deaths (Figure 6-5). This proportion was similar in women and men (9% versus 6%; p=0.06, Figure 6-6).

6.5 Discussion

The disease association study confirmed that hospitalisation for biliary tract disease is more common among people with PKD than people without, and that the absolute excess risk was larger than for serious liver complications and a range of other better described extrarenal manifestations of PKD.

The Halt Progression of Polycystic Kidney Disease Study A (HALT-PKD-A) has characterised the biliary tract and liver imaging features of PKD.[216] Common bile duct dilatation was present in 17% of the cohort, but was the only biliary tract abnormality described. These data corroborate earlier observations from a Japanese study of 55 people with autosomal dominant PKD, where the prevalence of common bile duct dilatation was 40%, compared to 7% in controls.[207] A higher prevalence of common bile duct dilatation in the Japanese study may be accounted for by more advanced PKD, as one-half of the Japanese PKD patients had started haemodialysis, whilst all HALT-PKD-A participants had an estimated glomerular filtration rate >60 mL/min/1.73m^2. No study which had assessed if there was an excess risk of clinically significant biliary tract disease associated with PKD. The presented results therefore represent the first quantification of the association between PKD and serious biliary tract disease.

Another important finding in this disease association study was that the relative size of the PKD versus non-PKD RRs for serious liver complications was higher among women than men, but the reverse was true for biliary tract disease associations. Other PKD studies, including the HALT-PKD-A study, have also found the prevalence of liver cysts is higher in women with PKD compared to men.[204,216] Oestrogen receptors are expressed in the epithelium of liver cysts,[196,203,217,218] and female sex, exogenous oestrogen use and pregnancy all appear to increase cyst cell proliferation and liver cyst size.[196,203,217,218]

However, liver enlargement in PKD results from both cystic change and increased liver parenchymal volume, and men with PKD have been found to have increased height-adjusted liver parenchymal volume.[216] The differing patterns of associations in our subgroup analyses by age and sex suggest that cystic change in the liver - which has been reported to cause obstructive jaundice[219-224] - is not the key cause of biliary tract complications in PKD. Instead other mechanisms for disrupted biliary tract epithelial function may exist. Some have suggested the bile duct glands can develop cysts,[225] and others have raised the possibility of a shared biliary phenotype between mutations which cause autosomal recessive and autosomal dominant PKD.[226-228]

Biliary tract disease has featured in the results of recent randomized trials of treatments aimed at inhibiting renal cyst cell proliferation and fluid secretion. In a trial of a somatostatin analogue, octreotide, the rate of kidney volume increase was slowed compared to placebo,[229] and post-hoc analyses suggested octreotide may also reduce liver parenchyme and cyst expansion.[230] However, it also led to increased numbers of non-serious reports of gallstones (octreotide 10/40 [25%] versus placebo 0/39 [0%]) and 'biliary sand' (7/40 [18%] versus 1/39 [3%]). The 2 reported serious cases of acute cholecystitis in this study were both among those allocated octreotide.[229] These results are consistent with previous reports of octreotide associated-gallstones, which is attributed to reduced post-prandial gallbladder contractility and biliary stasis (indicated by increased fasting gallbladder volumes).[231] Octreotide exerts its beneficial effects on cysts through inhibition of the secondary messenger cyclic adenosine monophosphate in biliary epithelial cells. However, inhibiting this pathway with the vasopressin V2-receptor blocker, tolvaptan, significantly reduces the rate of increase in total kidney volume compared to placebo without any reported excess of upper abdominal pain, gallstones or biliary tract adverse events.[232]

Although not our primary aim, these data represent the largest confirmatory study of the size of associations between PKD and a range of previously described extra-renal manifestations.[203,213] Interestingly, despite a known increased prevalence of incompetent mitral and aortic values in PKD,[233] after taking account of renal function, serious cardiac valve disease was no more common in people with PKD and ESRD than in those with other causes of ESRD. This finding may influence how nephrologists counsel PKD patients. Testing other hypotheses, no evidence that PKD was associated with increased risk of hospitalisation with gastro-esophageal reflux disease, renal stones or aortic aneurysms among those with treated ESRD was found (Figure 1 footnote).

This study uses 'big data' to test bedside observations made over ~50-years, but there are certain limitations. First, since HES does not include laboratory data, differences in renal function may confound associations in the PKD versus non-PKD hospital control analyses. Analyses stratified by ESRD overcome this limitation, but residual confounding may still exist. A second limitation is that distinguishing sources of infection in admissions for sepsis is often difficult so rates of infection from particular sources may be underestimates. Lastly, PKD definitions were not directly confirmed. Nevertheless, excellent agreement between nurse-recorded primary renal diagnosis and PKD recorded in HES data has been shown previously, so any misclassification is unlikely to have led to much underestimation in the size of RRs.[162,212]

In summary, the hypothesis that autosomal dominant PKD is associated with clinically significant biliary tract disease as well as serious liver complications was tested. Women with PKD are at higher relative risk of a liver complication than men, but the reverse was observed for the positive association between PKD and biliary tract disease, suggesting liver and biliary complications of PKD have distinct disease mechanisms. The absolute excess

risks of biliary tract complications in people with PKD are similar to the absolute excess risks of some of the better established complications, and so biliary tract disease should be a key differential diagnosis in patients with PKD presenting with abdominal pain or sepsis.

6.6 Illustrative materials/tables and figures for Chapter 6

Table 6-1: Baseline characteristics of patients with polycystic kidney disease versus control populations at date of entry (all England HES 1998–2012)

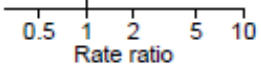
Characteristic	All Patients			Patients with Treated ESRD		
	Polycystic Kidney Disease	Hospital Controls	*P* Value	Polycystic Kidney Disease	Other ESRD Causes	*P* Value
N	23,454	6,412,754		5813	62,519	
Demographics						
Women	10,789 (46%)	3,349,541 (52%)	<0.001	2665 (46%)	23,813 (38%)	<0.001
Median age (IQR), yr	58 (44–70)	48 (34–67)	<0.001	57 (48–66)	62 (48–73)	<0.001
20–30	1679 (7%)	1,140,480 (18%)	<0.001	95 (2%)	3177 (5%)	<0.001
30–40	2822 (12%)	1,253,004 (20%)	<0.001	382 (7%)	6078 (10%)	<0.001
40–50	3753 (16%)	946,595 (15%)	<0.001	1291 (22%)	8368 (13%)	<0.001
50–60	4558 (19%)	862,344 (13%)	<0.001	1689 (29%)	10,527 (17%)	<0.001
60–70	4646 (20%)	833,212 (13%)	<0.001	1365 (23%)	14,002 (22%)	0.06
70–80	4273 (18%)	847,183 (13%)	<0.001	793 (14%)	14,782 (24%)	<0.001
≥80	1723 (7%)	529,936 (8%)	<0.001	198 (3%)	5585 (9%)	<0.001
Ethnicity						
White	20,011 (85%)	5,209,271 (81%)	<0.001	5086 (87%)	49,059 (78%)	<0.001
Nonwhite	2133 (9%)	464,484 (7%)	<0.001	647 (11%)	12,233 (20%)	<0.001
Unknown	1310 (6%)	738,999 (12%)	<0.001	80 (1%)	1227 (2%)	0.002
Quintiles of IMD score						
Quintile 1, lowest	3714 (16%)	979,301 (15%)	0.02	998 (17%)	8323 (13%)	<0.001
Quintile 2	5253 (22%)	1,401,590 (22%)	0.05	1348 (23%)	12,181 (19%)	<0.001
Quintile 3	5015 (21%)	1,395,153 (22%)	0.17	1202 (21%)	13,197 (21%)	0.44
Quintile 4	4931 (21%)	1,357,995 (21%)	0.57	1227 (21%)	14,041 (22%)	0.02
Quintile 5, highest	4541 (19%)	1,278,715 (20%)	0.03	1038 (18%)	14,777 (24%)	<0.001
Region of residency						
East Midlands	1810 (8%)	397,065 (6%)	<0.001	414 (7%)	3986 (6%)	0.03
East of England	2020 (9%)	578,715 (9%)	0.03	587 (10%)	5222 (8%)	<0.001
Northeast	397 (2%)	122,249 (2%)	0.02	92 (2%)	820 (1%)	0.08
Northwest	1111 (5%)	325,304 (5%)	0.02	247 (4%)	2368 (4%)	0.08
Southeast	2910 (12%)	703,644 (11%)	<0.001	703 (12%)	6563 (10%)	0.001
Southwest	1525 (7%)	447,399 (7%)	0.01	376 (6%)	3670 (6%)	0.06
West Midlands	807 (3%)	251,870 (4%)	0.001	245 (4%)	2541 (4%)	0.58
Yorkshire and Humber	203 (1%)	81,723 (1%)	<0.001	59 (1%)	635 (1%)	>0.99
Other	12,671 (54%)	3,504,785 (55%)	0.05	3090 (53%)	36,714 (59%)	<0.001
Year of entry						
1998	4979 (21%)	1,032,212 (16%)	<0.001			
1999	3661 (16%)	959,561 (15%)	0.01			
2000	2613 (11%)	740,815 (12%)	0.05	563 (10%)	5363 (9%)	0.004
2001	2039 (9%)	591,746 (9%)	<0.01	473 (8%)	4855 (8%)	0.31
2002	1705 (7%)	504,447 (8%)	0.001	480 (8%)	4737 (8%)	0.06
2003	1505 (6%)	447,877 (7%)	0.001	458 (8%)	4700 (8%)	0.32
2004	1246 (5%)	387,909 (6%)	<0.001	413 (7%)	4679 (7%)	0.29
2005	1070 (5%)	335,854 (5%)	<0.001	426 (7%)	4721 (8%)	0.54
2006	964 (4%)	295,583 (5%)	0.001	447 (8%)	5222 (8%)	0.08
2007	868 (4%)	267,603 (4%)	0.001	526 (9%)	5484 (9%)	0.48
2008	823 (4%)	246,447 (4%)	0.01	512 (9%)	5421 (9%)	0.72
2009	726 (3%)	219,299 (3%)	0.01	453 (8%)	5626 (9%)	0.002
2010	619 (3%)	192,632 (3%)	0.001	487 (8%)	5509 (9%)	0.26
2011	503 (2%)	155,615 (2%)	0.01	486 (8%)	5102 (8%)	0.59
2012	133 (1%)	35,154 (1%)	0.70	89 (2%)	1100 (2%)	0.20
Comorbidities						
Diabetes	906 (4%)	189,858 (3%)	<0.001	470 (8%)	20,119 (32%)	<0.001
Vascular	1747 (7%)	181,832 (3%)	<0.001	765 (13%)	16,820 (27%)	<0.001
Cancer	681 (3%)	77,098 (1%)	<0.001	245 (4%)	5321 (9%)	<0.001

Data are *n*, *n* (%), or median (IQR). The hospital controls were individuals who had been admitted to the hospital for any one of a wide range of minor medical or surgical conditions across 12 years (excluding any patient with polycystic kidney disease). These included admissions with diagnoses of squint, cataracts, otitis externa/media, varicose veins, hemorrhoids, upper respiratory tract infections, nasal polyps, teeth disorders, nail diseases, sebaceous cyst, soft tissue knee complaints, bunions, contraceptive advice, limb fractures, dislocations sprains and strains, minor head injury and superficial injuries or contusions, and operations, including appendiectomy, dilation and curettage, primary lower limb arthroplasties, tonsillectomy, and adenoidectomy. IQR, interquartile range.

Figure 6-1: Association between polycystic kidney disease and risk of hospitalisation for different diseases in all−England Hospital Episode Statistics 1998−2012

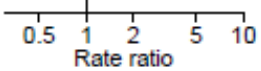
A: All patients

Outcome	Number of events (% per year): Polycystic kidney disease (n=23,454)	Hospital controls (n=6,412,754)	Rate ratio (95% CI)
End−stage renal disease	5,981 (2.82%)	14,104 (0.03%)	112 (109−116)
Cerebral aneurysm	311 (0.14%)	12,867 (0.02%)	5.95 (5.31−6.66)
Serious liver complication	767 (0.31%)	37,232 (0.07%)	4.67 (4.35−5.02)
Other abdominal wall hernia	1,050 (0.46%)	60,963 (0.11%)	4.22 (3.97−4.49)
Urinary tract infections	5,897 (3.21%)	546,411 (1.01%)	3.19 (3.11−3.27)
Cardiac valve disease	1,305 (0.53%)	125,584 (0.23%)	2.34 (2.22−2.47)
Biliary tract disease	**2,617 (1.31%)**	**319,621 (0.59%)**	**2.24 (2.16−2.33)**
Diverticular disease	3,151 (1.38%)	354,432 (0.65%)	2.12 (2.05−2.20)
Inguinal hernia	1,225 (0.43%)	174,625 (0.32%)	1.35 (1.27−1.42)



B: Treated end−stage renal disease patients

Outcome	Number of events (% per year): Polycystic kidney disease (n=5,813)	Other primary renal diagnosis (n=62,519)	Rate ratio (95% CI)
Cerebral aneurysm	37 (0.13%)	150 (0.06%)	2.23 (1.53−3.26)
Serious liver complication	197 (0.70%)	1,561 (0.62%)	1.15 (0.98−1.33)
Other abdominal wall hernia	365 (1.23%)	1,242 (0.50%)	2.47 (2.19−2.80)
Urinary tract infections	1,369 (6.29%)	11,268 (4.93%)	1.28 (1.20−1.35)
Cardiac valve disease	366 (1.47%)	4,128 (1.63%)	0.90 (0.81−1.00)
Biliary tract disease	**494 (1.92%)**	**4,014 (1.61%)**	**1.19 (1.08−1.31)**
Diverticular disease	738 (2.70%)	4,069 (1.64%)	1.65 (1.52−1.79)
Inguinal hernia	269 (1.00%)	1,490 (0.59%)	1.70 (1.49−1.95)

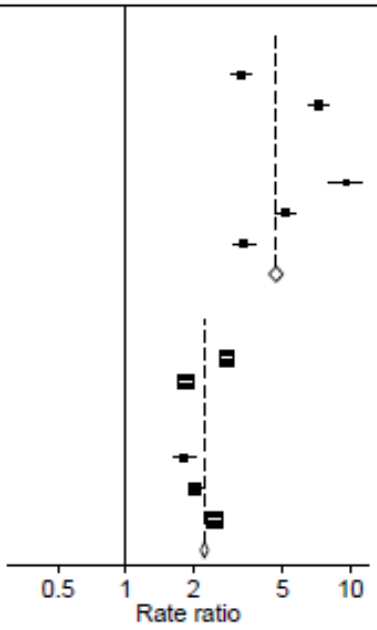


CI = confidence intervals. Outcomes include admissions with relevant diagnostic codes in any diagnostic position or any relevant procedural codes. Adjusted for age at entry as a continuous variable (using both linear and quadratic terms), sex, ethnicity, quintile of patients' Index of Multiple Deprivation score, region of residence, calendar year of first recorded admission (or year of renal replacement therapy start) and comorbidities (grouped into vascular, cancer and diabetes). Rate ratios (95% CI) for aortic or other aneurysms are 3.74 (3.53−3.97) for all patients and 0.96 (0.84−1.11) for treated end−stage renal disease patients. Rate ratios (95% CI) for hiatus hernia and gastroesophageal reflux disease are 1.58 (1.53−1.63) for all patients and 1.03 (0.95−1.12) for treated end−stage renal disease patients. Rate ratios (95% CI) for renal stones are 4.53 (4.39−4.67) for all patients and 0.96 (0.81−1.15) for treated end−stage renal disease patients. Rate ratios (95% CI) for breast cancer (negative control) are 1.00 (0.88−1.12) for all patients and 0.62 (0.45−0.86) for treated end−stage renal disease patients.

Figure 6-2: Association between polycystic kidney disease and risk of hospitalisation for biliary tract and serious liver complications by age and sex in all−England Hospital Episode Statistics 1998−2012

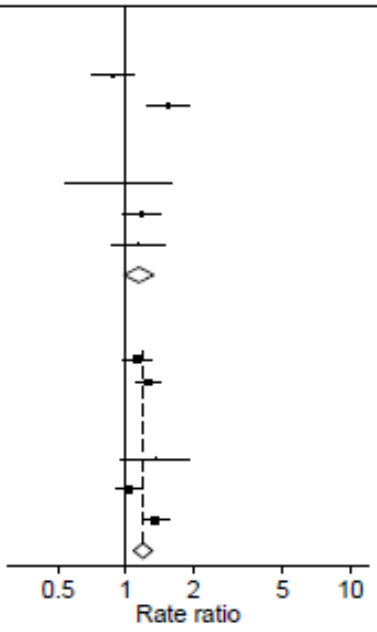
A: All patients

Outcome	Number of events (% per year): Polycystic kidney disease (n=23,454)	Hospital controls (n=6,412,754)	Rate ratio (95% CI)	Het/trend tests
Serious liver complication				
Male	344 (0.26%)	20,215 (0.08%)	3.25 (2.92−3.62)	p<0.001
Female	423 (0.41%)	170,17 (0.06%)	7.22 (6.56−7.95)	
< 40y	136 (0.27%)	6,367 (0.03%)	9.55 (8.06−11.32)	
≥ 40, < 60y	363 (0.46%)	14,470 (0.09%)	5.13 (4.62−5.69)	p<0.001
≥ 60y	268 (0.31%)	16,395 (0.09%)	3.37 (2.99−3.80)	
Overall			**4.67 (4.35−5.02)**	
Biliary tract disease				
Male	1,331 (1.08%)	96,626 (0.38%)	2.82 (2.67−2.98)	p<0.001
Female	1,286 (1.41%)	222,995 (0.76%)	1.85 (1.75−1.95)	
< 40y	300 (0.63%)	75,171 (0.35%)	1.82 (1.62−2.03)	
≥ 40, < 60y	857 (1.16%)	89,525 (0.57%)	2.04 (1.90−2.18)	p<0.001
≥ 60y	1,460 (2.28%)	154,925 (0.91%)	2.50 (2.38−2.64)	
Overall			**2.24 (2.16−2.33)**	



B: Treated end−stage renal disease patients

Outcome	Number of events (% per year): Polycystic kidney disease (n=5,813)	Other primary renal diagnosis (n=62,519)	Rate ratio (95% CI)	Het/trend tests
Serious liver complication				
Male	88 (0.58%)	1,022 (0.66%)	0.88 (0.70−1.09)	p<0.001
Female	109 (0.85%)	539 (0.55%)	1.55 (1.25−1.91)	
< 40y	14 (0.49%)	287 (0.53%)	0.93 (0.54−1.58)	
≥ 40, < 60y	123 (0.83%)	651 (0.71%)	1.18 (0.97−1.44)	
≥ 60y	60 (0.66%)	623 (0.57%)	1.14 (0.87−1.50)	p=0.70
Overall			**1.15 (0.98−1.33)**	
Biliary tract disease				
Male	224 (1.64%)	2,253 (1.46%)	1.12 (0.98−1.29)	p=0.22
Female	270 (2.31%)	1,761 (1.83%)	1.26 (1.11−1.44)	
< 40y	34 (1.16%)	459 (0.86%)	1.35 (0.95−1.92)	
≥ 40, < 60y	221 (1.50%)	1,305 (1.45%)	1.04 (0.90−1.20)	p=0.09
≥ 60y	239 (2.89%)	2,250 (2.13%)	1.36 (1.18−1.55)	
Overall			**1.19 (1.08−1.31)**	



CI = confidence intervals. Het = heterogeneity. Outcomes include admissions with relevant diagnostic codes in any diagnostic position or any relevant procedural codes. Adjusted for age at entry as a continuous variable (using both linear and quadratic terms), sex, ethnicity, quintile of patients' Index of Multiple Deprivation score, region of residence, calendar year of first recorded admission (or year of renal replacement therapy start) and comorbidities (grouped into vascular, cancer and diabetes).

Table 6-2: Diagnostic and procedural codes used to define biliary tract disease, serious liver complications and extra-renal complications

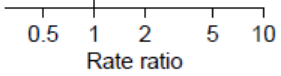
ICD-10 (ICD-9) codes	ICD-10 descriptions	OPCS-4 codes	OPCS-4 descriptions
Biliary tract disease			
K80.0-K80.2 (574.0, 547.1, 574.2, 574.6-574.9, 575)	Gallbladder calculi – with or without cholecystitis	J20.2	Closure of cholecystotomy
K82.1-K82.3 (575.2-575.5)	Hydrops of gallbladder, perforation or fistula	J21.1-J21.3, J24.1-J24.9, J26.1	Open and percutaneous removal of calculus from gallbladder and drainage of gallbladder
K82.8-K82.9 (575.8, 575.9)	Other diseases of the gallbladder	J18.1-J18.9	Partial/Total cholecystectomy and exploration of common bile duct
K80.3-K80.5 (574.3-574.5, 574.6-574.9)	Calculi in bile ducts with/without cholecystitis or cholangitis	J25.8, J25.9, J26.1, J26.8, J26.9	Other gallbladder and calculus procedures
		J24.1-J24.8	Percutaneous treatments to stones
K80.8, K81.0, K81.1, K81.8, K81.9 (575.0, 575.1)	Other cholelithiasis, cholecystitis	J41.1, J76.1	Endoscopic retrograde extraction of calculus from bile duct
K83.0 (576.1)	Cholangitis	J33.1-J34.3, J35.1-J35.9, J38.1-J39.1	Sphincterotomy/-plasty
K83.1-K83.3 (576.2)	Obstruction of bile duct	J48.5-J49.2	Percutaneous drainage of liver/gallbladder, t-tube insertion
K83.8-K83.9 (576.8, 576.9)	Other diseases of the biliary tract	J43.3	Endoscopic retrograde cholangiopancreatography and collection of bile
K74.3-K74.5 (571.6)	Biliary cirrhosis	J42.3	Endoscopic retrograde removal of calculus from pancreatic duct
K85 (577.0)	Acute pancreatitis		
Serious liver complication			
K74.0-K74.2	Hepatic fibrosis, Sclerosis	J02.1-J02.9	Liver resection
K74.6 (571.5)	Other and unspecified cirrhosis of liver	J08.1, J08.2	Investigation of liver and gallbladder
K76.9 (571.9)	Liver disease, unspecified	Y06.2	Deroofing of cyst of organ
K75.0 (572.0)	Abscess of liver	J08.8, J08.9	Unspecified therapeutic endoscopic operations on liver using laparoscope
Z94.4	Liver transplant status	J01.1-J01.3, J01.5-J01.9	Transplantation of liver
T86.4	Liver transplant failure and rejection		
End-stage renal disease			
Complex algorithm			
Cerebral aneurysm			
I60 (430)	Subarachnoid haemorrhage	L33-L34	Operation on cerebral aneurysm
Other abdominal wall hernia			
K41 (551.0, 552.0, 553.0)	Femoral hernia	T22-T23	Femoral hernia repair
K42 (551.1, 552.1, 553.1)	Umbilical hernia	T24	Umbilical hernia repair
Urinary tract infections			
N10, N13.6, N15.1, N30, N39.0 (590, 595)	Urinary tract infections		
Cardiac valve disease			
I34.0 (424.0)	Mitral valve regurgitation	K25, K30.1	Mitral valve repair
I34.1 (424.0)	Mitral valve prolapse	K26, K30.2	Aortic valve repair
I34.2 (394.0)	Mitral valve stenosis		
I35.1 (424.1)	Aortic valve regurgitation		
I35.0 (424.1)	Aortic valve stenosis		
Breast cancer			
C50 (174-175)			
Diverticular disease			
K57 (562.1)	Diverticular disease		
Inguinal hernia			
K40 (550)	Inguinal hernia	T20-T21	Inguinal hernia repair
Aortic or other aneurysms			
I71.1-I71.2 (441.1-441.2)	Thoracic aortic aneurysm	L18-L19, L27-L28	Abdominal aneurysm repair
I71.0 (441.0)	Aortic dissection	L48-49	Iliac artery aneurysm repair
I71.3-I71.6 (441.3-441.9)	Abdominal aortic aneurysm		
I72 (442)	Other aneurysm		
Hiatus hernia and gastroesophageal reflux disease			
K44, Q40.1, Q79.0 (551.3, 552.3, 553.3, 750.6, 756.6)	Diaphragmatic hernia		
K20-K21 (530.1-530.2)	Gastro-oesophageal reflux disease or oesophagitis		
Renal stones			
N20-N23 (592, 594)	Urolithiasis		

ICD = International Classification of Disease. OPCS= Office of Population Censuses and Surveys' Classification of Interventions and Procedures.

Figure 6-3: Association between polycystic kidney disease and risk of hospitalisation for different disease by diagnostic position in all−England Hospital Episode Statistics 1998−2012 (sensitivity analysis)

All patients

Outcome	Number of events (% per year) Polycystic kidney disease (n=23,454)	Hospital controls (n=6,412,754)	Number of events (% per year) Polycystic kidney disease (n=23,454)	Hospital controls (n=6,412,754)	Primary and secondary diagnosis Rate ratio (95% CI)	Primary diagnosis only Rate ratio (95% CI)
Cerebral aneurysm	311 (0.14%)	12,867 (0.02%)	283 (0.13%)	11,262 (0.02%)	5.95 (5.31−6.66)	6.25 (5.55−7.03)
Serious liver complication	767 (0.31%)	37,232 (0.07%)	314 (0.13%)	15,310 (0.03%)	4.67 (4.35−5.02)	4.64 (4.15−5.19)
Other abdominal wall hernia	1,050 (0.46%)	60,963 (0.11%)	867 (0.38%)	52,567 (0.09%)	4.22 (3.97−4.49)	4.08 (3.82−4.37)
Urinary tract infections	5,897 (3.21%)	546,411 (1.01%)	3,570 (1.86%)	275,893 (0.50%)	3.19 (3.11−3.27)	3.71 (3.59−3.84)
Cardiac valve disease	1,305 (0.53%)	125,584 (0.23%)	370 (0.14%)	40,448 (0.07%)	2.34 (2.22−2.47)	1.88 (1.69−2.08)
Biliary tract disease	**2,617 (1.31%)**	**319,621 (0.59%)**	**1,704 (0.85%)**	**266,019 (0.49%)**	**2.24 (2.16−2.33)**	**1.74 (1.66−1.82)**
Diverticular disease	3,151 (1.38%)	354,432 (0.65%)	1,511 (0.64%)	175,350 (0.32%)	2.12 (2.05−2.20)	2.02 (1.92−2.13)
Inguinal hernia	1,225 (0.43%)	174,625 (0.32%)	1,046 (0.36%)	165,553 (0.30%)	1.35 (1.27−1.42)	1.21 (1.14−1.29)

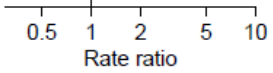


CI = confidence intervals. Outcomes include admissions with relevant diagnostic codes in either any diagnostic position or primary diagnostic position only, or any relevant procedural codes. Adjusted for age at entry as a continuous variable (using both linear and quadratic terms), sex, ethnicity, quintile of patients' Index of Multiple Deprivation score, region of residence, calendar year of first recorded admission and comorbidities (grouped into vascular, cancer and diabetes).

Figure 6-4: Association between polycystic kidney disease and risk of hospitalisation for different diseases by diagnostic position in all−England Hospital Episode Statistics 1998−2012 (sensitivity analysis)

Treated end−stage renal disease patients

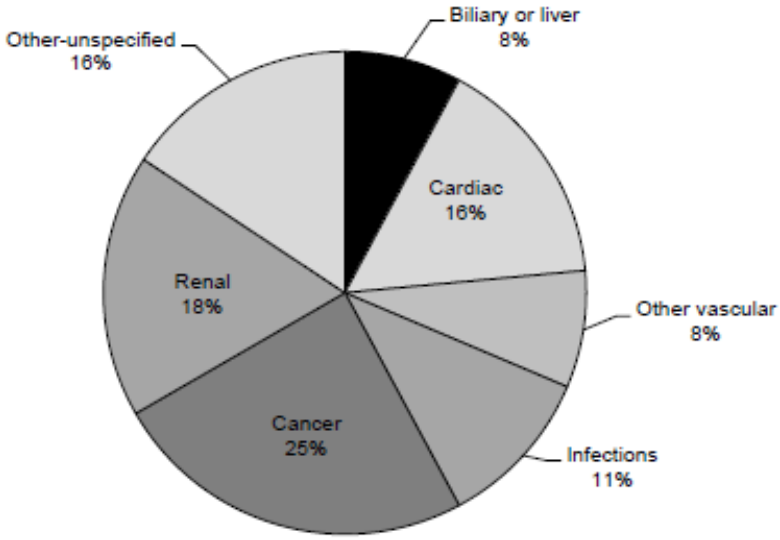
Outcome	Number of events (% per year)		Number of events (% per year)		Primary and secondary diagnosis	Primary diagnosis only
	Polycystic kidney disease (n=5,813)	Other primary renal diagnosis (n=62,519)	Polycystic kidney disease (n=5,813)	Other primary renal diagnosis (n=62,519)	Rate ratio (95% CI)	Rate ratio (95% CI)
Cerebral aneurysm	37 (0.13%)	150 (0.06%)	32 (0.11%)	118 (0.05%)	2.23 (1.53−3.26)	2.44 (1.61−3.68)
Serious liver complication	197 (0.70%)	1,561 (0.62%)	61 (0.21%)	314 (0.12%)	1.15 (0.98−1.33)	1.67 (1.26−2.23)
Other abdominal wall hernia	365 (1.23%)	1,242 (0.50%)	295 (0.93%)	943 (0.38%)	2.47 (2.19−2.80)	2.45 (2.14−2.81)
Urinary tract infections	1,369 (6.29%)	11,268 (4.93%)	874 (3.64%)	6,373 (2.66%)	1.28 (1.20−1.35)	1.37 (1.27−1.47)
Cardiac valve disease	366 (1.47%)	4,128 (1.63%)	108 (0.36%)	951 (0.38%)	0.90 (0.81−1.00)	0.95 (0.78−1.17)
Biliary tract disease	**494 (1.92%)**	**4,014 (1.61%)**	**321 (1.16%)**	**2,237 (0.89%)**	**1.19 (1.08−1.31)**	**1.30 (1.15−1.47)**
Diverticular disease	738 (2.70%)	4,069 (1.64%)	321 (1.01%)	1,559 (0.62%)	1.65 (1.52−1.79)	1.62 (1.43−1.84)
Inguinal hernia	269 (1.00%)	1,490 (0.59%)	230 (0.82%)	1,240 (0.49%)	1.70 (1.49−1.95)	1.67 (1.44−1.93)



CI = confidence intervals. Outcomes include admissions with relevant diagnostic codes in either any diagnostic position or primary diagnostic position only, or any relevant procedural codes. Adjusted for age at entry as a continuous variable (using both linear and quadratic terms), sex, ethnicity, quintile of patients' Index of Multiple Deprivation score, region of residence, calendar year of renal replacement therapy start and comorbidities (grouped into vascular, cancer and diabetes).

Figure 6-5: Underlying causes of death in all people with polycystic kidney disease by; prior biliary tract or serious liver complication (panel A), or without such complications

A: (1,128 deaths in 3,136 patients)



B: (6,192 deaths in 20,318 patients)

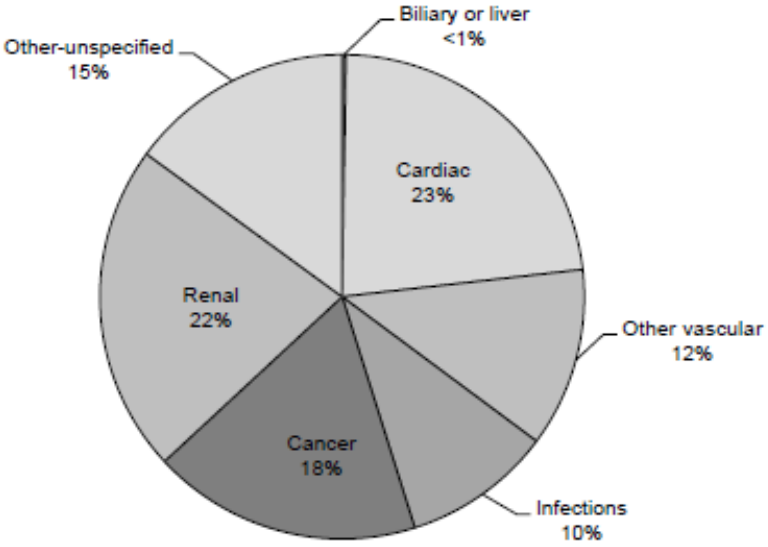
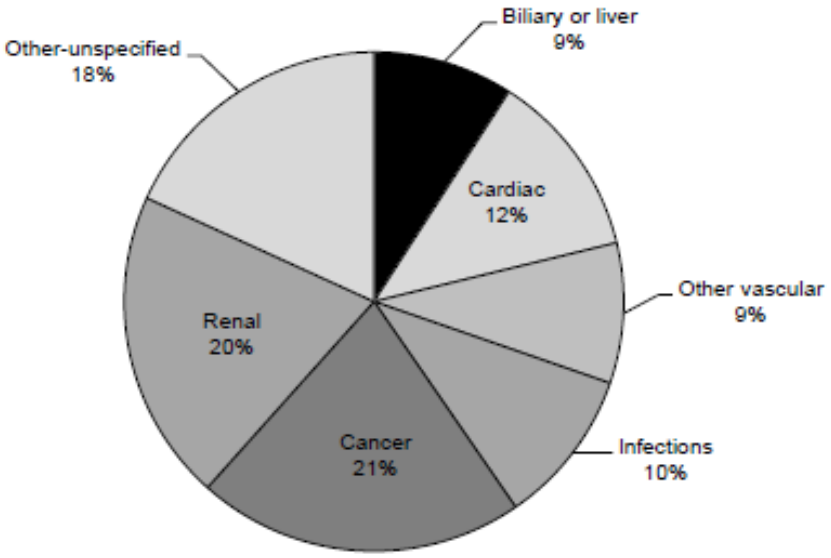
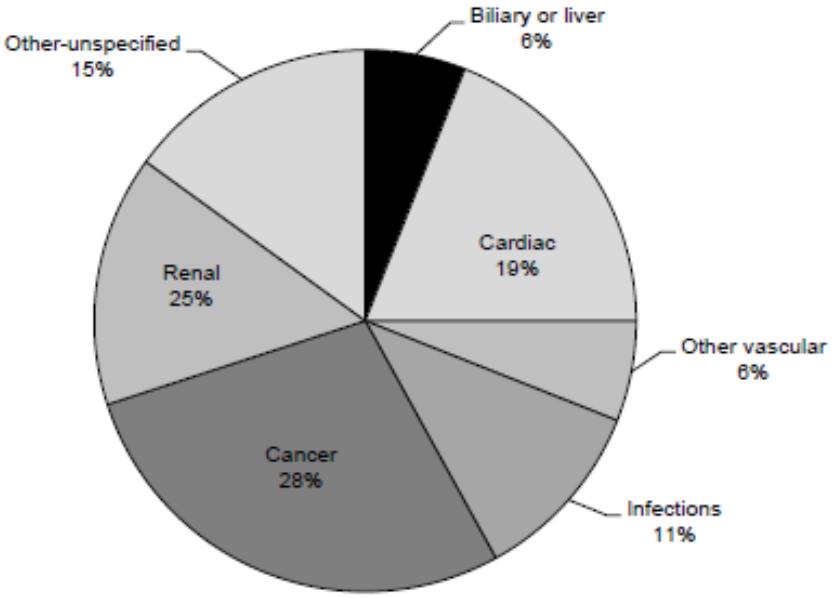


Figure 6-6: Underlying causes of death in all people with polycystic kidney disease and prior biliary tract or serious liver complications in; females (panel A), or males (panel B)

A: Females (509 deaths in 1,580 patients)



B: Males (619 deaths in 1,556 patients)



6.7 Bullet points of Chapter 6

- Autosomal dominant polycystic kidney disease (PKD) is the most common inherited renal condition and has recognized extra-renal manifestations.

- The diagnostic coding of PKD is limited to two distinct codes in ICD-10.

- PKD as the primary renal disease, causing ESRD, is easily identifiable from HES.

- Hospitalisation rates were calculated, and compared to a general population for a pre-defined group of ‘biliary tract disease’ and ‘serious liver complications’ for both a PKD population and general population.

- Rate ratios for patients with PKD were 2.24 times and 4.7 times more likely to have hospital admissions with biliary tract disease or serious liver complications than controls.

Chapter 7 Concluding remarks

Conclusions

This thesis was conceived with four aims, which may be useful to have re-stated before the concluding remarks.

1) Derive and validate a cohort of end-stage renal disease (ESRD) patients exclusively from anonymised, individually-linked prospectively collected hospital inpatients datasets

2) Analyse the temporal trends of age, sex and comorbidity adjusted mortality rates in the ESRD cohort

3) Concurrently derive a comparative general population to provide an opportunity to compare trends between the ESRD and general populations

4) Demonstrate other uses of routinely collected hospital inpatients datasets in renal epidemiology

I aimed to test whether more reliable trends of morbidity and mortality could be performed using an ESRD population identified exclusively from routinely collected hospital inpatient data. Treatment of ESRD, in the form of maintenance RRT, has developed over the last half a century, having begun in the 1960s/1970s under atmosphere of societal and medical scepticism. Yet with the perseverance of the early practitioners', evolving technologies and parallel developments in the sphere of organ transplantation, it became obvious that maintenance RRT not only saved lives but it also had the capacity to restore patients' health back to a level where they could continue to contribute to society. As the provision of renal services grew any historical 'prioritisation' of patients selected onto RRT programmes dwindled to be irrevocably replaced by older patients with increasingly complex comorbid illnesses. To date, no long-term study has had access to the linked mortality and comorbidity data of these early recipients of RRT *and* a cohort of modern day patients. Uniquely, this thesis identified and consequently could adjust for the stark changes in patient demographics (particularly age and baseline prevalence of comorbid illness) within the ESRD cohort, with foreknowledge that comorbidity is a key determinant of mortality. Moreover, I was able to compare mortality trends in an ESRD cohort to a *contemporaneously* identified general hospital-control population allowing analyses which could suggest whether improvements (or not) were also reflected in the general population; to date, the inability to analyse secular changes in the prevalence of comorbidities in a general population has hampered any such analysis. Researchers have hitherto, relied on national mortality statistics, which do not generally provide comorbid data, making statistical adjustments limited to only age and sex.

Using a unique combined resource of ORLS, the oldest source of linked routinely collected hospital inpatient admissions [1965-1998] in England, and all-England HES [1998-2011], a derivation algorithm was designed to identify maintenance RRT patients (ie patients receiving dialytic therapies or a transplant and surviving for >90 days). This provided a 40-

year regional ESRD cohort from Oxfordshire and a cohort of English patients since the turn of the century, with mortality data being obtained via directly linked data from Office of National Statistics; providing fact and date of death alongside an underlying cause of death (UCD). The anonymised identification of treated ESRD patients was novel and involved a series of logical (yet clinically informed) steps to initially identify RRT, before determining whether this treatment was given as a *maintenance* therapy and then restricting the cohort to only incident cases. This process was iterative and involved the manual mapping of clinical terms (both diagnostic and procedural terms) which were relevant to renal disease and major comorbidities and the categorisation of death codes. In all, these codes were mapped across four versions of the ICD and three versions of OPCS.

The final cohort provided baseline characteristics of over 40,000 newly treated ESRD patients since 1970 and showed the enormous change in terms of their age structure and comorbidity profile of incident ESRD patients consistent with the historical context of ESRD provision. The descriptive changes are particularly striking especially when analysing the magnitude of such changes in ESRD to changes in the comparative general population. This highlighted the point that in any proposed assessment of mortality trends there needed to be statistical adjustment for comorbid illness for more reliable results to be obtained. Historically, data held by renal registries did not have any reliable comorbid variables, only inferences obtained from age and occasionally primary renal disease. Uniquely, the ESRD and its comparative contemporaneous general populations had their respective baseline comorbidity derived from the same datasets and over the same time-period permitting analogous standardization techniques.

As the ESRD cohort was anonymously identified, validation of my identification steps was performed using a series of indirect and direct techniques. For indirect comparisons,

summarized statistics of the counts of ESRD patients and demographic details from the UK-RR, UK-TR, and OKU were used. For the HES derived portion of the cohort it was also possible to validate directly the algorithm using clinically-adjudicated ESRD outcomes from prospective randomised controlled trials of patients with renal disease ("3C" and "SHARP"). Following this validation work it became apparent that the derived cohorts did indeed provide sufficiently reliable identification of treated ESRD patients to allow descriptions of long-term changes in mortality rates to be performed.

The results chapter showed that the full extent of mortality declines among RRT patients since 1980 is only apparent when changes in comorbidity are taken into account. With such an approach it suggested that mortality rates in RRT patient have halved since 1970, faster than declines in the mortality in the general population hospital controls. Declines in standardized 3-year mortality rates were evident among those who received a kidney transplant and those who remained on dialysis suggesting that transplantation has not been the only reason for the improvements and that there has been fundamental improvements in dialytic care. (See Appendix 1.2 for the peer-reviewed *Kidney International journal* [Impact Factor=8.4] publication of the results.

Having the available resource of all-England HES data allowed another aspect of renal epidemiology to be explored: a disease association study of polycystic kidney disease, the commonest genetic cause of renal failure. A cohort of PKD patients was identified using ICD-10 codes and directly validated against participants in the 3C study. A number of outcomes variables including diagnostic and procedural codes for well recognised and hypothesis generating disease associations were collected. This demonstrated that hospitalisation rates for biliary tract disease and serious liver complications to be 2.2 and 4.7 times higher in those PKD patients than the general population.

Future uses

While this body of work has focussed principally on mortality trends, it may open opportunities to explore the burden of non-fatal outcomes, which often besets these patients. However, this would involve considerable new work as working at the episode level of HES data, as suppose to using *spell-level* data (ie summary codes), would bring substantial challenges in deciding what are prevalent versus incident clinical events and any such analyses would perhaps need to consider competing risk models, which is not necessary in all-cause mortality.

I have designed, validated and studied a new method, which reliably identifies treated ESRD which could offer opportunities for participants in randomised controlled trials to be followed up in the longer-term which may provide either safety or efficacy signals. Any such direct HES linkage could also provide a streamline tool to adjudicate intra-trial clinical events, perhaps reducing the need for laborious and often expensive formalised adjudication. Other uses of the methods I have described could be used, for example in the UK Biobank Study or other prospective British cohort studies, to capture patients who reach ESRD with fresh opportunities to study any underlying associations from the exhaustive baseline data which particularly UK Biobank holds.

Another body of work to this, but not one that is *not* achievable with HES, would be to measure patient related outcomes (such as fatigue, itch or quality of life metrics) over time in separate studies and combine these data with more traditional outcomes from HES to analyse whether the apparent improvements are reflected in patients experiences. Aligned to this, health economics analyses could be performed, suing HES data, which could help in ascribing the true burden of ESRD.

Summary

In summary, in this thesis I have demonstrated that routinely collected hospital inpatient data can indeed be used to derive a cohort of patients on maintenance RRT in England and describe temporal changes in mortality and morbidity, after taking account of the major temporal changes in selection of people receiving RRT, and considering the secular changes in comorbidity. With this, I have shown that standardized three year-mortality rates among patients on RRT have halved since 1970, faster than declines in the mortality in a general population hospital controls identified from the same resource. This headline result should be cautiously celebrated, because whilst these reductions are manifestly welcomed, ESRD patients remain at considerable absolute risk of premature death, both from vascular and non-vascular causes. The focus for the nephology community should be to proactively identify a range of focussed hypotheses, applicable to broad range of patients with advanced CKD, and then to design large-scale randomised clinical trials to test any hypotheses in the perpetual aim to narrow this mortality gap.

Chapter 8 Supplemental material

Supplemental material

8.1 Information governance toolkit

Figure 8-1: Information Governance Toolkit from NHS Digital

IG Toolkit Assessment Summary Report
University of Oxford - Medical Sciences Division - Nuffield Department of Population Health - Unit of Health-Care Epidemiology (Hosted Secondary Use Team/Project)
Assessment Report - EE133863-MSD-NDOPH-UHCE

Information Governance Management

Assessment	Stage	Level 0	Level 1	Level 2	Level 3	Total Req'ts	Overall Score	Self-assessed Grade	Reviewed Grade	Reason for Change of Grade
Version 13 (2015-2016)	Published	0	0	2	2	4	83%	Satisfactory	Satisfactory	n/a

Confidentiality and Data Protection Assurance

Assessment	Stage	Level 0	Level 1	Level 2	Level 3	Total Req'ts	Overall Score	Self-assessed Grade	Reviewed Grade	Reason for Change of Grade
Version 13 (2015-2016)	Published	0	0	2	2	4	83%	Satisfactory	Satisfactory	n/a

Information Security Assurance

Assessment	Stage	Level 0	Level 1	Level 2	Level 3	Total Req'ts	Overall Score	Self-assessed Grade	Reviewed Grade	Reason for Change of Grade
Version 13 (2015-2016)	Published	0	0	5	1	6	72%	Satisfactory	Satisfactory	n/a

Overall

Assessment	Stage	Level 0	Level 1	Level 2	Level 3	Total Req'ts	Overall Score	Self-assessed Grade	Reviewed Grade	Reason for Change of Grade
Version 13 (2015-2016)	Published	0	0	9	5	14	78%	Satisfactory	Satisfactory	n/a

Grade Key

Not Satisfactory	Not evidenced Attainment Level 2 or above on all requirements (Version 8 or after)
Satisfactory with Improvement Plan	Not evidenced Attainment Level 2 or above on all requirements but improvement actions provided (Version 8 or after)
Satisfactory	Evidenced Attainment Level 2 or above on all requirements (Version 8 or after)

Version 13 (2015-2016) History

Status	Date
Reviewed (Satisfactory)	08/09/2016 12:46
Published	25/05/2016 11:12
Started	31/03/2016 12:17

8.2 Ethics approval documentation

Figure 8-2: Ethics letter of approval

NHS
Health Research Authority

South West - Central Bristol Research Ethics Committee

Whitefriars
Level 3, Block B
Lewin's Mead
Bristol BS1 2NT
Email: nrescommittee.southwest-bristol@nhs.net

Tel:
Fax:

31 October 2016

Professor Michael Goldacre
Professor of Public Health, Oxford University
Oxford University
Unit of Health-Care Epidemiology, Department of Public Health,
Oxford University, Old Road Campus, Old Road,
Oxford
OX3 7LF

Dear Professor Goldacre

Study Title:	**Epidemiological and health services research using routine NHS data: work programme of the Unit of Health-Care Epidemiology, Oxford University, funded by the National Co-ordinating Centre for Research Capacity Development**
REC reference:	**04/Q2006/176**
IRAS project ID:	

Thank you for sending the progress report for the above study dated 08/03/2016. The report will be reviewed by the Chair of the Research Ethics Committee, and I will let you know if any further information is requested.

The favourable ethical opinion for the study continues to apply for the duration of the research as agreed by the REC.

04/Q2006/176:	**Please quote this number on all correspondence**

Yours sincerely

Amy Peters

E-mail: nrescommittee.southwest-bristol@nhs.net

Copy to: *Carol Cornelius,*

8.3 Contributions; by chapter

My own contributions, fully and explicitly indicated were as follows.

Chapter 1

To finalise the conception of the study in conjunction with my supervisor.

I approached the curators of the datasets (MG and then subsequently MJL) to gain their approval to use ORLS and HES for this body of work.

Enduring ethics approval was already in place.

I drafted, edited and wrote all parts of the chapters.

Chapter 2

I sourced and converted hard copies of historical diagnostic and procedural manuals into usable formats using excel.

I interrogated these coding manuals and extracted relevant diagnostic and procedural codes which could potentially identify an ESRD cohort.

I mapped across these coding manuals, the clinical codes for all the accompanying terms used to identify prior comorbid illness, primary renal disease and categories of underlying the causes of death.

I designed the rules used to identify the ESRD cohort, iteratively tested these rules and adapted them into an order to be able to extract the patient cohort used in the analyses.

I reviewed all the clinical extracts of patients identified as potentially having ESRD in the ORLS period to determine whether rules for maintenance RRT were satisfied.

CH and NS, statistical colleagues, handled cleaned and processed the raw data. CH embedded the clinical algorithm into the the derivation programme.

I drafted, edited and wrote all parts of the chapters.

Chapter 3

In the baseline characteristics, I reproduced the baseline tables from a cleaned dataset provided by CH and reproduced the significance testing for the difference across year groups. I created the stratified tables used for various baseline characteristics by initial modality of RRT, sex and age. I adapted the conditions and procedures used to identify the general population hospital control cohort which was extracted from the original ORLS dataset by Raph Goldacre (Research Fellow at UHCE) before being given to CH to be used in subsequent analyses. The methods used by UHCE have been published previously.

Chapter 4

I wrote and requested that UK-TR provide me with information on the number of kidneys transplant performed in England between 2000-2009, used as the basis for the indirect comparison.

I extracted the relevant UK-RR annual reports and extracted summary statistics on the baseline characteristics of incident RRT patients.

I was able, in my role as Renal Specialist Registar at the Oxford Kidney Unit, to use PROTON to extract all incident RRT patients treated by OKU from 1967 to 2008. From this, I extracted baseline characteristics and incorporated them into Table 4-3.

The direct validation of the HES derived treated ESRD cohort was performed by CH, using my algorithm. I performed the direct validation of participants from the 3C study, which formed the impetus to Chapter 6.

Chapter 5

I led, but worked alongside, statistical colleagues (CH and NS) to design the relevant mortality analyses, decided on what sensitivity analyses would be appropriate. I choose the final tables and figures in the manuscript which I fully drafted, revised and later finalized after edits from co-authors before submission. CH ran the Poisson regression model and generated the figures that were used in main manuscript.

Chapter 6

Writing a manuscript in which a disease association study complimented a case series of the hepatobiliary complications in polycystic patients treated in the Oxford Kidney Unit, occurred in discussion with the paper's main author PJ, with whom I shared an office at CTSU. In conjunction with RH and WH we took forward the disease association study. This clinical quartet in addition to NS and CH, designed and executed the study which used the derivation algorithm which I had designed for my thesis to identify the ESRD population, and the subset of PCKD patients. I performed a literature search on the prevalence of conditions which are traditionally associated with PKD and helped co-write the manuscript.

The thesis solely contains my own words and any errors I take full responsibility.

Chapter 9 References

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