The Incidence and Outcomes of Chronic Kidney Disease Amongst Indigenous Australians

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A thesis submitted for the degree of Doctor of Philosophy

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November 2015
Declaration

I hereby declare that the work herein, now submitted as a thesis for the degree of Doctor of Philosophy at Charles Darwin University, is the result of my own investigations. This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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4th November 2015
Abstract

Over the last thirty years an end-stage kidney disease (ESKD) epidemic has occurred amongst Aboriginal and Torres Strait Islander (Indigenous) Australians. This thesis uses existing data to examine the outcomes of Indigenous ESKD patients receiving renal replacement therapy (RRT), and in more detail the outcomes of both treated ESKD and chronic kidney disease (CKD) in the Northern Territory (NT) of Australia (whose Indigenous peoples have especially high rates of kidney disease).

Using national RRT registry data, unadjusted analysis suggested that past differences in survival between Indigenous and non-Indigenous Australians had closed more recently. However, adjusting for substantial population differences uncovered significant persisting disparities in survival despite improvements overall. Analysis limited to dialysis patients aged 15–64 years showed that survival differences between Indigenous and non-Indigenous patients have improved over time, but that Indigenous transplant rates have worsened. Analysis comparing transplant recipients to similar dialysis-only patients (using propensity score methods) revealed that Indigenous transplanted patients had better survival than similar dialysis-only patients but relatively fewer suitable Indigenous patients were transplanted.

Linked NT hospital and RRT registry data revealed large variations in haemodialysis treatment attendance. Lower attendance was associated
with being Indigenous (rather than relocation from remote areas), and with higher rates of death and hospitalisation and much lower rates of transplantation.

Ambulatory laboratory data from the main pathology service for the Top End of the NT were examined. Rates of testing were high and rising, particularly in remote districts with high CKD prevalence. Among those with albuminuria, extremely high rates of progressive CKD were found.

Taken together these findings suggest that current Indigenous/non-Indigenous disparities in ESKD outcomes are attributable to low transplantation rates and lower treatment attendance. High rates of CKD progression in remote areas are also concerning. These findings raise questions about the quality and equity of care for Indigenous patients. Further analysis requires linked datasets.
Acknowledgements

Very few theses can be completed without the assistance and work of others. This is not one of those theses.

Professor Joan Cunningham, my principal supervisor, has been a particularly generous, patient, inspiring, thoughtful and insightful mentor and guide over the life of my PhD candidature. I doubt there are many better supervisors. Professor Matthew Jose and Dr Yuejen Zhao, associate supervisors, have also been encouraging and supportive throughout; both have made substantial contributions to the work presented here.

The Health Gains Planning Branch of the Northern Territory Department of Health, led by Dr Steve Guthridge (and in his absence by Dr Jo Wright), was a wonderful place for sabbatical leave and then the early phase of the PhD journey. As well as Steve, Jo and Yuejen I thank Ramakrishna Chondur, Karen Dempsey, Shu Qin Li and Jiqiong (Judy) You for their camaraderie and generosity teaching me quantitative research skills and allowing me space to work. Karen Dempsey deserves special mention as the data linkage “third party” administrator for the work presented in Chapter Five of this thesis.

The Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) is an extraordinary resource for kidney disease research. As
well as the ever-cheerful and responsive staff of the Registry in Adelaide,
I thank the staff and patients of the Australian and New Zealand
nephrology community for providing information for and maintaining the
Registry.

This work was supported by a National Health and Medical Research
Council Postgraduate Scholarship (#1038721). Mr. Mick Gooda, the
Aboriginal and Torres Strait Islander Social Justice Commissioner,
provided timely and useful guidance.

Thanks also to Dr Paul Snelling, who inspired me to pursue a career in
Indigenous health care; and to Professors Alan Cass & Stephen
McDonald, who came before. If I have seen further, it is only by standing
on the shoulders of giants.

Thanks to my parents Michael Fachtna Lawton and Catherine Margaret
Stephanie Lawton, whose love, hard work and sacrifices made me.

Finally, particularly heartfelt thanks to my wife Megan Louise Lawton
and our children: Cornelius James, Amie Frances and Emma Catherine.
The love and joy you have given me every day has made this both possible
and worthwhile.
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<th>Full Form</th>
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<tr>
<td>AATSIHS</td>
<td>Australian Aboriginal and Torres Strait Islander Health Survey</td>
</tr>
<tr>
<td>ABS</td>
<td>Australian Bureau of Statistics</td>
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<tr>
<td>AIHW</td>
<td>Australian Institute of Health and Welfare</td>
</tr>
<tr>
<td>ANZDATA</td>
<td>Australia and New Zealand Dialysis and Transplant Registry</td>
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<tr>
<td>ARIA+</td>
<td>Accessibility/Remoteness Index of Australia</td>
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<tr>
<td>AusDiab</td>
<td>Australian Diabetes, Obesity and Lifestyle Study</td>
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<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>CI</td>
<td>Confidence Intervals</td>
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<tr>
<td>CKD</td>
<td>Chronic Kidney Disease</td>
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<td>CKD-EPI</td>
<td>Chronic Kidney Disease Epidemiology Consortium</td>
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<tr>
<td>CR-PH</td>
<td>Competing Risks Proportional Hazards</td>
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<tr>
<td>eGFR</td>
<td>Estimate of Glomerular Filtration Rate</td>
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<td>ESKD</td>
<td>End Stage Kidney Disease</td>
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<tr>
<td>HHD</td>
<td>Home Haemodialysis</td>
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<tr>
<td>HLA</td>
<td>Human Leukocyte Antigen</td>
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<td>HR</td>
<td>Hazard Ratio</td>
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<tr>
<td>HREC</td>
<td>Human Research Ethics Committee</td>
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<tr>
<td>IDMS</td>
<td>Isotope Dilution Mass Spectrometry</td>
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<td>Abbreviation</td>
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<tr>
<td>IMPAKT</td>
<td>Improving Patient Access to Kidney Transplantation Study</td>
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<tr>
<td>IRSAD</td>
<td>Index of Relative Social Advantage or Disadvantage</td>
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<td>IRR</td>
<td>Incidence Rate Ratio</td>
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<td>MDRD</td>
<td>Modification of Diet in Renal Disease</td>
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<td>MRR</td>
<td>Mortality Rate Ratio</td>
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<tr>
<td>NHMS</td>
<td>National Health Measures Survey</td>
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<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
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<tr>
<td>NT</td>
<td>Northern Territory of Australia</td>
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<tr>
<td>OR</td>
<td>Odds Ratio</td>
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<tr>
<td>PATS</td>
<td>Patient Assistance and Travel Scheme</td>
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<tr>
<td>PD</td>
<td>Peritoneal Dialysis</td>
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<tr>
<td>PH</td>
<td>Proportional Hazards</td>
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<tr>
<td>RR</td>
<td>Risk Ratio</td>
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<tr>
<td>RRT</td>
<td>Renal Replacement Therapy</td>
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<td>SHR</td>
<td>Sub-Hazard Ratio</td>
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<tr>
<td>Tx</td>
<td>Transplantation</td>
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<tr>
<td>UACR</td>
<td>Urinary Albumin-to-Creatinine Ratio</td>
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<tr>
<td>USRDS</td>
<td>United States Renal Data System</td>
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<tr>
<td>WDP</td>
<td>Western Diagnostic Pathology</td>
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“We may reject the contention that the ordering of institutions is always defective because the distribution of natural talents and the contingencies of social circumstance are unjust, and this injustice must inevitably carry over to human arrangements. Occasionally this reflection is offered as an excuse for ignoring injustice, as if the refusal to acquiesce in injustice is on a par with being unable to accept death. The natural distribution is neither just nor unjust; nor is it unjust that persons are born into society at some particular position. These are simply natural facts. What is just and unjust is the way that institutions deal with these facts. Aristocratic and caste societies are unjust because they make these contingencies the ascriptive basis for belonging to more or less enclosed and privileged social classes. The basic structure of these societies incorporates the arbitrariness found in nature. But there is no necessity for men to resign themselves to these contingencies. The social system is not an unchangeable order beyond human control but a pattern of human action. In justice as fairness men agree to avail themselves of the accidents of nature and social circumstance only when doing so is for the common benefit. The two principles are a fair way of meeting the arbitrariness of fortune; and while no doubt imperfect in other ways, the institutions which satisfy these principles are just.”

— John Rawls, “A Theory of Justice” (1971), Chapter II, Section 14, pg. 87-88
Chapter 1: Introduction

1.1 “These sorts of people don’t do very well ...”

In 1995 a paper titled “These sorts of people don’t do very well’: race and allocation of health care resources” appeared in the *Journal of Medical Ethics* (Lowe, Kerridge & Mitchell 1995). The authors presented a case where a nephrologist decided not to proceed with pre-emptive living-related donor kidney transplantation for a 53 year old Aboriginal Australian woman with type 2 diabetes mellitus, ischaemic heart disease and peripheral vascular disease from a regional centre because “These sorts of people don’t do very well ...”.

They suggested that purely utilitarian health care resource allocation decisions “may embody subtle racial discrimination” when the disadvantages marginalised or minority groups face are used against them, and the definition of “success” may be influenced by cultural biases. They argued that if race, culture and the difficulties minority groups face were ignored, then “selection criteria that embody inherently racist assumptions may become convenient tools to support policies and behaviour that further disadvantage already vulnerable groups.”
They suggested that since choices have to be made and consensus about the definition of reasonable outcome criteria is unlikely in a modern, pluralistic society, the emphasis must lie with the process by which such choices are made: centred on adequate communication, cultural sensitivity, an understanding of the patient’s health needs and social conditions, shared decision making between patients and their carers and a process of empowerment at individual and minority community levels (Lowe, Kerridge & Mitchell 1995).

Twenty years on, how well do “these sorts of people” do? If disparities in outcome have existed in the past, have these “gaps” closed? If not, where and why are the disparities and how big are they?

1.2 Chapter Overview

This chapter briefly summarises the demography of Indigenous Australians; describes what is known about the incidence, prevalence and antecedents of kidney disease amongst Indigenous Australians and explores what is known about the outcomes of chronic kidney disease and (separately) end-stage kidney disease for Indigenous peoples in the United States, Canada, New Zealand and Australia. After highlighting several unresolved questions, the chapter then discusses various methodological issues arising from the use of existing data for observational research to address them.
1.3 Demography of Indigenous Australians

The Aboriginal and Torres Strait Islander peoples of Australia (hereafter respectfully referred to as Indigenous Australians) are culturally, linguistically and geographically diverse. They make up 3.0% of the total Australian population. Twenty-one per cent of all Indigenous Australians live in remote or very remote areas of Australia, where the proportion of the population who are Indigenous is relatively high: in 2011, 45% of people living in very remote areas and 16% of people living in remote areas were Indigenous (Australian Institute of Health and Welfare 2015).

The Indigenous population has a relatively young age structure. In 2011, the median age was 21.8 years compared to 37.6 years for the non-Indigenous, while 36% were aged under 15 years compared with 18% of non-Indigenous people (Australian Bureau of Statistics 2012a).

Compared to non-Indigenous Australians, Indigenous people have much lower levels of school retention and attainment, are more likely to be unemployed, homeless or living in overcrowded houses, much more likely to be imprisoned and have a lower disposable income (Australian Institute of Health and Welfare 2015).

By most quantifiable methods, the health of Indigenous Australians is much worse than non-Indigenous Australians. For example, the age-

1.4 Kidney Disease in Indigenous Australians

1.4.1 End-Stage Kidney Disease Incidence and Prevalence in Indigenous Australians

The Australia and New Zealand Dialysis and Transplant Registry (the ANZDATA Registry) is a registry of incidence, prevalence and outcome information about patients with end-stage kidney disease (ESKD) receiving renal replacement therapy (RRT) – that is, dialysis or kidney transplant treatment. Formed in 1977, there is voluntary but complete participation from all treating units in Australia and New Zealand. As a result, it is a national resource in both countries that can be used to answer many questions about RRT and, by inference, about ESKD.

Since the mid-1980s, Indigenous Australians have had a higher incidence of ESKD receiving RRT than non-Indigenous Australians (Disney 1995;
Spencer et al. 1998). This is most prominent for people aged 35–64 years of age; Indigenous women have a much higher relative incidence rate than Indigenous men, who in turn have a much higher relative incidence rate than non-Indigenous Australians (ANZDATA Registry 2015b).

The higher incidence is reflected in the prevalence of ESKD receiving RRT: in 2013, 12.6% of patients receiving dialysis treatment in Australia were Indigenous (an increase from 10.1% in 2003). In contrast, only 2.1% of patients with a functioning kidney transplant in Australia in 2013 were Indigenous (2.0% in 2003) (ANZDATA Registry 2015b; Jose et al. 2008).

Both the incidence and prevalence of ESKD receiving RRT amongst Indigenous Australians varies greatly across Australia. Although the majority live in urban, inner regional and outer regional areas (predominantly in New South Wales, and Queensland) (Australian Institute of Health and Welfare 2015), most Indigenous Australians commencing RRT come from remote or very remote areas of central and northern Australia (ANZDATA Registry 2015b).
1.4.2 Chronic Kidney Disease Prevalence in Indigenous Australians

For epidemiological purposes, chronic kidney disease (CKD) is now usually defined and classified according to three measures:

i) an estimate of glomerular filtration rate (eGFR), based on one of a number of different and increasingly refined formulae incorporating age, sex and serum creatinine levels (reported in ml/min/1.73m²) (Johnson et al. 2012a)

ii) a measure of urinary protein excretion, now most commonly a spot urinary albumin-to-creatinine ratio (UACR; reported in mg/mmol in Australia and mg/g elsewhere) (Johnson et al. 2012b)

iii) a measure of chronicity, defined as persistent abnormalities for three months or more.

The international consensus regarding this definition is relatively recent (Levey et al. 2011). Although Australia has been an “early adopter” of both the definitions and the standardisation of biochemical assays and reporting (Anavekar et al. 2005; Johnson et al. 2012a; Johnson et al. 2012b), some variation in these exists in the pre-consensus literature over the past twenty years both from Australia and elsewhere. Moreover, many studies of the epidemiology of kidney disease to date have relied on cross-sectional single-survey design or single-sample recruitment for longitudinal follow-up: the measure of chronicity is therefore absent and
prevalence estimates may be overestimated (Bottomley et al. 2011; Selvin et al. 2013).

Indigenous Australians have a higher prevalence of kidney disease than other Australians. In the 2012–2013 Australian Aboriginal and Torres Strait Islander Health Survey (AATSIHS), 1.8% of Indigenous survey participants from across Australia reported having kidney disease; 17.9% of those who provided urine and blood samples had either a spot UACR $\geq 2.5$ mg/mmol (for men) or $\geq 3.5$ mg/mmol (for women) or an eGFR $\leq 60$ ml/min/1.73m$^2$ or both. Comparing to the 2011–2012 Australian Health Survey and National Health Measures Survey (which were nationally representative and therefore largely non-Indigenous) and taking age differences into account, Indigenous Australians were 3.7 times as likely to report kidney disease and 2.1 times as likely to have markers of kidney disease on testing than non-Indigenous Australians (Australian Bureau of Statistics 2014).

The prevalence of kidney disease amongst Indigenous Australians varies according to where they live. In the AATSIHS, 33.6% of Indigenous people living in remote or very remote areas had markers of kidney disease, compared to 13.1% of those living in non-remote areas (Australian Bureau of Statistics 2014). This mirrors previous research showing high rates of albuminuria in remote Indigenous communities of
the Top End of the Northern Territory (Hoy et al. 2001; McDonald et al. 2004; Shemesh et al. 2007) and somewhat lower rates (albeit still higher than national rates once age-adjusted) amongst urban-living Indigenous Australians (Maple-Brown et al. 2011).

1.4.3 Mortality due to CKD amongst Indigenous Australians

CKD was the underlying or associated cause of death for 15.8% of Indigenous deaths between 2008 and 2012, and the age standardised death rate for Indigenous Australians for CKD as an underlying cause was 3.5 times the non-Indigenous rate (Australian Institute of Health and Welfare 2015). Between 2008 and 2012 kidney disease contributed 5% of the total disparity between Indigenous and non-Indigenous mortality (using underlying causes only) (Australian Institute of Health and Welfare 2014b).

1.4.4 Hospitalisation of Indigenous Australians for CKD

Because the majority of Indigenous Australians receiving RRT are treated with nurse-supported “in-centre” or “satellite” haemodialysis (and therefore recorded as “same-day” hospital in-patient stays), their high prevalence of ESKD receiving RRT is also reflected in hospitalisation rates. In 2012–2013, 45% of all hospitalisations for Indigenous Australians had a principal diagnosis of CKD (almost all for care involving dialysis): a rate of 251 hospitalisations per 1,000 population.
Based on age-standardised rates, Indigenous Australians were 10 times as likely to be hospitalised for CKD than non-Indigenous Australians. Hospitalisation rates due to CKD amongst Indigenous Australians varied greatly by jurisdiction due to differences in the rates of “same-day” dialysis visits, from 15 per 1,000 population in Tasmania to 1,140 per 1,000 population in the Northern Territory (Australian Institute of Health and Welfare 2015).

1.4.5 The Antecedents of CKD Amongst Indigenous Australians

Much has been written about the associations and causes of CKD in Indigenous Australians. A multi-determinant model has been proposed, consisting of a number of direct and indirect pathways linking kidney disease with disadvantage (Cass et al. 2004). When conceptualised in this way, ESKD can be considered the ultimate outcome of serial insults over decades from before birth into adult life.

In one well-studied very remote community of Aboriginal Australians, markers of kidney disease have been associated with low birth weight (Hoy et al. 1998), which has been subsequently linked to reduced nephron endowment (Bertram et al. 2011; Hoy et al. 2006) and glomerulomegaly (Hoy et al. 2011; Puelles et al. 2011), reduced renal volume (Singh & Hoy 2004), previous episodes of post-infectious glomerulonephritis (Hoy et al. 2014; White, Hoy & McCredie 2001), obesity (with possible
hyperfiltration) (Hoy et al. 2014), earlier-onset diabetes (Wang & Hoy 2013) and vascular damage (Hoy et al. 2012). An association between a single gene polymorphism and a marker of kidney disease in another remote Aboriginal Australian community (McDonald et al. 2002) has not yet been confirmed elsewhere.

The clear association between area-level markers of Indigenous socioeconomic status and their incidence of ESKD receiving RRT also highlights the broader societal context when considering kidney disease causation amongst Indigenous Australians (Cass et al. 2002; Cass et al. 2004). The following have been associated with and can plausibly add to explanations for higher rates of CKD and ESKD receiving RRT amongst Indigenous Australians living in remote and very remote Australia (Cass et al. 2004):

i) overcrowding in housing with poor health-related infrastructure

ii) low levels of health literacy associated with lower levels of formal educational attainment

iii) unemployment and limited disposable income in circumstances where higher nutritional quality food cost more (such as remote and very remote areas)

iv) access to and use of culturally appropriate primary health care and tertiary health care.
1.5 Outcomes of CKD Amongst Indigenous Peoples

As for Indigenous Australians, higher incidence rates of ESKD receiving RRT have been described amongst Indigenous peoples of the United States of America (Hochman et al. 2007; Hoy & Megill 1989; Megill, Hoy & Woodruff 1988; Newman et al. 1990; Pasinski & Pasinski 1987; Saran et al. 2015), Canada (Dyck & Tan 1994, 1998), and New Zealand (ANZDATA Registry 2015b; Disney 1995; Stewart, McCredie & McDonald 2004). Less common are reports of data that examine the risk of and rate of progression of earlier stage CKD amongst Indigenous peoples.

1.5.1 Outcomes of CKD Amongst Indigenous Peoples of the United States of America

The high prevalence of CKD in some of these Indigenous populations has also been described, particularly in the Zuni people of New Mexico (Hoy, Megill & Hughson 1987; Shah et al. 2003) and the Navajo people of the south-western United States of America (Hoy et al. 1996).

The most extensively studied are the Pima Indians from the Gila River Indian Community in Arizona. The studies conducted there were amongst the first to demonstrate that overt albuminuria (a UACR >300 mg/g) was a potent risk factor for a rapid decline in glomerular filtration rate (Nelson et al. 1996; Nelson et al. 1997). Subsequent reports showed that, while the incidence of proteinuria increased over time, the incidence of
ESKD declined after 1990, coinciding with improved control of blood pressure and hyperglycaemia (Pavkov et al. 2006).

1.5.2 Outcomes of CKD Amongst Indigenous Peoples of Canada

Using a population derived from ambulatory laboratory measurement of serum creatinine, with the data linked to administrative health and provincial renal program datasets, both the prevalence of measured CKD and the mortality rate for those with CKD in Alberta, Canada were estimated (Gao et al. 2007). First Nations age-, gender- and diabetes-adjusted mortality rates were between 1.58 and 1.75 times non-First Nations rates. The risk of reaching end-stage kidney disease was not examined in that study.

Similar methodology and more recent data from Alberta were used to estimate rates of progression by First Nations status and calculate the relative hazard of progression to kidney failure for First Nations compared with non-First Nations people by level of albuminuria and eGFR. Rates of progression to kidney failure were consistently 2- to 3-fold higher among First Nations people than among non-First Nations people across all levels of albuminuria and estimated GFR, adjusted for age, sex, comorbidities, rural residence, residential income quintile and recent specialist care (Samuel et al. 2014).
Using competing risks methods, a retrospective population-based cohort study of administrative data in Saskatchewan between 1980 and 2005 showed that First Nations diabetics were more likely to reach end-stage kidney disease than non-First Nations diabetics, but less likely to die without reaching end-stage kidney disease. However, when different group age structures were accounted for First Nations diabetics had both an increased risk of dying without reaching end-stage kidney disease and reaching end-stage kidney disease. First Nations peoples developed diabetes at a much younger age and therefore, due to an age-related lower cardiovascular mortality, were more likely to survive long enough for end-stage kidney disease to occur (despite a higher age-adjusted cardiovascular mortality than non-First Nations people) (Jiang et al. 2014).

1.5.3 Outcomes of CKD Amongst Indigenous Peoples of New Zealand

The earliest outcome data for kidney disease in New Zealand comes from the New Zealand glomerulonephritis study, which enrolled 803 biopsy-proven cases of glomerulonephritis in adults between 1972 and 1983 in a central register (Bailey et al. 1989). “Polynesian (predominantly Māoris)” were over-represented (relative to their background population prevalence) compared to “New Zealanders of European descent”. Five years after enrolment,
“an adverse outcome (entry into a dialysis-transplant programme, death from renal failure, nonrenal death) was more frequent for Polynesians than Europeans. The difference in survival between Polynesians and nonPolynesians was highly significant (p=0.02)” (Neale & Bailey 1990).

The higher prevalence of albuminuria amongst Māori New Zealanders with diabetes compared to “European” New Zealanders has been noted recently (Kenealy et al. 2012).

A cohort of 765 patients with type 2 diabetes who attended either diabetes specialist services or randomly selected general practitioners in 1990 and 1991 in Auckland, New Zealand was followed administratively for five years to ascertain the rate and causes of death. Māori patients were more likely to have died than New Zealander Europeans. Differences in the risk of death with ESKD as a cause were particularly stark (Simmons et al. 1999).

A retrospective cohort of 7,900 patients with diabetes identified from a regional disease register, without administrative evidence of kidney disease, was followed administratively for three years. Māori patients were much more likely than New Zealander European patients to require specialist care for kidney disease and either dialysis or transplantation;
they were no more likely to die of a renal cause than New Zealander Europeans. Their progression to these events was also much faster than their European compatriots, both before the first attendance for renal care and from this attendance to dialysis or transplantation (Joshy et al. 2009).

Recently, a four year follow-up of a 12 month randomised controlled trial of a health service intervention in 65 Māori diabetic patients with stage 3 or 4 CKD and proteinuria showed a median decline in eGFR of between 3.1 and 5.5 ml/min/1.73m²/year (using the Modification of Diet in Renal Disease equation) (Levey et al. 1999), with 74% of patients reaching a composite end-point of death, ESKD or RRT (Tan et al. 2015).

1.5.4 Relevance of International Data to Indigenous Australians with CKD

Although these observations are from the United States, Canada and New Zealand, they are relevant to Indigenous Australian peoples with kidney disease.

Patients with kidney disease from most of the Indigenous populations described (Zuni and Navajo of the United States of America, First Nations Canadians, Māori New Zealanders) have renal pathology findings that are substantially similar to those described for Indigenous
Australians (Hoy et al. 2012). These findings are characterised by glomerulomegaly, mesangial expansion with immune complex deposits and focal segmental glomerulosclerosis; a minority have the more classically described nodular glomerulosclerosis of diabetes (Dyck & Tan 1998; Hoy et al. 1993; Hughson et al. 1989; Smith et al. 1989; Smith & Tung 1985; Zwi et al. 2014). Only in Pima Indians is this “classical” pathological picture of diabetic nephropathy predominant (Kamenetzky et al. 1974). Although the cause of ESKD recorded in registry data for Indigenous peoples is most often recorded as being diabetes-related (Dyck 2001; McDonald & Russ 2003a, 2003b; Megill, Hoy & Woodruff 1988; Newman et al. 1990; Pasinski & Pasinski 1987; Stewart, McCredie & McDonald 2004), these studies of pathology suggest a better characterisation would be “diabetes-associated”. As discussed elsewhere, there is no single label that adequately describes the pathology seen in renal biopsy specimens from Indigenous peoples (Cass et al. 2004); however, it is notable that broadly similar lesions are seen in most well-studied Indigenous populations.

Primary health system arrangements are also similar for all the Indigenous populations studied, even though the broader health systems are quite different in each country. Indigenous peoples have subsidised access to health care and medication through some form of universal health insurance system within the four countries (Si et al. 2010; Smylie
et al. 2006). Cultural and language divides, and geographical remoteness, are often barriers to access to health care for each of these Indigenous groups (Smylie et al. 2006); broader socio-economic disadvantage has been well described for each of these populations (Gracey & King 2009; King, Smith & Gracey 2009).

1.5.5 Outcomes of CKD Amongst Indigenous Australians

Data about the progression and outcomes of CKD amongst Indigenous Australians is sparse. Despite the very high estimated overall prevalence of CKD (Australian Bureau of Statistics 2014) and ESKD requiring RRT amongst Indigenous Australians (ANZDATA Registry 2015b), a relatively low prevalence of patients with moderate or severe CKD (an eGFR ≤60 ml/min/1.73m²) has been found in cross-sectional community-wide surveys (Australian Bureau of Statistics 2014; Maple-Brown et al. 2011; McDonald 2003b). The reasons for this are not clear, but amongst possible explanations are that some Indigenous Australians have:

(i) a faster rate of kidney disease progression to end-stage

(ii) a higher proportion of patients reaching ESKD choosing to have RRT (perhaps because of their younger age at ESKD onset)

(iii) a higher “competing risk” of death compared to progression to moderate to severe CKD in those with earlier stage CKD and albuminuria

(iv) a tendency to relocate away from studied communities when
diagnosed with moderate to advanced CKD (Zhao et al. 2013).

In Australia, rates of progression of CKD have been examined in the people of the Tiwi Islands, with findings that higher levels of albuminuria correlated closely with a decline in eGFR (Hoy et al. 2001). In this analysis there was a mean fall in eGFR of 6.8 ml/min/year amongst 21 people with a baseline UACR between 100 and 200 g/mol and 11.6 ml/min/year amongst nine people with a baseline UACR over 200 g/mol. It should be noted that these results were based on very small numbers, a creatinine assay pre-dating traceability to the Isotope Dilution Mass Spectrometry (IDMS) standard (Levey et al. 2006) and the Cockroft-Gault formula (Cockroft & Gault 1976) for eGFR estimation.

Other clinically relevant outcomes were assessed in three separate analyses of a broader selection from the same population. Two examined all-cause mortality and “circulatory” (cardiovascular) mortality (McDonald 2003; McDonald, Wang & Hoy 1999). In these studies of 983 individuals 15 years of age or older with median follow-up of 6.6 years, overt albuminuria (a UACR of 34 g/mol or greater) was a strong predictor of all-cause mortality (unadjusted Hazard Ratio [HR] 5.2, 95% Confidence Interval [CI] 3.2–8.6; adjusted for age and sex HR 3.3, 95% CI 1.9–5.7), referent to those without any albuminuria. Overt albuminuria was an even greater predictor of circulatory death (unadjusted HR 14 [95% CI
An eGFR less than 60 ml/min/1.73m² (using the 186-Modification of Diet in Renal Disease formula [Levey et al. 2006]) increased the crude risk of all-cause death compared to those with an eGFR equal to or greater than 100 ml/min/1.73m² (unadjusted HR 8.0 [95% CI 4.0–16], adjusted for age and sex HR 1.8 [95% CI 0.79–4.1]) but had a more pronounced effect on circulatory death risk (unadjusted HR 27 [95% CI 5.7–127], adjusted for age and sex HR 5.9 [95% CI 1.0–34]).

The other analysis from the same population examined the risks of ESKD (starting RRT or dying of ESKD) or “all-cause natural deaths” (Hoy et al. 2001). Analysis of 825 individuals 18 years of age or older with mean follow-up of 5.79 years showed that all cases of ESKD arose from those with overt albuminuria at baseline, with most (14 of 16) from those with a UACR greater than 100 g/mol at baseline. Most cases of ESKD (11 of 16) also arose from those with a baseline eGFR less than 60 ml/min (using the Cockroft-Gault formula).

Data from follow-up of other cohorts of Indigenous Australian patients is limited, with recently presented data from the eGFR Follow-Up Study with mean follow-up of 2.9 years showing decline of at least 5.8 ml/min/1.73m²/year (95%CI 3.9–7.8) in eGFR in 33 participants with a baseline UACR greater than 30 g/mol (Hughes et al. 2015). This
contrasts with recently presented data from 14 year follow-up of the Australian Diabetes, Obesity and Lifestyle (AusDiab) Study, which showed that macroalbuminuria at baseline was associated with a decline of 1.7 ml/min/1.73m²/year (p<0.001) in eGFR in a largely non-Indigenous Australian population-based survey (Dunstan et al. 2002; Wyld et al. 2015). Data-linkage based follow-up of another cohort of Indigenous Australians from the city of Darwin (some of whom have CKD) has commenced but data on outcomes are not yet available (Barr et al. 2015; Cunningham et al. 2006; Maple-Brown et al. 2011).
1.6 Outcomes of ESKD Receiving RRT Amongst Indigenous Peoples

For those reaching ESKD and commencing RRT, what is their outcome? Some minority and disadvantaged populations have been well-studied (Feehally 2010), notably African Americans (Pugh, Tuley & Basu 1994) but also other non-Indigenous minority populations in the United States of America (Frankenfield et al. 2009; Wong et al. 1999) and the United Kingdom (Roderick et al. 2009). Most have reported that mortality is either the same or lower in ethnic minorities receiving RRT than the dominant (usually Caucasian or white) patients, despite the reverse being the case for those without kidney disease (Caskey 2013; Kalantar-Zadeh et al. 2007; Rhee et al. 2014). Rates of transplantation lower than the majority population have also been commonly reported (Caskey 2013; Hall et al. 2011; Hall et al. 2005; Purnell et al. 2013; Rhee et al. 2014; Udayaraj et al. 2010), although this may no longer be the case for African Americans in the United States (Sood et al. 2015).

1.6.1 Outcomes of ESKD Receiving RRT Amongst Indigenous Peoples of the United States of America

The survival of American Indians receiving RRT for ESKD was first described for Zuni and Navajo Indians in 1989 (Hoy & Megill 1989). They found an annual death rate of 6% among Navajo Indians without diabetes
receiving dialysis for ESKD, and 22% for those with diabetes. They suggested that results among Navajo renal transplant recipients receiving cyclosporine-based therapy were “good” (although most were non-diabetic). Subsequent survival analysis of 136 diabetic Pima Indians beginning RRT for ESKD between 1973 and 1990 showed median survival improving from 31 months (95% CI 11–48) in 1973–1981 to 44 months (95% CI 32–56) in 1982–1990. After adjustment for age, sex, duration of diabetes and RRT modality the second half risk of death was 0.54 times that of the first half (95% CI 0.33–0.88), attributed in part to a reduction in deaths in the first 90 days of RRT (Nelson et al. 1996).

Crude analysis of 1987 Health Care Finance figures showed that “Native Americans” appeared to have similar rates of deceased donor and live donor transplantation to “white” Americans, in contrast to the lower rates seen amongst black Americans (Kasiske et al. 1991). Data about the outcomes of those Native Americans transplanted were not available.

In a study linking administrative and registry data about 27,876 centre-treated haemodialysis patients between 1995 and 1998 inclusive, Native Americans were no more likely to be hospitalised or die than “whites”, and had equivalent or better markers of dialytic care (Frankenfield et al. 2004).
A prospective observational cohort study of 6,677 haemodialysis patients in the United States between 1996 and 2001 inclusive showed that while unadjusted mortality was lower for all “racial/ethnic minority categories” (including Native Americans) than the majority white/non-Hispanic group, this difference was lost after adjustment for age, sex, comorbidity, nutritional and laboratory values. Of note, ethnicity mortality rates were not influenced substantially by different rates of kidney transplantation (Robinson et al. 2006). Competing risks methods were not used.

An analysis of United States Renal Data System (USRDS) registry data about 503,090 people aged 18–64 years old who started haemodialysis between 1995 and 2006 inclusive (followed to the end of 2008) showed that compared to “whites”, “American Indian/Alaskan Native” patients had a reduced chance of deceased donor kidney transplantation (unadjusted HR 0.39 95% CI 0.35–0.43). Most of this difference was not accounted for by measured factors (HR 0.56 95% CI 0.51–0.61 after adjustment for age, sex, comorbidities, functional status, drug or tobacco use, body mass index category, albumin and haemoglobin level, health insurance category and residential zip code area-level poverty score, household linguistic isolation score and Organ Procurement Organisation region). The reduced rate of transplantation amongst American Indian/Alaskan Native patients reflected both lower rates of waitlisting
and lower rates of transplantation amongst those waitlisted (Hall et al. 2011).

Most recently, analysis of national RRT data in the USRDS Annual Data Report estimated the age, sex and primary diagnosis adjusted five year survival from 2007–2012 amongst Native Americans at 46.8%, similar to African American survival (45.3%) and greater than “white” survival (38.8%, 95% CI not provided) (Saran et al. 2015).

1.6.2 Outcomes of ESKD Receiving RRT Amongst Indigenous Peoples of Canada

Work examining the outcome of patients with diabetes receiving RRT for ESKD in Saskatchewan Province in Canada between 1981 and 1990 showed overall median survival of less than two years for both “native” and “non-native” patients, with no differences in survival seen in crude survival analysis or adjusted for age, sex, diabetes type or RRT modality. The authors noted:

“Whereas nondiabetic native people with end stage renal disease were almost as likely as their non-native counterparts to receive a transplant (28% vs. 35%), native people with diabetes were only half as likely as non-native diabetic people to receive a renal graft (14% vs. 27%). This finding appeared to be due to a larger
proportion of younger people with insulin dependent diabetes mellitus in the non-native diabetic population.” (Dyck & Tan 1994)

In subsequent analysis of the outcome of patients with non-diabetic ESKD receiving RRT in Saskatchewan over the same time period, crude mortality rates, causes of death and transplantation rates were similar in the “native” and “non-native” populations, although the authors were unable to adjust for differences in age (Dyck & Tan 1998).

Data for those starting RRT for ESKD in Alberta, Manitoba and Saskatchewan in the subsequent decade (1991–2000 inclusive) were subsequently evaluated, examining the relationship between Aboriginal status and patient survival and the likelihood of transplantation. A greater risk of death for Aboriginal dialysis patients (HR 1.15 [95% CI 1.02–1.30]) was not observed after adjustment for comorbid conditions (adjusted HR 0.89 [95% CI 0.77–1.02]). However, Aboriginal patients were less likely to receive a kidney transplant, even after adjustment for possible confounders (HR 0.43 [95% CI 0.35–0.53]) (Tonelli et al. 2004).

These findings were confirmed in an analysis of all Canadian patients starting RRT from 1990–1998. After adjustment for patient differences in age, sex, primary diagnoses and comorbidities, all minority ethnic groups were less likely to receive kidney transplants than majority “white”
patients, including “aboriginals” (HR 0.54 [95% CI 0.45–0.63]) (Yeates et al. 2004).

The reasons for this disparity in transplantation rates were explored shortly thereafter. All patients who had been established on haemodialysis for six months or more in Alberta were interviewed by a physician and data for transplantation referral, assessment process and waiting list status sourced from transplant programs. After adjustment for age, Aboriginal patients were not significantly less likely to be referred for transplantation than non-Aboriginal patients (HR 0.80 [95% CI 0.59–1.08]). However, Aboriginal patients were more likely than non-Aboriginal patients to be in the process of workup (69.9% vs. 26.9%, p<0.01) and less likely to be deemed suitable for transplantation (30.4% vs. 73.3%, p<0.01). As a result, Aboriginal patients were less likely to be active on the waitlisting for transplantation (HR 0.46 [95% CI 0.27–0.78]) (Tonelli et al. 2005).

Further work also suggested that, in Canada, the distance from a transplant centre did not explain the lower rate of transplantation among Aboriginal people, evident in all regions of Canada (Tonelli et al. 2006). This quantitative analysis contradicts and contrasts with a small qualitative study of Canadian kidney health professionals, which identified the most notable reported barrier to transplantation for
Aboriginal patients being their remote living location (Anderson et al. 2009).

Analysis of national RRT registry data from 2000 to 2009 confirmed that Aboriginal adult dialysis patients continued to be less likely to receive a kidney transplant than Caucasian patients (Cox HR 0.66 [95% CI 0.57–0.77]), that younger adult Aboriginal patients were less likely to receive a transplant than similar Caucasian patients, and that using competing risks methods to take differing mortality risks into account had an important modifying effect on estimates of the likelihood of transplantation compared to standard Cox techniques (Promislow et al. 2013).

This disparity in the likelihood of transplantation was also confirmed for Aboriginal child patients using national RRT registry data (excluding Quebec) from 1992 to 2007. Compared to “white” children, Aboriginal children were less likely to receive a transplant (HR 0.54 95% [CI 0.40–0.74]) and less likely to receive a transplant from a living donor (HR 0.36 [95% CI 0.21–0.61]), with a longer time from start of RRT to transplantation. Unadjusted graft and patient five- and ten-year survival were similar between groups (Samuel et al. 2011).
Data about the outcome of specific dialysis modalities for Aboriginal Canadians is also available. Despite peritoneal dialysis appearing to be a “dialysis modality of choice” for a remote-dwelling Indigenous population, Aboriginal patients in Manitoba, Saskatchewan and Alberta from 1990 to 2000 were less likely to start therapy on peritoneal dialysis than white patients (HR 0.51 [95% CI 0.40–0.65]). Adjusted survival appeared similar for Aboriginal and white peritoneal dialysis patients, and for Aboriginal haemodialysis patients (Tonelli et al. 2005). In contrast, data from Manitoba alone from 1997 to 2007 showed that mortality was increased among Aboriginal patients receiving peritoneal dialysis compared to non-Aboriginal patients, regardless of urban or rural place of residence (Sood et al. 2010). Subsequent analysis of national RRT registry data from 2000 to 2009 demonstrated that while Aboriginal patients on haemodialysis had a comparable mortality risk to Caucasians (HR 1.04 [95% CI 0.96–1.11]), those receiving peritoneal dialysis had a higher mortality risk (1.36 [95% CI 1.13–1.62]) (Sood et al. 2012).

1.6.3 Outcomes of ESKD Receiving RRT Amongst Indigenous Peoples of New Zealand

The first comparison of survival between non-Indigenous and Māori New Zealanders with ESKD came from a retrospective review of records from a single centre between 1975 and 1988. Māori were “disproportionately over-represented” in the group with diabetes. Those with diabetes,
“regardless of race”, had two and five year actuarial integrated treatment patient survival of 53% and 24.1% respectively, compared with non-diabetic figures “exceeding” 85% and 75% respectively. Only stratified actuarial survival methods were used: regression methods were not (Neale & Bailey 1990, Thompson et al. 1991).

A more recent comparison of five year survival between non-Indigenous New Zealanders and Māori (limited to those receiving treatment in New Zealand, and accounting for group differences using regression methods) was included in the ANZDATA Registry report in 2008 (Jose et al. 2008). This demonstrated that there had been a significant improvement in five-year survival for Māori patients starting RRT from 2001–2007 compared to 1991–2000, with a corresponding reduction in disparity in five-year survival outcomes between non-Indigenous New Zealanders and New Zealand Māori (although the difference in five-year survival remained significant for the 2001–2007 period). When censored at time of first transplant (that is, limited to time on dialysis only) there were no significant differences in five year survival between non-Indigenous New Zealanders and Māori for either time period. Adjustment for age, sex, primary renal disease and recorded comorbidities did not alter these conclusions. Following first transplantation between 1991 and 2000, a small but significant difference in five year patient survival between non-Indigenous New Zealanders and Māori without adjustment was no longer
apparent after adjustment for age, sex, primary renal disease and comorbidities. This disparity in survival was also seen after first transplants between 2001 and 2007 but was not accounted for by adjustment for recorded group differences.

1.6.4 Relevance of International Data to Indigenous Australians with ESKD

Using national United States, Canadian, Australian and New Zealand RRT registry data from 1995 to 2005 inclusive, Yeates and colleagues compared the likelihood of transplantation of “white” patients aged 18–64 years with that of similar Indigenous patients in each country. The authors concluded that:

“Compared with white patients, the adjusted likelihood of receiving a transplant for indigenous patients was significantly lower in Australia (HR 0.23), Canada (HR 0.34), New Zealand (HR 0.23), and the United States (HR 0.44). In all four countries, indigenous patients had significantly longer overall median waiting times compared to white patients.” (Yeates et al. 2009)

These findings are tempered by several caveats:

(i) a substantial and significant variation in the transplant rate for referent white participants between countries, which was highest for New Zealand and lowest for the United States of America (and
therefore affected the absolute Indigenous transplant rate in each country)

(ii) an inability to examine the effect of residential remoteness on transplantation, due to a lack of access to accurate information about residence location across all data sets

(iii) the inclusion of non-Indigenous Pacific Islanders in the “Indigenous” group for New Zealand

(iv) the exclusion of other ethnic groups from analysis

(v) the use of “standard” Cox proportional hazards regression models (which assume non-informative censoring) rather than competing risks methods taking differing Indigenous and non-Indigenous mortality rates into account.

Nevertheless, the consistency in disparity in access to kidney transplantation for Indigenous peoples across all four countries is striking.

There is no similar work examining variation in the risk of death across ethnicities for patients with ESKD (whether receiving dialysis or a kidney transplant) between countries. Conceptually, concerns raised about the role of various confounders and biases in the comparison of RRT incidence rates between countries (such as changing demographic patterns, different competing risks and propensities for treatment, for example) (McDonald et al. 2005; Stewart et al. 2007) also apply to the
international comparison of outcomes for those who have commenced RRT.

Despite a lack of direct comparison, consistent themes in the literature from the United States, Canada and New Zealand about outcomes for Indigenous peoples with ESKD receiving RRT emerge:

(i) at least equal five-year survival on dialysis overall compared with non-Indigenous compatriots (adjusted for age, sex and disease burden differences), particularly recently

(ii) consistently lower rates of kidney transplantation compared to non-Indigenous compatriots (adjusted for age, sex and disease burden differences)

(iii) overall, simpler “classical” time-to-event analytic methods have been used, with competing risks methods only relatively recently used in one analysis from Canada (Promislow et al. 2013).

1.6.5 Quantitative Outcomes of ESKD Receiving RRT Amongst Indigenous Australians

The outcomes for Indigenous Australian patients requiring RRT from 1983 to 1992 were first highlighted by Disney in 1995 (Disney 1995). Adjusted for age, sex, dialysis modality and primary renal disease, Aboriginal dialysis patients had a higher mortality risk than non-Indigenous patients (HR 1.66 [95% CI 1.27–2.16]). Their likelihood of
transplantation was not examined. Both Māori and Indigenous 
Australian transplant recipients had significantly worse (unadjusted) 
graft and patient survival than the “white (European descent) racial 
group” (Disney 1995).

McDonald and Russ used national RRT (ANZDATA) registry data to 
examine the incidence, treatment and outcomes of RRT for Indigenous 
Interestingly, Indigenous Australian patients were compared with Māori 
(whether they started treatment in Australia or New Zealand), Pacific 
Islanders (non-Indigenous in either country) and a combined group of all 
other non-Indigenous Australians and New Zealanders. Both Indigenous 
Australians (HR 1.7 [95% CI 1.5–1.9]) and Māori (HR 1.7 95% CI 1.5–1.9) 
had an increased risk of death after starting RRT compared to the non-
Indigenous group, adjusting for age, sex and co-morbidities; Pacific 
Islanders did not (HR 1.0[ 95% CI 0.86–1.2]). In a multiple logistic 
regression analysis, Indigenous groups (combined, including Pacific 
Islanders) were less likely than the non-Indigenous group to be waitlisted 
for transplantation (Odds Ratio [OR] 0.48 [95% CI 0.42–0.54]). Once 
waitlisted, the combined “Indigenous” group was less likely to receive a 
transplant, with similar rates among each of the indigenous groups 
(overall OR 0.35 [95% CI 0.29–0.43]). “Indigenous” transplant recipients 
had worse five year graft survival but similar five year patient survival to 
the non-Indigenous group (both unadjusted), with increased risk of death
after deceased donor transplantation (compared to Indigenous waitlisted patients on dialysis) in the first three months after transplantation and a reduced risk of death from six months onwards (adjusted for age strata only) (McDonald & Russ 2003b).

McDonald went on to compare transplant outcomes between Indigenous and non-Indigenous recipients in Australia between 1997 and 2003 using ANZDATA. He demonstrated that both unadjusted graft and patient survival was around three times worse for Indigenous than non-Indigenous patients. Correcting for age, sex and recorded comorbidities, Indigenous patients had almost twice the rate of graft loss of non-Indigenous patients (HR 1.95 [95% CI 1.22–3.11]), due to both graft loss with survival and death with a functioning graft. While Indigenous recipients faced substantial disadvantages in comorbidities (particularly coronary artery disease and diabetes) and organ allocation (greater HLA mismatches, higher peak panel reactive antibody levels, longer waiting time), only comorbidities were accounted for in the comparison. A comparison between Indigenous transplant recipients and Indigenous waitlisted patients on dialysis was inconclusive, lacking statistical power (McDonald 2004).

Some of the reasons for poorer transplant outcomes for Indigenous compared to non-Indigenous Australians were subsequently explored in
an analysis of all transplant recipients from the Northern Territory of Australia between 1984 and 2004 (Rogers, Lawton & Jose 2006). The authors confirmed longer waiting times, greater sensitisation and human leukocyte antigen (HLA) mismatch and overall poorer unadjusted graft survival for Indigenous patients (HR 4.13 [95% CI 2.0–8.5]) compared to non-Indigenous patients, with patient death with a functioning graft being the main reason for graft loss. In multivariate logistic regression, only five or more HLA mismatches (and not being Indigenous, peak panel reactive antibody level, waiting time over four years, gender or age over sixty) was associated with graft loss (OR 2.3 [95% CI 1.2–4.2]). Compared to non-Indigenous recipients, Indigenous patients were more likely to have a transplant biopsy, more likely to have acute rejection (Risk Ratio [RR] 2.5 [95% CI 1.8–3.5]), bolus doses of steroids (2.0 vs. 1.2 boluses per patient, p<0.01), monoclonal antibody treatment for rejection (RR 2.1 [95% CI 1.8–2.5]), hospitalisation (RR 3.9 [95% CI 3.2–4.9]) with a longer length of stay (mean 10.3 vs. 3.0 days, p<0.001) and infection post-transplant (RR 4.1 [95% CI 3.5–4.7]), particularly bacterial and fungal infections. Infection was the dominant cause of death for Indigenous patients (17 of 23 deaths); no non-Indigenous patients died during the study period (Rogers, Lawton & Jose 2006).

Temporal trends in outcomes for both Indigenous and non-Indigenous Australian RRT patients were first reported in the 2008 ANZDATA report (Jose et al. 2008). A comparison unadjusted for population
differences suggested that a disparity in RRT five year survival between Indigenous and non-Indigenous patients evident for the 1991–2000 period had closed for the 2001–2007 period. When population differences in age, sex, primary renal disease and recorded comorbidities were accounted for, this disparity was more pronounced for the 1991–2000 period and was still apparent (although perhaps narrower) for the 2001–2007 time period. These findings of continued Indigenous:non-Indigenous disparity in five year survival were still apparent with censoring at time of first transplant (that is, limited to time on dialysis, but noting that competing risks methods were not used) and were even more starkly apparent when comparing survival following first transplant, after adjustment for differences in age, sex, primary renal disease and comorbidities.

The disparity in five-year survival was also explored in Indigenous and non-Indigenous Australian patients over 64 years old who started RRT between 2001 and 2011 inclusive. Unadjusted five year survival was 27% for Indigenous and 35% for non-Indigenous patients; adjustment for age, gender, primary renal disease, comorbidities, body mass index, smoking, late referral and initial treatment modality revealed an increased risk of death for Indigenous patients (HR 1.20, [95% CI 1.02–1.41]) (McKercher et al. 2014).

Marley and colleagues compared the mortality rates of Indigenous haemodialysis patients from the Kimberley region of Western Australia
with other Indigenous Australian haemodialysis patients and non-Indigenous Australian haemodialysis patients receiving treatment between 2003 and 2007 inclusive (Marley et al. 2010). Compared to non-Indigenous Australians, they found that patients from the Kimberley had a mortality rate ratio (MRR) of 0.53 (95% CI 0.35–0.80) without adjustment, and an MRR of 0.87 (95% CI 0.57–1.33) after adjustment for age, sex and comorbid conditions. The mortality rate ratios for other Indigenous haemodialysis patient groups were higher but not significantly so (for the Northern Territory MRR 1.17 95% CI 0.98–1.39 after adjustment).

The national experience of outcomes with peritoneal dialysis between 1999 and 2003 by Indigenous status has also been explored, demonstrating higher rates of peritonitis both before and after adjustment for age, body mass index category and the peritoneal dialysate-to-plasma ratio (Lim, Johnson & McDonald 2005). In subsequent analysis of adult patients commencing peritoneal dialysis between 1995 and 2008 in Australia, stratified by remoteness of residence and Indigenous status and corrected age, sex, primary renal disease, body mass index category, comorbidities and dialysis era, remote-origin Indigenous patients had higher rates of peritonitis (HR 1.92 [95% CI 1.69–2.18]), peritonitis-related mortality (HR 2.13 [95% CI 1.13–4.00]) and all-cause mortality (HR 1.61 [95% CI 1.34–1.93]) (Lim et al. 2011).
1.6.6 Qualitative Outcomes of ESKD Receiving RRT Amongst Indigenous Australians

A rich and disturbing literature about outcomes for Indigenous ESKD patients requiring RRT using qualitative research methods has grown since 1995, when 11 Indigenous previous recipients of kidney transplants (most without functioning grafts) through one centre in Queensland were interviewed (Bennett et al. 1995). All but three lived away from their home due to their disease, and all displaced patients strongly wished to return home to their “own country” and their families: separation from kin and country was felt by respondents to be a significant factor in poor outcomes.

In 1998 Devitt and McMasters published their findings of interviews with 54 Aboriginal ESKD patients receiving RRT in Central Australia (Devitt & McMasters 1998a, 1998c). Amongst the issues explored were various factors influencing attendance at haemodialysis, low levels of patient knowledge about their treatment, disjunction between patients and their medical carers, and the importance of dislocation from family and social support (as 91% were from communities remote from treatment facilities). They described a “debilitating isolation of the patient”, which “is itself a life-threatening factor” (Devitt & McMasters 1998c). The powerful and moving stories from these patients were compiled and
edited (Devitt & McMasters 1998b), as well as explored and discussed in depth (Devitt & McMasters 1998a).

Interviews with 6 Indigenous dialysis patients receiving treatment in Perth, Western Australia in 2007 highlighted their overwhelming sense of disempowerment due to dependency on treatment and health care professionals, exacerbated by cultural differences and a perceived lack of education (Burnette & Kickett 2009). The authors also noted their experience of dislocation, which included geographical relocation, inability to access dialysis at home, missing family, dislocation of culture and the value of kinship (Burnette & Kickett 2009).

As part of the national mixed-methods Improving Patient Access to Kidney Transplantation Study (IMPAKT), in 2005–2006 143 Indigenous and 95 non-Indigenous ESKD patients from nine renal units across Australia (which together treat the majority of Indigenous ESKD patients receiving RRT) were interviewed about their personal history of illness, social and psychosocial context, attitudes to treatments including transplantation, adequacy of information and communication, and satisfaction with services (Devitt et al. 2008). As subsequently described:

“Patient interviews suggested several factors shaped their treatment experience including: the impacts of late diagnosis; the consequences of family separations necessitated by moving to
treatment centres; the physical and psychosocial demands of
dialysis; and, ineffective communication between patients and
their care providers. None of these factors were unique to
Indigenous patients: some non-Indigenous patients also had
communication difficulties, some were also diagnosed at a late,
acute stage, some endured family separations and so on. But, in
stark contrast to Indigenous patients none were likely to
experience the combined, interactive and continuing effects of all
these factors. The conjunction of treatment-related circumstances,
with a profile of disadvantage and social marginalisation, posed a
substantial challenge for Indigenous patients to engage with their
treatments.” (Anderson et al. 2012a)

These findings were echoed in subsequent work in a single outer regional
setting in New South Wales, where 18 Aboriginal patients receiving
haemodialysis were interviewed (Rix et al. 2014). Six themes emerged in
this analysis: the shock of late diagnosis and starting dialysis, the
development of ambivalent attitudes to treatment; the importance of
family as motivation and support, the lack of cultural safety in acute
hospital settings, poor communication from service providers, and a
strong desire to educate others to prevent kidney disease.
1.7 Unresolved Issues

1.7.1 Outcomes of CKD Amongst Indigenous Australians

The existing literature about the outcomes of Indigenous Australians with CKD (see section 1.5.5) has relied upon data from one small remote community in the Top End of the Northern Territory of less than 1000 adults and a particularly high incidence rate of ESKD requiring RRT. This is in contrast with province-wide work from Saskatchewan and Alberta in Canada, using administrative data linked to laboratory and national RRT registry data (see section 1.5.2).

The highest incidence rate of ESKD requiring RRT amongst Indigenous Australians occurs in the Northern Territory. What is not clear is whether this high burden is due to:

(i) a high background incidence of CKD overall
(ii) a high rate of progression of CKD
(iii) a lower competing risk of death (compared to the risk of ESKD)
(iv) a high uptake of RRT
(v) a combination of these various factors.

Answering most of these questions would likely require a jurisdictional-level study of linked administrative, laboratory and RRT registry data, similar to the Canadian work. However, the first two may be able to be answered regionally using laboratory data alone.
1.7.2 Outcomes of ESKD Amongst Indigenous Australians

As mentioned (see section 1.6.5), the survival outcomes for all Indigenous Australians with ESKD requiring RRT have been studied up to 2007. It appeared that disparities in RRT patient survival were narrowing; the “gap” was closing in patient survival while a substantial disparity in kidney transplantation rates persisted.

Substantial research and infrastructure investments to improve this situation have been made since the mid-1990s, not only in the Northern Territory but across Australia (Australian Health Ministers Conference 2006; Carruthers & Warr 2004; Devitt et al. 2008; Gorham, Cass & Snelling 2001; Gorham, Wagner & Jose 2005; Kneipp et al. 2004; Marley et al. 2010; Villarba & Warr 2004). Have these investments subsequently born fruit? In detail:

(i) has Indigenous RRT survival “closed the gap” with non-Indigenous survival in Australia?

(ii) if there is a disparity, is this due to poor dialysis survival, poor transplant survival or low rates of transplantation?

(iii) does remoteness of residence play a role in poorer quantitative outcomes for Indigenous patients?

(iv) do Indigenous ESKD patients experience survival benefits from transplantation?
given that “non-compliance” is a major reason for non-referral for transplantation and transplantation rates are very low for Indigenous Australians (particularly so in the Northern Territory), what is the pattern of dialysis attendance across the Northern Territory haemodialysis population?

(vi) are people who have fewer haemodialysis treatments in the Northern Territory more likely to die, more likely to be hospitalised for other illnesses or less likely to receive a kidney transplant?

While the first four of these questions can be answered exclusively with national RRT registry data, the last two require access to administrative hospital and health department data linked to RRT registry data.

1.8 Methodology

1.8.1 The Use of Existing Data

The work included in this thesis relies on the analysis of existing data. The analysis of existing data is an attractive initial proposition when examining the outcomes of a disadvantaged, diverse, disparate and dispersed population such as Indigenous Australians. As no new data need to be collected, there is no further imposition upon the research subjects and the costs of research are minimal. However, existing data have almost always already been collected for another (primary) purpose: analysis of existing data for a secondary purpose is usually somewhat
more challenging as the data structure and definitions were designed without the secondary purpose in mind (Rothman, Lash & Greenland 2012).

Amongst the substantial data collected routinely and collated about patients and their treatment in Australia are laboratory data, primary care and hospital administrative data and (in certain cases) registry data. In the case of CKD in Australia in the 21st century, there are several advantages:

(i) the widespread adoption of a standardised definition and staging system for CKD (Levey et al. 2011; Mathew 2011)

(ii) the standardisation of serum creatinine assays (Anavekar et al. 2005) and the use of International Classification of Disease 10th Edition (Australian Modification) (ICD-10-AM) coding definitions for hospital administrative data, with increasing refinements over several editions (Henderson, Shepheard & Sundararajan 2006)

(iii) the existence of a “complete” national registry of all patients receiving maintenance RRT for ESKD (the ANZDATA Registry)

(iv) existing datasets that often have longitudinal data, allowing the analysis of trends and changes over time.

However, there are several difficulties to the use of existing data to examine questions about CKD in Australia currently:
(i) a largely privatised primary health care system (despite a
universal health insurance scheme) has dispersed and disjointed
data systems
(ii) the relatively recent adoption of computerised patient records in
primary health care, particularly in remote communities
(iii) rigorous and highly restrictive processes for the use of centrally-
collated national universal health insurance and hospital
administrative data for research purposes
(iv) research data linkage systems still in development phase in most
state or territory jurisdictions.

As a result, research about CKD in Australia that uses existing clinical or
administrative data has been limited; most observational research has
focused on those with ESKD receiving RRT, due to the availability of data
through the ANZDATA Registry.

1.8.2 Time-to-Event Analytical Methods

The techniques used to analyse and present information about outcomes
in observational health research have evolved over recent years. The non-
parametric life table method of Kaplan and Meier (Kaplan & Meier 1958)
and Cox’s semi-parametric proportional hazards regression method (Cox
1972) are still the most widely used. However, both methods assume
“non-informative censoring”: that is, that those censored from the study
due to incomplete follow-up (who have not suffered the event of interest) have the same chances of suffering the event of interest (despite not being followed up) as those continuing in the study (Bland & Altman 1998).

This becomes an issue when two groups are being compared that have differing probabilities of both the event of interest and another “competing” event: a “competing risk”. As has been demonstrated by others in various contexts in nephrology epidemiology, if “classical” Kaplan-Meier or Cox methods are used in this situation then the risks of the event of interest will be overestimated, particularly if the “competing risk” (of the other event not of primary interest) is considerable or not trivial (Lim et al. 2010; Noordzij et al. 2013; Teixeira et al. 2013; Verduijn et al. 2011).

An example demonstrated in this thesis is the comparison of Australian Indigenous and non-Indigenous dialysis patients, who have differing probabilities of both death and transplantation. Analyses of either the likelihood of death or transplantation that do not take the other “competing risk” into account will lead to overestimates of the probability of the event of interest in both groups, and therefore an underestimate of any differences in the probability of the event of interest between groups. Competing risks methods (such as those of Coviello and Boggess (Coviello & Boggess 2004), or the proportional hazards regression method of Fine
and Gray (Fine & Gray 1999) are therefore essential when accurately determining disparities in outcome between groups on occasions where there is more than one outcome and the probabilities of these outcomes differ between groups.

1.8.3 Confounding

Another key issue in analysis is the problem of comparison of two groups that are quite different in measured characteristics. As demonstrated in this thesis, Indigenous and non-Indigenous patients with ESKD receiving RRT are demonstrably quite different. The methods most often used to control for this confounding in observational research include restriction, stratification, statistical adjustment and matching.

Restricting analysis to a subset of the data with common characteristics is used in Chapter Three, which describes the likelihood of death or transplantation in the subset of adult patients who are of “transplantable age” — 18 to 64 years of age, inclusive.

Stratification is another relatively transparent way of recognising and controlling for confounders. In some circumstances, the use of interaction variables between the “main effect” and potentially confounding variables can be used as a form of stratification to demonstrate the differing effects of levels of the confounding variable on the main effect. This can be useful
even when including the interaction term in the model is not statistically significant. In this thesis, non-significant interaction terms are used in Chapters Two to Five inclusive to demonstrate possible differences in the effects of remoteness and the era of commencement of RRT on Indigenous and non-Indigenous patients' outcomes.

Statistical adjustment using multivariable analysis is the only feasible way of controlling for many potentially confounding variables at one time. In this thesis the main methods used are the proportional hazards regression techniques of Cox, and Fine and Gray (for analysis of competing risks).

Matching can also be used to create similar groups for comparison. However, it has traditionally been difficult to match subjects on more than a few variables because of practical difficulties in finding enough subjects who match all of the criteria. However, matching on a score of the propensity for a particular treatment can be a way of using many variables: the score is created using all the variables (except the variable of interest, a particular treatment) in a logistic regression model to generate the odds (and through transformation the probability) of a subject receiving the treatment. The technique assumes that those with similar scores (some of whom had the treatment, and some of whom did not) had a similar chance of receiving the treatment (based on the other
measured variables): the “conditional independence assumption” (Austin 2011; Rubin 1997). In Chapter Four of this thesis, this “propensity score matching” technique is used to compare the outcomes of patients who received a kidney transplant with those who continued on dialysis therapy, stratified by Indigenous status.

Of course, all of these techniques can only control for those potential confounders that have been measured and exist as variables within the dataset. Unmeasured confounders that are distributed unevenly between comparison groups would introduce bias. Very recently sensitivity analysis techniques for the effects of unmeasured confounders have been discussed in the literature of renal epidemiology using ANZDATA registry data (Kasza et al. 2015), but are not explored in this thesis.

1.8.4 Measurement of potential confounders

Because many Indigenous people live in regional, remote and very remote areas of Australia, remoteness of residence is a potential confounder when Indigenous outcomes are considered. This is a particularly important issue given that the incidence of ESKD requiring RRT amongst Indigenous Australians varies with remoteness (Cass et al. 2001; McDonald, Jose & Hurst 2013; Preston-Thomas, Cass & O'Rourke 2007). Remoteness in Australia is generally measured using the Accessibility/Remoteness Index of Australia (ARIA+), a continuous
varying index with values ranging from 0 (high accessibility) to 15 (high remoteness), based on road distance measurements from over 12,000 populated localities to the nearest service centres in five categories based on population size. For most health sector analyses, this leads to the creation of a five-category classification of remoteness in Australia: major cities, inner regional, outer regional, remote and very remote areas (Australian Population and Migration Research Centre 2015). This classification is used throughout this thesis.

Compared to non-Indigenous Australians, Indigenous people have much lower levels of school retention and attainment, are more likely to be unemployed, homeless or living in overcrowded houses, much more likely to be imprisoned and have a lower disposable income (Australian Institute of Health and Welfare 2015). As a result, socioeconomic circumstances are likely confounders when considering Indigenous outcomes (an issue that has been raised regarding minority non-Indigenous populations overseas (Caskey 2013; Hall et al. 2008; Morton et al. 2015). However, because in northern Australia the majority of Indigenous Australians cluster prominently in the lowest decile of the most commonly used Index of Relative Social Advantage or Disadvantage (IRSAD), current available area-based summary data are not useful for teasing out the effect of this confounder (Kennedy & Firman 2004). In addition, applying such area-level socioeconomic status measures from
the whole population to Indigenous residents creates an “ecological fallacy” bias: Indigenous people suffer a high level of social and economic disadvantage in Australia regardless of whether they live in high or low socioeconomic status areas (Kennedy & Firman 2004). Cass and colleagues successfully overcame these issues with Indigenous-specific Australian Bureau of Statistics census data (Cass, Cunningham & Hoy 2002; Cass et al. 2002) that is no longer available. Research to deal with socioeconomic measurement issues amongst Indigenous Australians is still in its infancy (Biddle 2009): as a result it has not been possible to address socioeconomic status further in this thesis.

1.8.5 Bias

Indigenous Australians receiving RRT for ESKD are much less likely to receive a kidney transplant than similar non-Indigenous Australians, as explored in Chapter Three of this thesis. This introduces the possibility of indication bias, also known as confounding by indication — a type of selection bias — when considering treatment modality restricted patient outcomes (Psaty et al. 1999; Psaty & Siscovick 2010). For example, when Indigenous Australian ESKD patients are less likely to receive a kidney transplant, those few that do receive a transplant may be considered to have a better prognosis than apparently similar non-Indigenous patients simply because they are more highly selected (based on criteria that are not measured within the dataset). Those Indigenous patients who do not
receive a kidney transplant and remain on dialysis may be considered to also have a better prognosis than apparently similar non-Indigenous patients remaining on dialysis, as they will include patients who, had they been non-Indigenous, would have received a kidney transplant and not remained on dialysis. This is why Chapter Two comprises an analysis of all patients commencing RRT in Australia, regardless of initial or subsequent modality of treatment.

Immortal time bias is a problem when comparing time-dependent treatments (Liu et al. 2012; Shariff et al. 2008). An example (with solution) is presented in Chapter Five of this thesis, where patients who received a kidney transplant are compared with those remaining on dialysis treatment. Those who received a deceased donor kidney transplant (the majority) by definition survived on dialysis treatment for the time before transplantation. This time is “immortal” compared to time from commencement of treatment for those receiving dialysis only, and if included would introduce bias that is likely to exaggerate the survival benefit of transplantation over dialysis (Kim 2010). Solutions proposed to minimise immortal time bias include matching and analysis using time-dependent covariates (Shariff et al. 2008). Matching has been used to minimise the problem in Chapter Five of this thesis.
1.8.6 Ethics in Indigenous Health Research in Australia

In 2004 Thomas published “Reading Doctors’ Writing: race, politics and power in Indigenous health research 1870–1969” (Thomas 2004). In the introduction, he explained:

“Indigenous health research and the brutal history of colonialism in Australia are forever entangled: they are not identical, merged, parallel nor independent, but intricately and variously enmeshed.” (p. xiv)

Later, in concluding he pointed out:

“In spite of the enormous changes in the late 1960s and since — in Indigenous health research, Indigenous health care services and the politics of the relationship between Indigenous and non-Indigenous Australians — many elements of the stories of this early research endure. This history of the seemingly distant and different past still matters.” (p. 135)

In response to this history, the National Health and Medical Research Council has published guidelines for the ethical conduct of Aboriginal and Torres Strait Islander health research (NHMRC 2003). Two central concepts discussed in the guidelines are reciprocity and respect, which imply engagement with Indigenous communities in every step of the research pathway from conception and design through management to outcome and output (Jamieson et al. 2012). This is challenging for
researchers, particularly when state, territory or national research is planned: as of 2015, there are no representative bodies of Indigenous Australian peoples or communities with which researchers can consult and engage (such an elected and representative body was abolished by the Australian Government in 2005). While a process of discussion and dissemination of results from research in this thesis is planned in the Northern Territory, no method nationally is feasible or planned.

In considering parts of the research included in this thesis, the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research requested that any information that could identify individual Indigenous communities not be provided for analysis. Their concern was not that small numbers of people with kidney disease in individual communities risked individual identification, but that communities could be identified in the published results without those communities having given consent for identification (NHMRC 2014). This has limited the scope of research into the prevalence, incidence and outcomes of CKD in the Top End of the Northern Territory, explored in Chapter Six of this thesis.

1.8.7 Identification of Indigenous Status

“Whether or not a person identifies as Aboriginal and/or Torres Strait Islander” is the nationally recommended method for determining
Indigenous status in health settings (Australian Institute of Health and Welfare 2010). While this standard method can be said to have been followed in this thesis, the quality of ethnicity data held by the ANZDATA Registry has not been tested. Because the ANZDATA Registry is a repository of data sent to it by collaborating renal units in Australia and New Zealand, patient ethnicity data are not strictly by “self-report” but may be variously the data from health records (which continue to have jurisdiction-level variations in their accuracy of Indigenous identification despite national recommendations), ethnicity reported by patients to treating clinicians (which may be asked for and/or reported in a non-recommended manner) or ethnicity assumed and recorded by clinicians without direct questioning of the patient (in a non-recommended manner). Because this thesis uses existing data, these data quality issues have not been explored further.

1.9 Structure of this Thesis

This thesis consists of eight chapters, including this introductory first chapter comprising a review of the literature, a discussion of methodological issues and a summary of the questions raised.

Chapter Two is the paper “Survival of Indigenous Australians receiving renal replacement therapy: closing the gap?” published in the Medical Journal of Australia in March 2015.
Chapter Three is the publication-ready and submitted manuscript “What are my chances, Doc? The competing risks of death and transplantation for Indigenous Australian dialysis patients.”

Chapter Four is the publication-ready and submitted manuscript “They don’t do well, do they? Survival of propensity matched Indigenous transplant and dialysis patients in Australia.”

Chapter Five is the publication-ready manuscript “What’s wrong with missing dialysis? Pattern and outcomes of dialysis attendance in Australia’s Northern Territory, 1995–2011.”


Chapter Seven is the conclusion, and presents a summary and synthesis of thesis findings, a discussion of the implications for future care and suggestions for further research on the topic.

Chapter Eight is an appendix lists related papers published during the candidacy of the PhD that do not form a direct part of the thesis.
Chapter 2: Survival of Indigenous Australians Receiving Renal Replacement Therapy: Closing the Gap?

2.1 Chapter Overview

This chapter comprises a reprint of a paper published in the Medical Journal of Australia on 4th March, 2015.

2.2 Declaration of Authorship

The study was conceptualised and designed by Paul Lawton, who was responsible for all analysis of these data. Nick Gray provided initial thoughts about the analysis of outcome by remoteness and Karumathil Murali about the analysis of outcome over time. Analysis was checked by Mark Chatfield; he and Yuejen Zhao also provided advice about statistical assumptions. The paper was written by Paul Lawton largely in discussion with Joan Cunningham and Matthew Jose, with critical editorial input from Mark Chatfield and Peter Baade (presentation of the results), Nick Gray (discussion of remoteness), Karumathil Murali and Yuejen Zhao. While Paul Lawton takes overall responsibility for the work, all authors reviewed and approved the manuscript before publication.
Survival of Indigenous Australians receiving renal replacement therapy: closing the gap

Abstract

Objectives: To compare mortality rates for Indigenous and non-Indigenous Australians commencing renal replacement therapy (RRT) over time and by categories of remoteness of place of residence.

Design, setting and participants: An observational cohort study of Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) data on Indigenous and non-Indigenous Australians registered with ANZDATA who commenced RRT from 1 January 1995 to 31 December 2011 and were followed until 31 December 2011.


Results: Indigenous patients were younger, more likely to have diabetes, be referred late and be from a more remote area than non-Indigenous patients. Age and comorbid conditions increased with successive cohorts for both groups. Unadjusted analysis (using the log-rank test) showed an increased risk of death for Indigenous patients in the 1995–1999 cohort (P < 0.02) and 2000–2004 cohort (P > 0.03) cohorts, but not for the 2005–2009 cohort (P > 0.7). However, a Cox proportional hazards model adjusted for covariates (age, sex, late referral and comorbid conditions (diabetes, coronary artery disease, peripheral vascular disease, cerebrovascular disease, lung disease) and body mass index < 18.5 kg/m² and ≥ 30kg/m²) showed the following Indigenous/non-Indigenous hazard ratios (with 95% CI) for major capital cities: 1995–1999, 1.47 (1.21–1.79); 2000–2004, 1.33 (1.12–1.63); and 2005–2009, 1.37 (1.14–1.65).

Conclusions: Although unadjusted analysis suggests that the survival gap between Indigenous and non-Indigenous patients receiving RRT has closed, there remains a significant disparity in survival after adjusting for the variables considered in our study.

Methods

Study population

The Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) collects observational data on all patients receiving chronic RRT in Australia and New Zealand; these data are submitted by treating renal units. This study included all patients aged ≥15 years or more who commenced RRT between 1 January 1995 and 31 December 2009 and who were maintained on RRT for more than 90 days to create three equal 5-year period inception cohorts (1995–1999, 2000–2004, 2005–2009, inclusive). Patients were followed until 31 December 2011. We compared Indigenous Australians (those who self-identified as being of Aboriginal or Torres Strait Islander origin) with non-Indigenous Australians (excluding those of any other ethnicity who commenced RRT in Australia).

Data collection

Comorbid conditions reported at commencement of RRT included coronary artery disease, peripheral vascular disease, cerebrovascular disease, chronic lung disease and diabetes. Comorbid conditions were recorded in three categories: no, yes or suspected. For this analysis, "no" and "suspected" were combined. Body mass index (BMI) was calculated from height and weight data at commencement of RRT. Late referral was defined as commencing RRT within 3 months of being referred to a nephrologist and data were collected from 1 April 1995.
Postcode data at commencement of RRT were collected from 1 April 1995. An Australian Bureau of Statistics correspondence file was used to map postcodes onto the Accessibility and Remoteness Index of Australia (ARIA+), a system based on the physical distance by road from each location point to the nearest town or service centre. This creates a five-category classification of remoteness: major cities, inter-regional, outer regional, remote and very remote areas.

**Statistical analyses**

The outcome for the study was all-cause mortality. Patient data were censored at 5 years after commencement of RRT, or at the date of recovery of renal function or at the date of last known follow-up if they had not died previously.

The probability of survival to 5 years after the commencement of RRT was assessed by calculating Kaplan-Meier failure curves with groups compared by the logrank test.

Using the Cox proportional hazards (PH) model, analysis of the hazard of death was performed using interaction terms between Indigenous status and cohort, and Indigenous status and remoteness category. Variables were added to this model to determine which contributed most to the outcome of the final model. Exploratory variables included cohort, Indigenous status, age, sex, comorbid conditions, BMI categories, late referral and remoteness category. Interactions between variables thought likely based on knowledge of the literature were modelled; the difference in calculated effect of the hazard ratio was less than 20% for all those assessed. For all Cox PH models, the Efroim method was used for resolving ties and the FH assumption was assessed by two different graphical means. Sensitivity analysis was conducted considering only confirmed comorbid conditions compared with both confirmed and suspected comorbid conditions combined on the outcome of the full Cox PH model.

### Characteristics of the whole population of 27,468 patients at first treatment, by time period and Indigenous status

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-Indigenous</strong></td>
<td>(n = 6321)</td>
<td>(n = 8232)</td>
<td>(n = 10,417)</td>
</tr>
<tr>
<td><strong>Indigenous</strong></td>
<td>(n = 504)</td>
<td>(n = 827)</td>
<td>(n = 107)</td>
</tr>
<tr>
<td>Male</td>
<td>392 (61.7%)</td>
<td>256 (42.2%)</td>
<td>476 (60.9%)</td>
</tr>
<tr>
<td>Mean (median) age</td>
<td>57.1 (62.4) years</td>
<td>65.5 (66.7) years</td>
<td>60.7 (59.1) years</td>
</tr>
<tr>
<td>Mean estimated glomerular filtration rate</td>
<td>5.3 mL/min/1.73m²</td>
<td>4.3 mL/min/1.73m²</td>
<td>5.6 mL/min/1.73m²</td>
</tr>
<tr>
<td>Late referral</td>
<td>1230 (21.2%)</td>
<td>212 (35.1%)</td>
<td>196 (24.1%)</td>
</tr>
<tr>
<td><strong>Comorbid conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>1696 (26.6%)</td>
<td>623 (10.2%)</td>
<td>643 (16.3%)</td>
</tr>
<tr>
<td>Coronary</td>
<td>1826 (31.9%)</td>
<td>152 (25.7%)</td>
<td>207 (52.6%)</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>634 (10.5%)</td>
<td>37 (6.7%)</td>
<td>81 (10.3%)</td>
</tr>
<tr>
<td>Peripheoral vascular</td>
<td>1204 (19.2%)</td>
<td>76 (13.0%)</td>
<td>154 (18.3%)</td>
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<tr>
<td>Lung</td>
<td>566 (82.2%)</td>
<td>64 (10.6%)</td>
<td>92 (11.6%)</td>
</tr>
<tr>
<td><strong>Body mass index (BMI)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean BMI</td>
<td>25.3 kg/m²</td>
<td>26.8 kg/m²</td>
<td>26.4 kg/m²</td>
</tr>
<tr>
<td>BMI &lt; 18.5 kg/m² (underweight)</td>
<td>340 (5.4%)</td>
<td>37 (6.7%)</td>
<td>34 (4.8%)</td>
</tr>
<tr>
<td>BMI 18.5–30 kg/m²</td>
<td>5071 (75.3%)</td>
<td>610 (10.0%)</td>
<td>503 (7.1%)</td>
</tr>
<tr>
<td>BMI &gt; 30 kg/m² (obese)</td>
<td>970 (15.3%)</td>
<td>157 (26.1%)</td>
<td>176 (23.4%)</td>
</tr>
<tr>
<td><strong>Remoteness classification</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major city</td>
<td>4572 (65.8%)</td>
<td>982 (16.1%)</td>
<td>598 (16.7%)</td>
</tr>
<tr>
<td>Inner regional</td>
<td>1146 (16.8%)</td>
<td>60 (10.0%)</td>
<td>156 (18.9%)</td>
</tr>
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<td>Outer regional</td>
<td>534 (8.5%)</td>
<td>106 (19.8%)</td>
<td>605 (7.4%)</td>
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<tr>
<td>Remote</td>
<td>57 (0.9%)</td>
<td>9 (0.2%)</td>
<td>6 (0.8%)</td>
</tr>
<tr>
<td>Very remote</td>
<td>12 (0.2%)</td>
<td>12 (2.1%)</td>
<td>7 (0.1%)</td>
</tr>
</tbody>
</table>

*Follow-up to 5 years not complete for the 2005–2009 cohort.

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**Research**

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All analyses were conducted using Stata/MP 12.1 (StataCorp). Approval for the study was granted by the combined Human Research Ethics Committee of the Northern Territory Department of Health & Menzies School of Health Research (HREC-2011-634); this process included an assessment by an Aboriginal ethics subcommittee with veto powers.

Results

Appendix 1 shows a flow chart of the study population and how the cohort of 27,486 patients available for study was derived. Baseline characteristics of the population available for study are outlined in Box 1, separated by cohort and Indigenous status. Data were censored for 78 patients at the date of recovery of renal function, and for 43 patients at the date of last known follow-up.

Indigenous patients commencing RRT were 10–12 years younger and more likely to be female and to have diabetes than non-Indigenous patients. Indigenous patients were more likely to have lower levels of endogenous kidney function at commencement of RRT, to be “late referred”, and to come from outer regional, remote or very remote regions than non-Indigenous patients. Fewer Indigenous patients received kidney transplants in the first 5 years of treatment.

There were also important differences between cohorts for both Indigenous and non-Indigenous patients. Compared with the earliest cohort, patients in later cohorts were older, more likely to be male and more likely to have diabetes or coronary artery disease. Later cohorts also had a higher proportion of overweight and a lower proportion of underweight patients, and mean endogenous kidney function was higher. Of particular note, the rise in age for non-Indigenous patients was greater than that for Indigenous patients.

Years of follow-up, the number of deaths and the death rate for each cohort and patient group are shown in Box 2, and Kaplan–Meier failure curves are shown in Box 3. The log-rank test confirmed a significant difference in the risk of death between Indigenous and non-Indigenous patients for 1995–1999 ($P = 0.02$) and 2000–2004 ($P = 0.03$) but not for 2005–2009 ($P = 0.7$).

A Cox PH model including only the main effects and interaction term between cohort and Indigenous status showed a small increase in the hazard ratio for death for Indigenous compared with non-Indigenous patients in earlier cohorts but no difference in the 2005–2009 cohort (Appendix 2). A dramatically different picture emerged once age was added to the model, with a greatly increased hazard ratio for Indigenous patients in all cohorts (Appendix 2). This second model also shows higher mortality rates for earlier cohorts compared with the 2005–2009 cohort of non-Indigenous patients.

This difference in mortality rates was attenuated but still clear in the fully adjusted Cox PH model that included all other comorbidity, late referral and remoteness terms (Box 4). There was no evidence of interaction by age or diabetes status or late referral on the relationship between Indigenous status and mortality (data not shown). However, different categories of remoteness interacted with the relationship between Indigenous status and mortality to varying degrees.

Box 5 shows the impact of the Indigenous–cohort interaction on the mortality hazard. Adjusting for all other variables, the mortality risk improved for both non-Indigenous and Indigenous patients over time. However, the risk was higher in all cohorts for Indigenous compared with non-Indigenous patients in each remoteness category (Box 4); the cohort interaction terms were not statistically significant ($2P = 1.14$; df = 2; $P = 0.6$).

The Indigenous–remoteness interaction terms are highlighted in Box 6. Although non-Indigenous patients from major capital cities had a lower hazard than non-Indigenous patients from other regions, this was not the
case for Indigenous patients (Box 4); however, the remoteness category interaction terms were not significant overall ($t^2 = 6.17, df = 4, p = 0.2$).

### Discussion

In this analysis of all people commencing RRT in Australia from 1998 to 2009, we found that there was a survival difference between Indigenous and non-Indigenous patients that has not been recently assessed by methods without adjustment for confounding differences in the patient populations. With adjustment (particularly for age and diabetes), it became apparent that survival for both Indigenous and non-Indigenous patients has indeed improved over time despite an increasing burden of comorbid conditions. However, the gap in survival between Indigenous and non-Indigenous patients has not narrowed.

The use of interaction terms allowed us to incorporate into one model factors of interest that may affect Indigenous and non-Indigenous patients differently. While increasing the complexity of the analysis, this enabled us to explore how any disparity between Indigenous and non-Indigenous patients varies over time and remoteness categories. By doing so, we have shown not only that a difference in adjusted risk of death continues between Indigenous and non-Indigenous patients but also that this difference has been maintained over the past 15 years in the face of improvements in both non-Indigenous and Indigenous survival.

In addition, we have shown that the relationship between remoteness category and mortality is different for Indigenous and non-Indigenous patients. For all cohorts, an Indigenous patient from a major capital city had a greater risk of death than a similar non-Indigenous patient; differences for other regions are less apparent. The variation in the risk of death by remoteness for non-Indigenous patients remains similar to previously published findings. Despite efforts to provide dialysis treatments closer to home in recent years, the risk of death for Indigenous patients from very remote areas remains higher than for those in major cities (Box 6).

When interpreting the results of the fully adjusted Cox PH model, it is important to remember that the Indigenous and non-Indigenous patient populations remain quite different, and that they both have changed over the period studied. For example, while the hazard ratio for diabetes applies equally to both groups, up to 74% of Indigenous patients have diabetes compared with rates half that or less for non-Indigenous patients. Similar differences exist for many other measured variables, particularly late referral (which remains more likely for Indigenous patients despite recent improvements) and age (which has become increasingly older in the non-Indigenous population over the period of the study) (Box 1).
There are clear differences between Indigenous and non-Indigenous patients in their likelihood of being treated with different RRT modalities, particularly kidney transplantation. The difference between Indigenous and non-Indigenous survival is smaller if transplantation is considered separately (data not shown), suggesting the lower transplant rate for Indigenous patients may be contributing to their higher risk of death after starting RRT, poorer outcomes notwithstanding.24 Since fewer Indigenous patients receive transplants, it is reasonable to assume that those few who do are carefully selected and that those Indigenous patients remaining on dialysis will include a number who may well have had a transplant if they were non-Indigenous. This latter group may have a better prognosis than other patients being treated by dialysis. To avoid this susceptibility bias, for our initial analysis, we assessed survival by pooling all patients together regardless of their initial or subsequent treatment modality, as was done in previous studies.24-26 Treatment modalities were not included as a term in any Cox PH models for the same reason. As a result, this study adds to previous work26-29 more recent data that are national in scope and encompass all RRT modalities.

The increased hazard for death for Indigenous patients receiving RRT, once other baseline variables recorded within ANZDATA are taken into consideration, requires explanation. Of note, similar studies from overseas examining survival differences for people starting RRT have shown either adjusted survival rates for those from minority groups,28-29 or at least equal survival in the case of aboriginal patients from the Prairie Provinces of Canada.30 Many Indigenous Australians receiving RRT come from remote settings that were overseas minority groups, but this does not explain the persistent increased hazard of death for Indigenous Australians from major capital cities. There may be different patterns of referral for RRT in different countries, although in all those quoted, the costs of RRT are covered by some form of national health insurance. The much lower likelihood of Indigenous Australian patients receiving a kidney transplant compared with non-Indigenous Australians accounts for only some of the difference between the two groups.

There are limitations inherent in this study. Data on characteristics such as social and economic circumstances that may confound Indigenous status are not collected within ANZDATA and are challenging to tease out even with existing Australian Bureau of Statistics Census area data.31 It is possible that the recorded postcode of residence for Indigenous people is inaccurate. Comorbidity data captured in ANZDATA are imperfect, in part because they are based on the opinion of the treating physician rather than objectively defined criteria. There is also no information on the severity of comorbid conditions. The analysis examined baseline characteristics only, rather than changes in comorbidity over time. This approach was taken to provide useful information to clinicians discussing prognosis with patients considering RRT.

The improving underlying probability of survival for both Indigenous and non-Indigenous patients starting RRT, once recorded factors are considered, makes the use of these data for predicting survival patterns challenging. Nevertheless, it is sobering to consider that the risk of death after starting RRT is 10-11 times higher than for many other diseases, including some cancers (Box 3). As a result, the highest priority must be to prevent as many people as possible (both Indigenous and non-Indigenous) from developing end-stage kidney disease in the first place.

Acknowledgments Paul Lavers is supported by a National Health and Medical Research Council (NHMRC) Postgraduate Scholarship (APP1074329). Kieren Chalmers is supported by NHMRC Senior Research Fellowship (APP1060465). Peter Black is supported by an NHMRC Career Development Fellowship (APP1053132). The data reported here were supplied by ANZDATA. We gratefully acknowledge the contributions of the Australian and New Zealand RRT registry to the preparation of information for and maintenance of the ANZDATA database, and the Health Services Planning Branch, Department of Health. This information and reporting of these data are the responsibility of the authors and are not an official audit or interpretation by ANZDATA, the NHMRC Department of Health or the NHMRC.

Conflict of interests No relevant disclosures.

Received 07 May 2014, accepted 31 July 2014.
Research


3.1 Chapter Overview

This chapter comprises a publication-ready and submitted manuscript titled “What are my chances, Doc? The competing risks of death and transplantation for Indigenous Australian dialysis patients.”

3.2 Abstract

Objective: To examine the chances of death and transplantation for Indigenous and non-Indigenous young and middle-aged adult Australian dialysis patients.

Design, setting and participants: An observational cohort study using Australia and New Zealand Dialysis and Transplant Registry data (ANZDATA). Indigenous and non-Indigenous Australians commencing dialysis aged 15–64 years from 1st April 1995 to 31st December 2009 were included and followed for five years, until 31st December 2012.

Results: 89.3% of all adult Indigenous but only 52.3% of all adult non-Indigenous dialysis patients were included; included Indigenous patients had more comorbidities than non-Indigenous patients. Unadjusted analysis showed significant differences between Indigenous and non-Indigenous patients in both risk of death (p<0.001) and transplantation (p<0.001).

For death, the Fine and Gray competing risks proportional hazards (CR-PH) model (adjusted for age, sex, late referral, comorbidities, cohort and remoteness category) showed the Indigenous:non-Indigenous gap narrowed: sub-hazard ratios (SHR, with 95% CIs) decreased for major capital cities (MC) from 1.43 (1.13–1.82) in 1995–1999 to 1.21 (0.97–1.52) in 2005–2009. For transplantation, the adjusted CR-PH model showed a widening gap in MC over time: 1995–1999 SHR 0.49 (95% CI 0.34–0.70) to 2005–2009 SHR 0.30 (95% CI 0.20–0.46). Transplantation increased by remoteness for non-Indigenous patients, with an opposite pattern for Indigenous patients.

Conclusions: Survival differences between Indigenous and non-Indigenous dialysis patients improved over time. Indigenous transplant rates worsened. Urgent attention is needed to ensure equitable outcomes.
3.3 Introduction

Much is known about the incidence of end-stage kidney disease (ESKD) requiring renal replacement therapy (RRT) in Indigenous Australians, and about the epidemiological antecedents and associations with the start of RRT (McDonald, Jose & Hurst 2013). Much less is known about the outcomes of RRT for Indigenous Australians, despite the very high financial and social costs of treatment (Anderson et al. 2012; You et al. 2002).

Transplant rates are lower and the risk of death is higher for Indigenous Australian compared to non-Indigenous RRT patients when population differences are taken into account (Lawton et al. 2015). However, previous analyses have either not teased out survival probabilities for dialysis patients alone (Lawton et al. 2015), not examined changes over time in the risk of death or transplantation for Indigenous Australians (Yeates et al. 2009), not been able to examine the role remoteness may play for Indigenous patients (Yeates et al. 2009) or have used techniques that may have overestimated rates of death or transplantation given the competing nature of these two events (Teixeira et al. 2013).

A competing risk is “an event whose occurrence either precludes the occurrence of another event under examination or fundamentally alters
the probability of occurrence of this other event” (Teixeira et al. 2013). If death occurs, transplantation cannot be observed; if transplantation occurs, a patient’s risk of death is altered. Commonly used “cause-specific” methods, such as the Kaplan-Meier and Cox proportional hazards methods, censor patients at the time of events that are not of primary interest (the competing events) but assume that, if the censored patient had continued on in the study, she would have had the same risk of the primary event of interest as those patients still included. This “non-informative censoring” assumption is violated if different events with different subsequent outcome probabilities can occur, and can lead to over-estimates of the primary event of interest if competing risks methods are not used (Gooley et al. 1999; Teixeira et al. 2013).

Virtually all (99.9%) Indigenous patients in Australia start RRT with a form of dialysis (haemodialysis or peritoneal dialysis) (McDonald, Jose & Hurst 2013). The majority (81.8%) of all patients (Indigenous and non-Indigenous) receiving kidney transplants in Australia in 2013 were aged 15–64 years (Clayton, Lim & Hurst 2013). In this registry-based study, we observed the competing chances of death and transplantation for Indigenous and non-Indigenous young and middle-aged adult Australians receiving any form of dialysis treatment, examined changes over time and the contribution co-morbidities and remoteness of residence make to these chances.
3.4 Methods

Study Population

The ANZDATA Registry collects observational data on all patients receiving chronic RRT in Australia and New Zealand, submitted by treating renal units. This study included all patients 15–64 years old who commenced any form of dialysis treatment in Australia between 1st April 1995 and 31st December 2009 and who were maintained on dialysis for more than 90 days. We compared Indigenous Australians (those identified as being of Aboriginal and/or Torres Strait Islander origin) with non-Indigenous Australians (including those of any other ethnicity commencing RRT in Australia).

Variables for Analysis

Co-morbid conditions reported at commencement of RRT included coronary artery disease, peripheral vascular disease, cerebrovascular disease, chronic lung disease and diabetes. Co-morbidities were recorded in three categories: no, yes or suspected. For this analysis, “no” and “suspected” have been combined. Body mass index (BMI) was calculated from height and weight data at commencement of RRT. Late referral data were collected from 1st April 1995 and was defined as commencing RRT within three months of being referred to a nephrologist. Other clinical
data available included the modality of RRT at commencement, the date of transplant and the date of death.

Postcode of residence at commencement of RRT was collected from 1st April 1995. An Australian Bureau of Statistics correspondence file was used to map postcodes onto the Accessibility and Remoteness Index of Australia (ARIA+) (Australian Bureau of Statistics 2006).

The outcomes for the study were transplantation and all-cause mortality. Patient data were censored at five years after commencing RRT or at the earliest of: the date of recovery of renal function; the date of last known follow-up; or at 31st December 2012. Depending on the analysis, patient data were also censored at the date of death (for analysis of transplantation rates) or date of transplantation (for analysis of death rates).

**Statistical Analyses**

Baseline characteristics for Indigenous and non-Indigenous patient groups were compared by the Mann-Whitney U test for continuous variables and the chi² test for categorical variables.

 Separately for Indigenous and non-Indigenous patients, the cumulative incidence of death was estimated in the presence of the competing risk of
transplantation (and vice versa) (Coviello & Boggess 2004; Gooley et al. 1999), with groups compared by calculating the weighted area between the two estimated functions using the method of Pepe and Mori (Pepe & Mori 1993).

Using the semi-parametric competing risks proportional hazards model of Fine & Gray (Cleves et al. 2010; Fine & Gray 1999), the hazard for the sub-distribution of death (SHR, with transplantation as the competing risk) was calculated using interaction terms between Indigenous status and inception time period cohort, and between Indigenous status and remoteness category, to allow comparison with previous literature (Lawton et al. 2015). Additional explanatory variables included age, sex, comorbid conditions, BMI category and late referral. Interaction between variables thought likely based on knowledge of the literature were modeled; these included interactions between Indigenous status and the variables sex, diabetes, the time period inception cohort and remoteness category, respectively. Interactions were assessed using likelihood ratio tests and retained at p-values less than 0.05; some interaction terms were not statistically significant but were included in the final models to allow comparison with previous literature and highlight certain effects. The assumption of proportional sub-hazards was assessed by introducing time-varying coefficients (Cleves et al. 2010). The process of fitting a Fine and Gray model was repeated in the same way for transplantation (with
death as the competing risk).

All analyses were conducted using Stata/MP4 12.1 (StataCorp, College Station, Texas, USA). Approval for the study was granted by the combined Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research (HREC-2011-1634); this process included an assessment by an Aboriginal Ethics Sub Committee with veto powers.

3.5 Results

Figure 3.1 shows a flow chart of exclusions and how the population of 14,547 patients available for study was derived. The final number accounted for 89.3% of the total adult Indigenous RRT population, but only 52.3% of the adult non-Indigenous RRT population. The outcomes of those not included (either because they had not received dialysis for 90 days or more, or because they were 65 years old or older) are presented in Table 3.1.

Baseline characteristics of the study population are outlined in Table 3.2, separated by Indigenous status. Indigenous patients receiving maintenance dialysis were more likely to be female, be “late referred”, have lower levels of endogenous kidney function at commencement of dialysis and come from outer regional, remote or very remote areas than
non-Indigenous patients. The increased burden of all comorbidities for Indigenous compared to non-Indigenous patients is particularly noteworthy given the age restrictions of the study.
Figure 3.1: Flow chart of study population including exclusions

28,870 patients commencing RRT

28,845 withpostcode

28,834 with remoteness area

26,705 completing at least 90 days of dialysis treatment

26,425 adults

14,750 adults less than 65 years old

14,593 with late referral information

14,547 maintenance dialysis patient records for analysis

25 missing postcodes

8 not in RA concordance file (and no RA category)
3 in RA concordance file but no RA category (in northern Tasmania)

2,129 not completing 90 days of dialysis (not fulfilling ANZDATA definition of “maintenance dialysis”: see Table 1)

382 less than 15 years of age excluded

11,675 aged 65 years or older (see Table 1)

157 without late referral information

38 without height
8 without weight
Table 3.1: Outcomes of patients not included in study (from Figure 3.1)

<table>
<thead>
<tr>
<th>Patients not completing 90 days of dialysis</th>
<th>Non-Indigenous</th>
<th>Indigenous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>2,018</td>
<td>111</td>
</tr>
<tr>
<td>Transplanted</td>
<td>1,123 (55.6%)</td>
<td>6 (5.4%)</td>
</tr>
<tr>
<td>Recovery of kidney function</td>
<td>121 (6.0%)</td>
<td>16 (14.4%)</td>
</tr>
<tr>
<td>Loss to follow-up</td>
<td>28 (0.1%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Died</td>
<td>746 (37.0%)</td>
<td>88 (79.3%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients aged 65+ years at start of treatment</th>
<th>Non-Indigenous</th>
<th>Indigenous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>11,406</td>
<td>269</td>
</tr>
<tr>
<td>Transplanted</td>
<td>255 (2.2%)</td>
<td>2 (0.7%)</td>
</tr>
<tr>
<td>Recovery of kidney function</td>
<td>145 (1.3%)</td>
<td>3 (1.1%)</td>
</tr>
<tr>
<td>Loss to follow-up</td>
<td>24 (0.2%)</td>
<td>0</td>
</tr>
<tr>
<td>Died</td>
<td>8,936 (78.3%)</td>
<td>220 (81.8%)</td>
</tr>
</tbody>
</table>
Table 3.2: Baseline characteristics by ethnicity

<table>
<thead>
<tr>
<th></th>
<th>Non-Indigenous</th>
<th>Indigenous</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>12,342</td>
<td>2,205</td>
<td></td>
</tr>
<tr>
<td><strong>Age (mean, years)</strong></td>
<td>48.6</td>
<td>47.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Sex (male)</strong></td>
<td>7,568 (61.1%)</td>
<td>976 (44.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>eGFR (median, ml/min/1.73m²)</strong></td>
<td>6.1</td>
<td>5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Late referral</strong></td>
<td>2,807 (22.7%)</td>
<td>751 (34.1%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Comorbidity**

<table>
<thead>
<tr>
<th></th>
<th>Non-Indigenous</th>
<th>Indigenous</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetes</strong></td>
<td>4,037 (32.7%)</td>
<td>1,692</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Coronary artery disease</strong></td>
<td>2,524 (20.5%)</td>
<td>603 (27.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Peripheral vasc. disease</strong></td>
<td>1,715 (13.9%)</td>
<td>399 (18.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Cerebrovascular disease</strong></td>
<td>872 (7.1%)</td>
<td>250 (11.3%)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Lung disease</strong></td>
<td>986 (8.0%)</td>
<td>243 (11.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Ever smoked</strong></td>
<td>6,303 (51.1%)</td>
<td>(63.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>BMI (mean, kg/m²)</strong></td>
<td>27.1</td>
<td>27.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>BMI &lt;18.5</strong></td>
<td>532 (4.3%)</td>
<td>108 (4.9%)</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>BMI &gt;30</strong></td>
<td>3,261 (26.4%)</td>
<td>708 (32.1%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Cohort**

<table>
<thead>
<tr>
<th></th>
<th>Non-Indigenous</th>
<th>Indigenous</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1995-99</strong></td>
<td>3,466 (28.1%)</td>
<td>517 (23.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>2000-04</strong></td>
<td>4,030 (32.7%)</td>
<td>730 (33.1%)</td>
<td>0.68</td>
</tr>
<tr>
<td><strong>2005-09</strong></td>
<td>4,846 (39.3%)</td>
<td>958 (43.4%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Remoteness category**

<table>
<thead>
<tr>
<th></th>
<th>Non-Indigenous</th>
<th>Indigenous</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major capital</strong></td>
<td>8,857 (71.8%)</td>
<td>305 (13.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Inner regional</strong></td>
<td>2,296 (18.6%)</td>
<td>192 (8.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Outer regional</strong></td>
<td>1,040 (8.4%)</td>
<td>630 (28.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Remote</strong></td>
<td>112 (0.9%)</td>
<td>421 (19.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Very remote</strong></td>
<td>37 (0.3%)</td>
<td>657 (29.8%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Initial treatment**

<table>
<thead>
<tr>
<th></th>
<th>Non-Indigenous</th>
<th>Indigenous</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haemodialysis</strong></td>
<td>9,108 (73.8%)</td>
<td>(83.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Peritoneal dialysis</strong></td>
<td>3234 (26.2%)</td>
<td>367 (16.6%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Years of follow-up, the number of deaths and transplants and the death rate and transplant rate for each cohort and patient group are shown in Table 3.3, and the cumulative incidence curves for both death and transplant by Indigenous status for the 2005–2009 cohort in Figure 2. The Pepe-Mori test confirmed a significant difference in both the risk of death (p<0.001) and risk of transplant (p<0.001) between Indigenous and non-Indigenous patients.

Table 3.3: Follow-up, number of deaths and death rate, by ethnicity

<table>
<thead>
<tr>
<th></th>
<th>Non-Indigenous</th>
<th>Indigenous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>12,342</td>
<td>2,205</td>
</tr>
<tr>
<td>Cumulative years of follow-up</td>
<td>35,303.8</td>
<td>7,272</td>
</tr>
<tr>
<td>Number of deaths</td>
<td>3,027</td>
<td>885</td>
</tr>
<tr>
<td>Number of transplants</td>
<td>4,727</td>
<td>203</td>
</tr>
<tr>
<td>Mortality rate (per 100 patient years)</td>
<td>8.6</td>
<td>12.2</td>
</tr>
<tr>
<td>Transplant rate (per 100 patient years)</td>
<td>13.4</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Note: data were censored for 160 patients at the date of recovery of renal function, and for 46 patients at the date of last known follow-up.
The Fine and Gray competing risks regression model for death (with transplant as the competing risk) including only an interaction term between Indigenous status and cohort revealed large and significant differences in the risk of death for Indigenous compared to non-Indigenous patients in all cohorts: 1995–1999 SHR 2.14 (95% CI 1.86–2.47), 2000–2004 SHR 2.19 (1.94–2.47) and 2005–2009 SHR 1.68 (1.48–1.90). These differences were even larger once age was added to the model: 1995–1999 SHR 2.65 (2.29–3.06), 2000–2004 SHR 2.44 (2.16–2.76) and 2005–2009 SHR 1.82 (1.60–2.06). This difference in mortality rates was partly reduced in the fully adjusted model that included all other comorbidity, late referral and remoteness terms; Indigenous status was
### Table 3.4: Fine & Gray PH fully adjusted models for risk of death and for risk of transplantation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Risk of Death</th>
<th>Risk of Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sub-Hazard Ratio</td>
<td>95% Confidence Interval</td>
</tr>
<tr>
<td>1995-99 (Indigenous:non-Ind)*</td>
<td>1.43</td>
<td>1.13</td>
</tr>
<tr>
<td>2000-04 (Indigenous:non-Ind)*</td>
<td>1.28</td>
<td>1.03</td>
</tr>
<tr>
<td>2005-09 (Indigenous:non-Ind)*</td>
<td>1.21</td>
<td>0.97</td>
</tr>
<tr>
<td>Age (per year increase)</td>
<td>1.036</td>
<td>1.032</td>
</tr>
<tr>
<td>Sex (male:female)</td>
<td>0.91</td>
<td>0.85</td>
</tr>
<tr>
<td>Diabetes (Y:N)</td>
<td>2.01</td>
<td>1.86</td>
</tr>
<tr>
<td>Coronary artery disease (Y:N)</td>
<td>1.44</td>
<td>1.34</td>
</tr>
<tr>
<td>Peripheral vascular disease (Y:N)</td>
<td>1.54</td>
<td>1.42</td>
</tr>
<tr>
<td>Cerebrovascular disease (Y:N)</td>
<td>1.40</td>
<td>1.26</td>
</tr>
<tr>
<td>Lung disease (Y:N)</td>
<td>1.62</td>
<td>1.48</td>
</tr>
<tr>
<td>BMI&lt;18.5 (:18.5-30)</td>
<td>1.89</td>
<td>1.63</td>
</tr>
<tr>
<td>BMI&gt;30 (:18.5-30)</td>
<td>0.93</td>
<td>0.87</td>
</tr>
<tr>
<td>Late referral (Y:N)</td>
<td>1.31</td>
<td>1.22</td>
</tr>
<tr>
<td>Major Capitals (Ind:non-Ind)§</td>
<td>1.21</td>
<td>0.97</td>
</tr>
<tr>
<td>Inner Regional (Ind:non-Ind)§</td>
<td>0.91</td>
<td>0.69</td>
</tr>
<tr>
<td>Outer Regional (Ind:non-Ind)§</td>
<td>0.90</td>
<td>0.74</td>
</tr>
<tr>
<td>Remote (Ind:non-Ind)§</td>
<td>0.91</td>
<td>0.62</td>
</tr>
<tr>
<td>Very Remote (Ind:non-Ind)§</td>
<td>1.12</td>
<td>0.56</td>
</tr>
</tbody>
</table>

* The sub-hazard ratios for each cohort for Indigenous compared to non-Indigenous patients are calculated as Indigenous status x cohort x Indigenous/cohort interaction term x Indigenous/remoteness interaction term, shown here for major capital cities (Figures 3.3a & 3.4a).

§ The sub-hazard ratios for each remoteness area for Indigenous compared to non-Indigenous patients are calculated as Indigenous status x remoteness area x Indigenous/remoteness interaction term x Indigenous/cohort interaction term, shown here for the 2005-2009 cohort (Figures 3.3b & 3.4b).
Figure 3.3: Risk of Death by ethnicity for cohorts and remoteness categories

**Adjusted Risk of Death for Cohorts by Indigenous Status**

- Indigenous
- Non-indigenous

**Cohort**
For Major Capital cities; adjusted for age, sex, late referral & comorbidities

**Adjusted Risk of Death for Remoteness Categories by Indigenous Status**

- Indigenous
- Non-indigenous

**Remoteness Category**
For 2005-2009 cohort; adjusted for age, sex, late referral & comorbidities
associated with a significantly increased risk of death for earlier cohorts but although still elevated was not significantly different for the 2005–2009 cohort (Table 3.4, Figure 3.3). There was no evidence of any interaction by age, diabetes, coronary artery disease or late referral on the relationship between Indigenous status and mortality (data not shown). Figure 3.3 demonstrates the calculated main effects by Indigenous status once interaction terms are incorporated. Residing outside Major Capitals at the start of treatment was associated with an increased risk of death for non-Indigenous patients; this trend was not as apparent for Indigenous patients.

The Fine and Gray model for transplant (with death as the competing risk) that included only an interaction term between Indigenous status and cohort showed very large and significant differences in the chances of transplantation between Indigenous and non-Indigenous patients which grew larger for later cohorts: 1995–1999 SHR 0.34 (0.27–0.42), 2000–2004 SHR 0.17 (0.13–0.22) and 2005–2009 SHR 0.16 (0.12–0.20). Adding age to the model increased the difference slightly: 1995–1999 SHR 0.28 (0.23–0.35), 2000–2004 SHR 0.16 (0.12–0.20) and 2005–2009 SHR 0.14 (0.11–0.18). In the fully adjusted model the chances of transplantation for non-Indigenous patients still increased significantly for later cohorts; in contrast, they fell for Indigenous patients and “the gap” widened over time (Table 3.4). Men were more likely to be transplanted than women;
this was more pronounced for Indigenous than non-Indigenous groups (data not shown). Increasing remoteness was associated with an increased chance of transplantation for non-Indigenous patients but a reduced chance for Indigenous patients. Examples of the calculated main effects once interactions were considered are in Figure 3.4.
Figure 3.4: Likelihood of transplantation by ethnicity for cohorts and remoteness categories

Adjusted Likelihood of Transplant for Cohorts by Indigenous Status

For women from major capital cities; adjusted for age, late referral & comorbidities
(Effect similar for males)

Adjusted Likelihood of Transplant for Remoteness Categories by Indigenous Status

For women in 2005-2009 cohort; adjusted for age, late referral & comorbidities
(Effect similar for males)
3.6 Discussion

This retrospective analysis of young and middle-aged adults commencing dialysis treatment confirmed a large unadjusted difference between Indigenous and non-Indigenous patients in the risk of death and an even larger one in the chances of kidney transplantation, as has previously been described (Yeates et al. 2009). Adjustment for population differences including demographic and clinical factors demonstrated that since 1995 the risk of death has decreased and the chances of receiving a kidney transplant improved for non-Indigenous Australians treated with dialysis. For Indigenous Australian dialysis patients, the risk of death has also fallen but so too has the chance of kidney transplantation. When demographic and clinical differences are accounted for, the gap between Indigenous and non-Indigenous patient survival on dialysis has narrowed and closed (Figure 3.3a); in contrast the gap in the chances of transplantation has widened (Figure 3.4a).

The effect of remoteness on the risk of death shown here (Figure 3.3b) is similar to previous work (Gray, Dent & McDonald 2012; Lawton et al. 2015). However, coming from a regional or remote area increased the chances of transplantation for non-Indigenous patients, but decreased it for Indigenous patients (Figure 3.4b). This is important given the much larger numbers and higher proportion of Indigenous patients from
regional and remote areas; it is critical when considering the social and cultural dislocation associated with their dialysis in an urban area (Devitt & McMasters 1998a) and their consistent and well-documented wish to receive treatment close to or at home (Anderson et al. 2012a).

The worsening of transplant rates for Indigenous Australians over time has occurred despite recent research exploring barriers to their transplantation. A survey of Australian nephrologists using randomised patient scenarios revealed that concerns about compliance with treatment were second only to age in importance when considering offering transplantation; ethnicity itself was not a significant factor (Cass et al. 2007). Determining compliance is problematic and subjective (Anderson et al. 2012b); data linking pre-transplant dialysis regimen compliance to post-transplant outcomes is “poor at best” (Cass et al. 2007). For Indigenous patients, despite interest in transplantation (Devitt & McMasters 1998a), communication difficulties can lead to a lack of knowledge about their situation, treatment and options (Anderson et al. 2008, 2012), which may lead to actual or perceived disengagement from clinicians ultimately responsible for transplant waiting lists. In the present study, co-morbidities had only a small effect on the gap in transplant rates; the majority of the difference in transplant rates between Indigenous and non-Indigenous patients was associated with ethnicity. This may be a surrogate for other factors not captured in
ANZDATA, including cultural distance (Anderson et al. 2008; Rix et al. 2013), perceived treatment compliance (Anderson et al. 2012; Rix et al. 2013) and socioeconomic disadvantage (Biddle 2009). In the absence of other explanations, this could be interpreted as institutional racism against Indigenous patients (Henry, Houston & Mooney 2004; Lowe, Kerridge & Mitchell 1995) which needs to be explored and addressed.

The data presented here reflect the probabilities over time of both transplantation and death for young adult to middle-aged dialysis patients, a group who would usually be thought to have a realistic possibility of transplantation and a low risk of death. Previous work examining transplant rates did not account for the competing risk of death (Yeates et al. 2009). Similarly, any estimation of the risk of death for dialysis patients must take into account the fact that, for both Indigenous and non-Indigenous patients, transplantation “fundamentally alters the probability of occurrence of [death]” (Gooley et al. 1999). This becomes particularly important when competing risk probabilities are not trivial; not considering them can lead to an overestimate of the risk of interest (Teixeira et al. 2013). Of note, there was incomplete follow-up for a portion of the last cohort (2005-2009) which may have led to an underestimate of both the risk of death and transplantation for this cohort. This is unlikely to have dramatically affected the magnitude of the disparity between Indigenous and non-Indigenous patients.
The use of interaction terms allowed us to examine the effects of time and remoteness of origin on outcomes for Indigenous and non-Indigenous patients separately, but still within the same model to enable comparison, as in previous work (Lawton et al. 2015). They also allowed us to show that the effects of comorbidities on the risks of death or transplantation are similar for both groups of patients. However, comorbidity data captured in ANZDATA are imperfect as they reflect the opinion of the treating physician rather than objectively defined criteria, and include no information about severity. Postcode of residence at first dialysis may be inaccurate, especially for Indigenous patients (Cass et al. 2001). ANZDATA data alone cannot tease out differences in the probability of being referred to the deceased donor waiting list, as these data are held by the National Organ Matching System. A recent analysis of such linked data suggests that Indigenous patients are much less likely to be put on the waiting list than non-Indigenous patients, after accounting for group differences (Khanal et al. 2015).

It is encouraging to see that in at least one important aspect (the risk of death), it has been possible to “close the gap” between Indigenous and non-Indigenous young to middle-aged dialysis patients, once different demographic and clinical profiles are taken into account. The fact that non-Indigenous patients from regional and remote Australia were
somewhat more likely to receive a kidney transplant indicates that the “tyranny of distance” can be overcome. Clearly other barriers to transplantation still exist for Indigenous Australian dialysis patients; many have already been identified (Anderson et al. 2012a, b; Cass et al. 2007; Cunningham, Cass & Arnold 2005; Henry, Houston & Mooney 2004; Lowe, Kerridge & Mitchell 1995), but overcoming them remains a challenge yet to be tackled successfully.
Chapter 4: They Don’t Do Well, Do They?
Survival of Propensity Matched Indigenous Transplant and Dialysis Patients in Australia

4.1 Chapter Overview

This chapter comprises a publication-ready and submitted manuscript titled “They don’t do well, do they? Survival of propensity matched Indigenous transplant and dialysis patients in Australia.”

4.2 Abstract

Objectives: To compare survival for Indigenous transplant patients with similar dialysis-only patients, contrasting with non-Indigenous patients.

Design, setting and participants: An observational cohort study using Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) data. Indigenous and non-Indigenous Australians who commenced renal replacement therapy (RRT) from 1st April 1995 to 31st December 2009 were included and followed until 31st December 2012. For each ethnicity, transplant recipients were paired by propensity score (using age, sex, late referral, comorbidities and remoteness) with similar

**Main outcome measures:** Five-year all-cause mortality for Indigenous and non-Indigenous patients in five residential remoteness categories.

**Results:** Proportionally fewer Indigenous than non-Indigenous patients were transplanted. Indigenous dialysis-only patients were similar to their transplanted pair at baseline, but paired non-Indigenous patients were less similar. Unadjusted analyses (using log-rank tests) showed better survival of transplanted patients than their dialysis-only pair for both non-Indigenous (p<0.001) and Indigenous patients (p=0.002). Adjusted Cox models comparing transplantation with dialysis-only patients showed that in major capital cities (MC) hazard ratios (HR, with 95% CIs) were similar for non-Indigenous (HR 0.18 [0.15–0.22]) and Indigenous (HR 0.23 [0.08–0.69]) patients. Among Indigenous patients, HRs were higher in remote regions (HR 0.69 [0.28–1.71]) than MC, but similar everywhere for non-Indigenous patients (remote HR 0.11 [0.03–0.48]).

**Conclusions:** Indigenous transplanted patients have better survival than similar dialysis-only patients, especially from major capitals, but relatively fewer suitable Indigenous patients are transplanted, raising important questions about the equity-utility balance.
4.3 Introduction

Incidence rates of end-stage kidney disease (ESKD) requiring RRT are much higher and ESKD occurs at a younger age for Indigenous Australians compared to non-Indigenous Australians (McDonald, Jose & Hurst 2013). However, kidney transplant rates are much lower for Indigenous patients (McDonald, Jose & Hurst 2013). Concerns have been raised that both patient and graft survival after kidney transplant may not be as good for Indigenous as for non-Indigenous recipients (McDonald 2004; McDonald, Jose & Hurst 2013; Rogers, Lawton & Jose 2006), and may be below benchmarks set for recommended minimum outcomes (Campbell et al. 2013). Recently published research suggests that, overall, patient survival has not been as good for Indigenous Australians starting RRT as for non-Indigenous Australian patients when demographic and comorbidity differences between the populations are taken into account (Lawton et al. 2015); that study was not able to examine transplant survival specifically. The reference standard of comparison — comparing only those dialysis patients on the deceased donor waiting list with those ultimately transplanted, ideally from time of entry on the waiting list (McDonald & Russ 2002; Wolfe et al. 1999) — is challenging since only 40 or fewer Indigenous Australian patients reach the waiting list each year (Cass et al. 2003; McDonald et al. 2012). An alternative but still clinically relevant comparison may be between those patients receiving a kidney transplant,
and patients continuing dialysis who are not necessarily on the waiting list but are as similar as possible in all other measured respects. Further adjustments are required to minimise immortal time bias (Liu et al. 2012).

These ends can be achieved by using propensity score techniques: these use logistic regression to create a probability score (or “propensity”) for a treatment based on measured baseline characteristics for both those ultimately treated and those not treated (Austin 2014; Gayat et al. 2012; Leuven & Sianesi 2003). Matched pairs can be created with a similar propensity score, where one has actually received treatment and the other has not. Pairing allows exclusion of immortal time bias by taking the time-at-risk from the time treatment started for both treated and untreated.

In this registry-based study, we sought to assess five-year patient survival after kidney transplantation compared to matched non-transplanted “dialysis-only” patient controls, separately for Indigenous and non-Indigenous groups, while excluding immortal time.
4.4 Methods

Study Population

The ANZDATA Registry collects observational data on all patients receiving chronic RRT in Australia and New Zealand, submitted by treating renal units. This study included all patients aged 15 years or more who commenced RRT in Australia between 1st April 1995 and 31st December 2009 and were maintained on RRT for more than 90 days. We compared Indigenous Australians with non-Indigenous Australians (including those of any other ethnicity commencing RRT in Australia).

Variables for Analysis

Co-morbid conditions reported at commencement of RRT included coronary artery disease, peripheral vascular disease, cerebrovascular disease, chronic lung disease and diabetes. Co-morbidities were recorded in three categories: no, yes or suspected. For this analysis, “no” and “suspected” have been combined. Body mass index (BMI) was calculated from height and weight data at commencement of RRT. Late referral data was collected from 1st April 1995 and was defined as commencing RRT within three months of being referred to a nephrologist. Other clinical data available included the modality of RRT at commencement and the date of transplant.
Postcode of residence at commencement of RRT was collected from 1st April 1995. An Australian Bureau of Statistics correspondence file was used to map postcodes onto the Accessibility and Remoteness Index of Australia (ARIA+).

The outcome for the study was all-cause mortality. Patient data were censored at five years after the actual or potential date of first transplant, at death or at the earliest of: the date of recovery of renal function; the date of last known follow-up; or 31st December 2012.

Propensity Score Matching and Statistical Analyses
Separately for Indigenous and non-Indigenous patients, baseline characteristics between future transplant and non-transplanted groups were compared by the Mann-Whitney U test for continuous variables and the chi² test for categorical variables.

Using logistic regression, separate propensity scores were calculated for Indigenous and non-Indigenous patients to estimate the probability (propensity) of receiving a first transplant, based on baseline characteristics of age, sex, late referral, comorbidities, remoteness category and the date RRT was commenced.
Patients who actually received a first kidney transplant were matched one-to-one without replacement using a nearest neighbor algorithm (using the publically available “psmatch2” [Leuven & Sianesi 2003]) to a never-transplanted “dialysis-only” patient with a similar propensity score within a caliper set at one fifth of the variance of the logit of the score, the same Indigenous status and from the same time period inception cohort (1995–1999, 2000–2004, 2005–2009) (Austin 2014; Gayat et al. 2012). Random assortment was performed to order patients with identical propensity scores before matching. Matching quality was assessed both by comparing the mean baseline characteristics of the two treatment groups and examining the standardised difference between the means of baseline characteristics (Austin 2009).

Immortal time bias was reduced by using the date of transplant (from the transplanted patient of the matched pair) as the date from which survival was assessed for both transplanted and dialysis-only patients.

The probability of survival to five years after study enrolment was assessed by calculating Kaplan-Meier failure curves (Bland & Altman 1998) separately for Indigenous and non-Indigenous propensity matched groups. Transplanted patients were compared to dialysis-only patients using an unadjusted Cox proportional hazards (PH) model with robust variance estimators that accounted for the paired nature of the study (Cleves et al. 2010).
For each Cox PH model, variables were added to these models to determine which ones contributed most to the outcome of the final models. Explanatory variables included actual transplant status, inception cohort, age, sex, comorbidities, BMI categories, late referral and remoteness category. Interactions between variables thought likely based on knowledge of the literature were modeled; these included interactions between actual transplant status and each of the following: diabetes, coronary artery disease, BMI greater than 30 kg/m², the time period inception cohort and remoteness category, respectively. Interactions were assessed using likelihood ratio tests and retained at p-values less than 0.05; some interaction terms were included in the final models to allow comparison with previous literature and highlight certain effects. For all Cox PH models, Efron’s method was used for resolving ties and the PH assumption was assessed by two different graphical means (Cleves et al. 2010): variation from the assumption of proportionality between transplanted and dialysis-only non-Indigenous patients was found in a log-log graph (but not in a comparison of Kaplan-Meier with Cox survivor functions), but the proportional assumption held for Indigenous patients. Sensitivity analysis was conducted considering only confirmed comorbidities compared to both confirmed and suspected comorbidities combined on the outcome of full Cox PH model.
All analyses were conducted using Stata/MP4 12.1 (StataCorp, College Station, Texas, USA). Approval for the study was granted by the combined Human Research Ethics Committee of the Northern Territory Department of Health & Menzies School of Health Research (HREC-2011-1634); this process included an assessment by an Aboriginal Ethics Sub Committee with veto powers.

4.5 Results

Figure 4.1 shows a flow chart of exclusions and how the population of 28,286 patients available for study was derived. Baseline characteristics of the non-Indigenous population followed by the characteristics of the matched cohort are outlined in Table 4.1 and for Indigenous patients in Table 4.2. Compared to non-Indigenous patients at baseline, Indigenous patients were younger, more likely to be female, to have diabetes, to be “late referred” and to come from outer regional, remote or very remote regions.
Figure 4.1: Flow chart of study population including exclusions

28,870 individual patient records

- 25 missing postcodes

28,845 with postcodes

- 8 not in RA concordance file (and no RA category)
- 3 in RA concordance file but no RA category (in northern Tasmania)

28,834 with remoteness area

- 385 less than 15 years of age excluded

28,449 adults

- 320 without late referral information

28,129 with late referral information

- 98 without height
- 19 without weight

28,012 whole cohort for analysis

- 25,440 non-Indigenous Australians
- 2,572 Indigenous Australians

25,440 non-Indigenous Australians

- 18,279 Dialysis only
- Matched
- 2,940 Dialysis only

2,572 Indigenous Australians

- 7,161 Transplants
- 2,294 Dialysis only
- Matched
- 2,940 Transplants
- 278 Transplants
- 176 Dialysis only
- Matched
- 176 Transplants
Table 4.1: Characteristics of dialysis only and transplanted non-Indigenous patients before and after propensity score match

<table>
<thead>
<tr>
<th></th>
<th>Dialysis only</th>
<th>Unmatched</th>
<th>Matched</th>
<th>Standardised difference</th>
<th>Standardised difference</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
<td>p-value</td>
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<td></td>
<td></td>
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<td>7161</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at start of RRT (years)</td>
<td>66.1</td>
<td>44.1</td>
<td>0.00</td>
<td>-1.73</td>
<td></td>
</tr>
<tr>
<td>eGFR at start of RRT (ml/min/1.73m²)</td>
<td>6.5</td>
<td>6.1</td>
<td>0.00</td>
<td>-0.13</td>
<td></td>
</tr>
<tr>
<td>Years of dialysis before transplant</td>
<td>2.0</td>
<td>2.0</td>
<td>0.00</td>
<td>-0.42</td>
<td></td>
</tr>
<tr>
<td>Sex (male, %)</td>
<td>60.1</td>
<td>62.5</td>
<td>0.00</td>
<td>-0.05</td>
<td></td>
</tr>
<tr>
<td>Late Referral (%)</td>
<td>24.8</td>
<td>17.0</td>
<td>0.00</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>Lung Disease (%)</td>
<td>15.4</td>
<td>3.4</td>
<td>0.00</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>Coronary Disease (%)</td>
<td>42.7</td>
<td>7.9</td>
<td>0.00</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>Peripheral Vascular Disease (%)</td>
<td>25.0</td>
<td>4.2</td>
<td>0.00</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular Disease (%)</td>
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<td>2.6</td>
<td>0.00</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>41.4</td>
<td>16.3</td>
<td>0.00</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td>Smoking ever (%)</td>
<td>55.2</td>
<td>42.8</td>
<td>0.00</td>
<td>0.25</td>
<td></td>
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<tr>
<td>Mean BMI (kg/m²)</td>
<td>26.9</td>
<td>25.7</td>
<td>0.00</td>
<td>-0.23</td>
<td></td>
</tr>
<tr>
<td>BMI&lt;18.5 (%)</td>
<td>4.2</td>
<td>4.3</td>
<td>0.59</td>
<td>-0.01</td>
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<td>BMI&gt;30 (%)</td>
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<td>17.3</td>
<td>0.00</td>
<td>0.19</td>
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<tr>
<td>Major city (%)</td>
<td>71.8</td>
<td>72.4</td>
<td>0.39</td>
<td>-0.01</td>
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<td>Inner regional (%)</td>
<td>19.3</td>
<td>18.1</td>
<td>0.03</td>
<td>0.03</td>
<td></td>
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<tr>
<td>Outer regional (%)</td>
<td>7.9</td>
<td>8.2</td>
<td>0.44</td>
<td>-0.01</td>
<td></td>
</tr>
<tr>
<td>Remote (%)</td>
<td>0.8</td>
<td>1.0</td>
<td>0.07</td>
<td>-0.02</td>
<td></td>
</tr>
<tr>
<td>Very remote (%)</td>
<td>0.2</td>
<td>0.3</td>
<td>0.01</td>
<td>-0.03</td>
<td></td>
</tr>
<tr>
<td>Haemodialysis to start RRT (%)</td>
<td>74.2</td>
<td>65.9</td>
<td>0.00</td>
<td>0.18</td>
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<tr>
<td>Peritoneal dialysis to start RRT (%)</td>
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<td>23.6</td>
<td>0.00</td>
<td>0.05</td>
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<td>Transplant to start RRT (%)</td>
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<td>10.4</td>
<td>0.00</td>
<td>-0.48</td>
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<tr>
<td>1995-99 (%)</td>
<td>23.4</td>
<td>29.5</td>
<td>0.00</td>
<td>-0.14</td>
<td></td>
</tr>
<tr>
<td>2000-04 (%)</td>
<td>32.4</td>
<td>34.3</td>
<td>0.00</td>
<td>-0.04</td>
<td></td>
</tr>
<tr>
<td>2005-09 (%)</td>
<td>44.2</td>
<td>36.2</td>
<td>0.00</td>
<td>0.16</td>
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<tr>
<td>1995-99 (%)</td>
<td>23.4</td>
<td>29.5</td>
<td>0.00</td>
<td>-0.14</td>
<td></td>
</tr>
<tr>
<td>2000-04 (%)</td>
<td>32.4</td>
<td>34.3</td>
<td>0.00</td>
<td>-0.04</td>
<td></td>
</tr>
<tr>
<td>2005-09 (%)</td>
<td>44.2</td>
<td>36.2</td>
<td>0.00</td>
<td>0.16</td>
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Table 4.2: Characteristics of dialysis only and transplanted Indigenous patients before and after propensity score match

<table>
<thead>
<tr>
<th></th>
<th>Dialysis only</th>
<th>Unmatched</th>
<th>Matched</th>
<th>Standardised difference</th>
<th>Dialysis only</th>
<th>Unmatched</th>
<th>Matched</th>
<th>Standardised difference</th>
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<td><strong>Number</strong></td>
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<td>278</td>
<td>176</td>
<td>176</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age at start of RRT (years)</strong></td>
<td>51.1</td>
<td>41.9</td>
<td>0.00</td>
<td>-0.83</td>
<td>43.2</td>
<td>42.9</td>
<td>0.76</td>
<td>-0.03</td>
</tr>
<tr>
<td><strong>eGFR at start of RRT (ml/min/1.73m²)</strong></td>
<td>5.1</td>
<td>4.6</td>
<td>0.00</td>
<td>-0.19</td>
<td>4.7</td>
<td>4.5</td>
<td>0.54</td>
<td>-0.07</td>
</tr>
<tr>
<td><strong>Years of dialysis before transplant</strong></td>
<td>3.0</td>
<td>3.0</td>
<td>0.00</td>
<td>-0.24</td>
<td>2.9</td>
<td>2.4</td>
<td>0.06</td>
<td>-0.21</td>
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<tr>
<td><strong>Sex (male, %)</strong></td>
<td>42.8</td>
<td>56.8</td>
<td>0.00</td>
<td>-0.28</td>
<td>54.5</td>
<td>54.5</td>
<td>1.00</td>
<td>0.00</td>
</tr>
<tr>
<td><strong>Late Referral (%)</strong></td>
<td>33.6</td>
<td>29.9</td>
<td>0.21</td>
<td>0.08</td>
<td>30.7</td>
<td>31.8</td>
<td>0.82</td>
<td>-0.02</td>
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<tr>
<td><strong>Lung Disease (%)</strong></td>
<td>13.0</td>
<td>4.7</td>
<td>0.00</td>
<td>0.30</td>
<td>6.3</td>
<td>4.0</td>
<td>0.33</td>
<td>-0.11</td>
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<tr>
<td><strong>Coronary Disease (%)</strong></td>
<td>31.2</td>
<td>12.6</td>
<td>0.00</td>
<td>0.46</td>
<td>13.1</td>
<td>14.2</td>
<td>0.76</td>
<td>-0.03</td>
</tr>
<tr>
<td><strong>Peripheral Vascular Disease (%)</strong></td>
<td>21.0</td>
<td>5.4</td>
<td>0.01</td>
<td>0.19</td>
<td>2.3</td>
<td>5.1</td>
<td>0.16</td>
<td>-0.15</td>
</tr>
<tr>
<td><strong>Cerebrovascular Disease (%)</strong></td>
<td>9.9</td>
<td>5.0</td>
<td>0.01</td>
<td>0.19</td>
<td>2.3</td>
<td>5.1</td>
<td>0.16</td>
<td>-0.15</td>
</tr>
<tr>
<td><strong>Diabetes (%)</strong></td>
<td>80.0</td>
<td>49.6</td>
<td>0.00</td>
<td>0.67</td>
<td>52.8</td>
<td>55.1</td>
<td>0.67</td>
<td>-0.05</td>
</tr>
<tr>
<td><strong>Smoking ever (%)</strong></td>
<td>63.1</td>
<td>59.7</td>
<td>0.27</td>
<td>0.07</td>
<td>61.4</td>
<td>59.7</td>
<td>0.74</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Mean BMI (kg/m²)</strong></td>
<td>27.7</td>
<td>27.3</td>
<td>0.29</td>
<td>-0.07</td>
<td>28.6</td>
<td>27.3</td>
<td>0.07</td>
<td>-0.194</td>
</tr>
<tr>
<td><strong>BMI&lt;18.5 (%)</strong></td>
<td>5.1</td>
<td>4.9</td>
<td>0.78</td>
<td>0.02</td>
<td>3.4</td>
<td>5.7</td>
<td>0.31</td>
<td>-0.11</td>
</tr>
<tr>
<td><strong>BMI&gt;30 (%)</strong></td>
<td>31.3</td>
<td>29.5</td>
<td>0.54</td>
<td>0.04</td>
<td>36.4</td>
<td>30.1</td>
<td>0.21</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>Major city (%)</strong></td>
<td>13.2</td>
<td>25.2</td>
<td>0.00</td>
<td>-0.31</td>
<td>22.7</td>
<td>26.7</td>
<td>0.39</td>
<td>-0.09</td>
</tr>
<tr>
<td><strong>Inner regional (%)</strong></td>
<td>8.9</td>
<td>9.7</td>
<td>0.67</td>
<td>-0.03</td>
<td>8.0</td>
<td>7.4</td>
<td>0.84</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Outer regional (%)</strong></td>
<td>29.3</td>
<td>28.4</td>
<td>0.75</td>
<td>0.02</td>
<td>27.3</td>
<td>33.5</td>
<td>0.20</td>
<td>-0.14</td>
</tr>
<tr>
<td><strong>Remote (%)</strong></td>
<td>18.7</td>
<td>16.9</td>
<td>0.47</td>
<td>0.05</td>
<td>24.4</td>
<td>15.3</td>
<td>0.03</td>
<td>0.23</td>
</tr>
<tr>
<td><strong>Very remote (%)</strong></td>
<td>29.9</td>
<td>19.8</td>
<td>0.00</td>
<td>0.23</td>
<td>17.6</td>
<td>17.0</td>
<td>0.89</td>
<td>-0.02</td>
</tr>
<tr>
<td><strong>Haemodialysis to start RRT (%)</strong></td>
<td>83.0</td>
<td>82.4</td>
<td>0.79</td>
<td>0.02</td>
<td>84.7</td>
<td>82.4</td>
<td>0.57</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Peritoneal dialysis to start RRT (%)</strong></td>
<td>17.0</td>
<td>16.2</td>
<td>0.73</td>
<td>0.02</td>
<td>15.3</td>
<td>15.3</td>
<td>1.00</td>
<td>0.00</td>
</tr>
<tr>
<td><strong>Transplant to start RRT (%)</strong></td>
<td>0.0</td>
<td>1.4</td>
<td>0.00</td>
<td>-0.17</td>
<td>0.0</td>
<td>2.3</td>
<td>0.04</td>
<td>-0.22</td>
</tr>
<tr>
<td><strong>1995–1999 (%)</strong></td>
<td>21.7</td>
<td>36.0</td>
<td>0.00</td>
<td>-0.32</td>
<td>34.1</td>
<td>34.1</td>
<td>1.00</td>
<td>0.00</td>
</tr>
<tr>
<td><strong>2000–2004 (%)</strong></td>
<td>33.0</td>
<td>36.3</td>
<td>0.27</td>
<td>-0.07</td>
<td>33.5</td>
<td>33.5</td>
<td>1.00</td>
<td>0.00</td>
</tr>
<tr>
<td><strong>2005–2009 (%)</strong></td>
<td>45.3</td>
<td>27.7</td>
<td>0.00</td>
<td>0.37</td>
<td>32.4</td>
<td>32.4</td>
<td>1.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>
While 40.4% of non-Indigenous transplant patients were matched, 64.4% of Indigenous transplant patients were, suggesting that overall Indigenous dialysis only and transplanted patients were more alike than non-Indigenous treatment groups.

There were also important differences between matched dialysis-only and transplanted patients within the non-Indigenous cohort. Once matched, compared to dialysis-only patients non-Indigenous transplanted patients were younger, had both a lower mean BMI and lower levels of obesity, had received dialysis for a shorter period, were less likely to have received haemodialysis as initial treatment and were somewhat less likely to come from a major capital city and more likely to come from outer regional areas. In contrast differences between Indigenous dialysis-only and transplanted patients were much less evident.

Years of follow-up, the number of deaths and the unadjusted death rate for each matched patient group are shown in Table 4.3, and Kaplan-Meier failure curves are shown in Figure 4.2 (for matched non-Indigenous patients) and Figure 4.3 (for matched Indigenous patients). The log-rank test confirmed a significant difference in the risk of death between dialysis-only and transplanted patients for both non-Indigenous (p<0.001) and Indigenous (p=0.002) groups.
Table 4.3: Follow-up, number of deaths and death rate of matched cohorts, by Indigenous and transplant status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-Indigenous</th>
<th>Indigenous</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dialysis only</td>
<td>Transplant</td>
</tr>
<tr>
<td>Number, matched</td>
<td>2,940</td>
<td>2,940</td>
</tr>
<tr>
<td>Cumulative years of follow-up</td>
<td>9,728.2</td>
<td>11,598.4</td>
</tr>
<tr>
<td>Number of deaths</td>
<td>997</td>
<td>243</td>
</tr>
<tr>
<td>Mortality rate (per 100 patient years)</td>
<td>10.2</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Figure 4.2: Kaplan-Meier failure curves for non-Indigenous matched cohort
The magnitude of the survival benefits of transplantation for the non-Indigenous matched cohort remained largely unchanged in unadjusted (HR 0.20, 95% CI 0.18–0.23) and propensity score adjusted (HR 0.23, 95% CI 0.18–0.30) Cox PH models, as well as the fully adjusted model (HR 0.18, 95% CI 0.15–0.22) that included all other comorbidity, late referral, inception time period and remoteness terms (Table 4.4). In the Indigenous matched cohort the reduction in the risk of death with transplantation was present but not as strong in unadjusted (HR 0.55, 95% CI 0.39–0.78) and propensity score adjusted (HR 0.68, 95% CI 0.31–1.51) Cox PH models as in the fully adjusted model (HR 0.23, 95% CI...
0.08–0.69). The magnitude of survival benefit with transplantation in Indigenous patients mirrored that of non-Indigenous patients with a fully adjusted model only with the addition of a transplant-remoteness interaction term.
Table 4.4: Cox PH models for non-Indigenous and Indigenous matched cohorts

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-Indigenous Hazard Ratio (95% CI)</th>
<th>Indigenous Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplant (:Dialysis only) §</td>
<td>0.18 (0.15–0.22)</td>
<td>0.23 (0.08–0.69)</td>
</tr>
<tr>
<td>Age at start of RRT (per year)</td>
<td>1.019 (1.013–1.023)</td>
<td>1.036 (1.02–1.05)</td>
</tr>
<tr>
<td>Years of dialysis (per year)</td>
<td>1.12 (1.10–1.15)</td>
<td>1.02 (0.94–1.11)</td>
</tr>
<tr>
<td>Sex (male:female)</td>
<td>0.99 (0.87–1.11)</td>
<td>1.03 (0.69–1.56)</td>
</tr>
<tr>
<td>Late referral (y:n)</td>
<td>1.21 (1.05–1.41)</td>
<td>1.43 (0.95–2.14)</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes (y:n)</td>
<td>1.75 (1.54–1.99)</td>
<td>1.34 (0.84–2.14)</td>
</tr>
<tr>
<td>Coronary artery disease (y:n) Transplant</td>
<td>1.29 (0.91–1.82)</td>
<td>1.61 (0.73–3.52)</td>
</tr>
<tr>
<td>Coronary artery disease (y:n) Dialysis only</td>
<td>1.45 (1.21–1.74)</td>
<td>1.27 (0.62–2.61)</td>
</tr>
<tr>
<td>Peripheral vascular disease (y:n)</td>
<td>1.59 (1.30–1.94)</td>
<td>1.50 (0.85–2.64)</td>
</tr>
<tr>
<td>Cerebrovascular disease (y:n)</td>
<td>1.48 (1.15–1.90)</td>
<td>0.61 (0.21–1.74)</td>
</tr>
<tr>
<td>Lung disease (y:n)</td>
<td>1.42 (1.11–1.80)</td>
<td>0.59 (0.17–2.05)</td>
</tr>
<tr>
<td>BMI &lt;18.5 (:18.5–30)</td>
<td>1.39 (1.06–1.82)</td>
<td>1.30 (0.40–4.26)</td>
</tr>
<tr>
<td>BMI &gt;30 (:18.5–30) Dialysis only</td>
<td>0.78 (0.66–0.91)</td>
<td>0.71 (0.41–1.23)</td>
</tr>
<tr>
<td>BMI &gt;30 (:18.5–30) Transplant</td>
<td>1.30 (0.97–1.75)</td>
<td>0.68 (0.31–1.50)</td>
</tr>
<tr>
<td>Ever smoked (y:n)</td>
<td>1.10 (0.98–1.24)</td>
<td>0.84 (0.56–1.25)</td>
</tr>
<tr>
<td>Time period</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1995–99 (:2005–09)</td>
<td>1.59 (1.38–1.84)</td>
<td>1.81 (0.98–3.36)</td>
</tr>
<tr>
<td>2000–04 (:2005–09)</td>
<td>1.42 (1.23–1.63)</td>
<td>1.74 (0.96–3.17)</td>
</tr>
<tr>
<td>Remoteness classification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major city (Transplant:Dialysis only)*</td>
<td>0.18 (0.15–0.22)</td>
<td>0.23 (0.08–0.69)</td>
</tr>
<tr>
<td>Inner regional (Transplant:Dialysis only)*</td>
<td>0.13 (0.09–0.19)</td>
<td>0.17 (0.02–1.84)</td>
</tr>
<tr>
<td>Outer regional (Transplant:Dialysis only)*</td>
<td>0.16 (0.10–0.25)</td>
<td>0.65 (0.30–1.38)</td>
</tr>
<tr>
<td>Remote (Transplant:Dialysis only)*</td>
<td>0.11 (0.03–0.48)</td>
<td>0.69 (0.28–1.71)</td>
</tr>
<tr>
<td>Very remote (Transplant:Dialysis only)*</td>
<td>0.07 (0.01–0.78)</td>
<td>0.78 (0.30–2.07)</td>
</tr>
</tbody>
</table>

* The hazard ratios for each remoteness area for transplant compared to dialysis–only patients are calculated as transplant status x remoteness classification x transplant/remoteness interaction term (Figure 4.4).

§ The “main effect” transplant:dialysis–only hazard ratios refer to major capital cities.
Figure 4.4 highlights the differing impact of the transplant-remoteness interaction term for the non-Indigenous and Indigenous matched cohorts. For non-Indigenous patients the point estimates of the risk of death with transplantation are very similar across all remoteness categories, with clear benefit compared to each non-transplanted comparator population. For Indigenous patients a magnitude of effect estimate similar to the non-Indigenous was present for those from major capital cities and inner regional areas, but was much weaker in outer regional, remote and very remote areas. Only in major capital cities did it appear that there was a clear and statistically significant benefit of transplantation over dialysis for Indigenous patients.
Figure 4.4: Effect of remoteness on mortality by transplant and Indigenous status

Adjusted Risk of Death by Remoteness Category & Transplant Status

**Non-Indigenous**
- Transplant
- Dialysis Only

**Indigenous**

*Remoteness Category*
Adjusted for age, sex, late referral, comorbidities & years of dialysis
* Indigenous inner regional transplant hazard ratio was zero
4.6 Discussion

In this analysis of Australian kidney transplant recipients matched to similar non-transplanted patients, we found that there was a large and enduring survival benefit for non-Indigenous Australians receiving a transplant compared with continuing dialysis. However, this survival benefit (though clear) was not as pronounced for Indigenous patients facing transplantation in unadjusted analysis, and was only evident for Indigenous recipients from major capital cities when any remaining differences in matched non-transplanted and transplant groups were adjusted for (Figure 4.4). The variation in the risk of death by remoteness for non-Indigenous patients (whether transplanted or continuing on dialysis) remains similar to previously published findings (Gray, Dent & McDonald 2012).

This difference in Indigenous transplant survival by remoteness raises the possibility of other factors besides ethnicity contributing to worse outcomes. Socioeconomic status among Indigenous Australians decreases steadily from major capital cities to very remote areas (Biddle 2009); poor living conditions may contribute to the increased risk of death due to infections previously described (Rogers, Lawton & Jose 2006). Individual socioeconomic status information is not available within ANZDATA.

Indigenous patients are less likely to be put on the waiting list and less likely to be transplanted (Cass et al. 2003). Part of the reason for the
more limited benefit in survival post-transplant seen here may be that a lower proportion of Indigenous patients who otherwise seemed suitable based on baseline ANZDATA variables (that is, had the same propensity for transplantation) were actually transplanted than non-Indigenous patients. If a higher proportion of Indigenous dialysis-only were transplanted we might have seen a larger difference between transplanted and dialysis-only patients, although this likely would have been because of a reduction in Indigenous dialysis-only survival rather than improvements in Indigenous transplanted survival.

Of note is that Indigenous transplant patient five year survival remains at around 75%, just below the arbitrary “expected” 80% level suggested in national guidelines for transplant recipient selection (Campbell et al. 2013). When considered from the Indigenous patient’s point of view, kidney transplantation may have other benefits (such as the ability to return home to remote locations) (Anderson et al. 2012a) and appears at least to have equal short-term survival and better long-term survival than dialysis. It is clear that many Indigenous dialysis patients are interested in transplantation, and see potential benefit in it (Devitt & McMasters 1998a). Whether these benefits come at the cost of more hospitalisation admissions or bed-days compared to similar dialysis patients has not been discussed in the literature and could be explored in the future using data linkage techniques.
The comparison outlined here (between transplant and dialysis within each ethnicity group) is more clinically and individually relevant than previous comparisons between Indigenous and non-Indigenous transplant recipients (McDonald 2004) (Rogers, Lawton & Jose 2006). Being an Indigenous Australian is not a treatment decision; transplantation is. Whilst it is important to understand the disparity in outcome between Indigenous and non-Indigenous patients, the more relevant disparity to compare is the difference in benefit for one treatment (transplant) over another (dialysis) for each group, not a direct head-to-head comparison of outcomes by ethnicity. Comparing the transplant-dialysis survival difference for Indigenous and non-Indigenous patients confirms that Indigenous transplant patient survival lags behind non-Indigenous survival, even as it shows that transplantation is associated with better outcomes than continuing on dialysis for Indigenous patients.

This is an observational study, not a prospective randomised trial: there is the possibility of residual confounding due to factors unmeasured and/or not recorded in the ANZDATA Registry. While collecting further prospective observational data about Indigenous transplant recipients appears highly desirable, a randomised trial of kidney transplantation for Indigenous dialysis patients is very unlikely, not least because of ethical issues. Comparing transplanted patients with those receiving dialysis who are waitlisted for transplant is the most appropriate methodology to minimise bias by indication, but only around 40 or fewer Indigenous
dialysis patients reach the waiting list every year, often for short periods of time (McDonald et al. 2012).

There are several other limitations to the study. It was not possible to match for time on dialysis, as matching based on the propensity score needed to occur before a (theoretical) time of transplantation could be assigned to dialysis-only patients. For this reason, only characteristics at the start of RRT could be used for matching, rather than characteristics at or near the time of transplant. The characteristics used for the calculation of the propensity score (and thus the matching) were limited to those available within the ANZDATA dataset, and thus did not include details about transplant assessment referrals or other comorbidities beyond those recorded. Thus, it was not possible to account for all potential confounders.

Some may see the less pronounced survival benefit for Indigenous patients receiving a transplant compared to non-Indigenous patients as a reason to restrict transplantation, particularly given the choice to give the same kidney to another (non-Indigenous) patient who would appear to derive greater benefit. Tensions exist between maximising the collective utility of a scarce resource and ensuring equity of access to over-represented marginalised or disadvantaged patient groups, and there is concern about how benefits are measured and by whom (Courtney & Maxwell 2009; Lim et al. 2011; Pussell, Bendorf & Kerridge 2009).
The data presented show Indigenous transplant patient survival to be similar to Australian non-Indigenous patient survival in the 1980s (Clayton, Lim & Hurst 2013); without continuing to offer transplantation to higher risk groups, improvements in outcome (like those for non-Indigenous patients transplanted since the 1980s) will not occur.

The survival benefits of transplantation for non-Indigenous recipients are dramatic. In contrast, survival benefits for Indigenous recipients, while present, are not as dramatic and are not apparent for at least a year. Excessive pessimism about kidney transplantation for Indigenous patients may be due to comparison of outcomes with non-Indigenous patients, rather than considering what may be in the best interests of individual Indigenous patients themselves. Developing data-driven tools that better predict risk for Indigenous patients facing kidney transplantation, and strategies that improve survival for Indigenous patients from regional and remote Australia, should be a priority.
Chapter 5: What’s Wrong with Missing Dialysis?
Pattern and Outcomes of Haemodialysis Attendance in Australia’s Northern Territory, 1995–2011

5.1 Chapter Overview
This chapter comprises a publication-ready manuscript titled “What’s wrong with missing dialysis? Pattern and outcomes of haemodialysis attendance in Australia’s Northern Territory, 1995–2011.”

5.2 Abstract
Aim: To describe the pattern and outcomes of variation of haemodialysis attendance in the Northern Territory (NT).

Background: No Australian reports and only few dated reports elsewhere have described rates and outcomes of haemodialysis attendance, which may impact on outcomes.

Methods: All patients starting haemodialysis in the NT between 1st January 1995 and 31st December 2011 were included by linking NT public hospitalisation, subsidised patient travel and ANZDATA registry data. Mean yearly attendance from haemodialysis start was calculated, and associations examined by multiple linear regression. Fine and Gray
competing risks proportional hazards models (CR-PH) were used to examine the chances of death and transplantation per year by mean yearly attendance category, adjusted for demographic and clinical differences; negative binomial regression (NBR) was used to model adjusted incidence rate ratios (IRR) for hospitalisation.

**Results:** Of 618 patients registered for haemodialysis for ≥1 year, 49.5% attended 2.0-2.75 haemodialysis sessions/week on average in the first year; 29.3% attended <2.0. Indigenous status was associated with lower mean attendance; relocation from remote areas was not. Lower mean attendance was associated with higher rates of death in adjusted CR-PH models: <2.0 sessions/week (compared with >2.75) sub-hazard ratio (SHR, with 95%CI) 3.47 (1.50-8.07), 2.0-2.75 sessions/week SHR 1.73 (0.75-3.96). No patients attending <2.0 sessions/week were transplanted, and few attending 2.0-2.75 (SHR 0.37 (0.07-1.91)). An adjusted NBR model showed higher rates of hospitalisation:<2.0 sessions/week IRR 2.95 (2.34-3.72), 2.0-2.75 sessions/week IRR 2.03 (1.67-2.47).

**Conclusions:** Attending <2.75 sessions/week on average was associated with poorer outcomes, with particular risks for <2.0 sessions/week. Relocation for treatment did not necessarily result in lower haemodialysis attendance in the first year. Understanding reasons for missing dialysis is needed to improve outcomes.
5.3 Introduction

Haemodialysis treatment with a “minimal utilisation rate” of three sessions a week has been widely regarded as the standard of care since at least 1964 (Scribner et al. 2004). Whilst a substantial body of literature about the patterns of haemodialysis treatment attendance has grown since then (Bello et al. 2013; Bieber et al. 2014; Bleyer et al. 1999; Block et al. 1998; DeOreo 1997; Haghighi et al. 2002; Hecking et al. 2004; Kutner et al. 2002; Leggat et al. 1998; Sherman et al. 1994; Taskapan et al. 2005), each setting will have particular social and economic circumstances, dialysis practices and population characteristics. All have been based on non-Australian and non-Indigenous experiences. Very few have focused on the relationship between attendance and outcomes such as mortality (Bander & Walters 1998; Hanson et al. 1999; Kimmel et al. 1998; Leggat et al. 1998; Lin et al. 2012; O'Brien 1990; Rahman et al. 2000; Saran et al. 2003; Stankuviene et al. 2010).

Study Setting

Indigenous Australians have a higher incidence of end-stage kidney disease (ESKD) requiring renal replacement therapy (RRT) than non-Indigenous Australians (McDonald, Jose & Hurst 2012). A high proportion of Indigenous patients come from rural and remote areas (Cass et al. 2001), which are associated with markers of poorer socioeconomic status (Biddle 2009). Relocation for treatment is common (Cass et al. 2001), and its impact has been well-described (Anderson et al. 2005).
Indigenous Australians are more likely to receive centre- or satellite-based haemodialysis and much less likely to receive a kidney transplant than non-Indigenous Australians (McDonald, Jose & Hurst 2012; Yeates et al. 2009). They have an increased risk of death on RRT compared to non-Indigenous patients when demographic and comorbidity differences are considered, although the reasons for this survival disparity are not clear from patient-level registry data alone (Lawton et al. 2015).

The Northern Territory (NT) of Australia is a large geographical area of over 1.4 million km² with a relatively small population comprised of a largely urban centralised non-Indigenous population and a smaller, largely remote, decentralised and disadvantaged Indigenous population that is culturally and linguistically heterogeneous. Around two-fifths of all Indigenous Australians receiving RRT are NT residents. RRT is coordinated from the two main urban centres (Darwin and Alice Springs). Although smaller satellite haemodialysis and self-care haemodialysis services have been established in a few more remote centres in recent years, the majority of patients are still treated with satellite haemodialysis in the main urban centres and all patients start treatment there (ANZDATA Registry 2015a, 2015c).

The existing literature about haemodialysis attendance for Indigenous Australians suggests that some may not attend all prescribed haemodialysis sessions, particularly those who need to relocate from home communities to urban centres to receive treatment (Anderson et al. 2012a).
“Compliance” with dialysis treatment has been highlighted by Australian nephrologists as very important when considering referral for kidney transplantation (Anderson et al. 2012; Cass et al. 2007). However, we are not aware of any published data about the rates, associations or outcomes of haemodialysis attendance variation from Australia. This may be one reason for the 40% higher risk of death on RRT for Indigenous compared to non-Indigenous Australians (Lawton et al. 2015).

The aim of this study was to describe the rates, associations and outcomes of haemodialysis attendance variation in the NT using linked hospital administrative and renal registry data.

5.4 Methods

Study Population and Data Sets

This study included data about all patients starting treatment with haemodialysis at any time in the NT between 1995 and 2011 inclusive. Data sources included the NT public hospital separations dataset (which record all hospital admissions including same day attendances at NT public hospitals and associated satellite haemodialysis centres) and the Patient Assistance and Travel System (PATS) dataset (which records all government-subsidised interstate travel for treatment), both held by the NT Department of Health. Data about NT patients were also obtained from the Australian and New Zealand Dialysis and Transplant...
(ANZDATA) Registry, which collects observational data, submitted by treating renal units, about all patients receiving chronic RRT in Australia and New Zealand. All NT patients have unique health record identifiers in both NT Health Department and ANZDATA datasets.

Data Linkage

ANZDATA and hospital data were linked using an independent third-party consultant (approved by data custodians) who used a deterministic algorithm followed by individual reviews of mismatched records. Records for a total of 1,088 patients starting haemodialysis between 1st January 1995 and 31st December 2011 inclusive were identified in both ANZDATA and NT public hospitals data. PATS data for those included were subsequently linked and all records de-identified before analysis.

Data Management

For all ANZDATA-registered NT patients, ICD-9-CM (for records prior to July 1998) and ICD-10-AM (from July 1998) diagnosis and procedure codes were used to extract data about all patients who had any hospital admissions or attendances for which either same-day dialysis as a diagnosis or haemodialysis as a procedure was recorded. Most haemodialysis treatments were provided as same-day admissions; patients admitted to hospital for one night or more, or interstate for any treatment (as recorded in PATS), were assigned a haemodialysis
frequency of three times a week for the duration of admission or interstate travel. Haemodialysis treatment frequency was calculated for each week from the recorded date of treatment commencement until censoring due to treatment modality change (including peritoneal dialysis, home haemodialysis or transplantation), death, loss to follow-up, recovery of renal function or the end of the study; this weekly treatment frequency was averaged over each year of haemodialysis treatment from commencement, or part thereof.

Measures

Indigenous status was recorded in NT public hospital separations data, and included those identified as being of Aboriginal and/or Torres Strait Islander origin for the majority of their admissions. All others were classified non-Indigenous. These data have been validated repeatedly (Foley, Zhao & Condon 2012).

Comorbid conditions recorded within ANZDATA at commencement of RRT and at each census date thereafter included coronary artery disease, peripheral vascular disease, cerebrovascular disease, chronic lung disease and diabetes. Comorbid conditions were recorded in three categories: yes, no or suspected. For this analysis, “no” and “suspected” were combined. Body mass index (BMI) was calculated from height and weight at commencement of RRT, and from estimated body weight without fluid
retention data at each measurement date thereafter. Late referral was defined as starting RRT within three months of being referred to a nephrologist. Estimated glomerular filtration rate (eGFR) at the start of RRT was calculated using the CKD-EPI formula (Johnson et al. 2012; Maple-Brown et al. 2012).

Relocation was defined using place of residence recorded on the date of first admission for haemodialysis within NT public hospital separations data, mapped onto the Accessibility and Remoteness Index of Australia (ARIA+). Patients were deemed “relocated to start treatment” if they received their first treatment in a different (more central) remoteness category than their place of residence, and not if they had received their first treatment within the same remoteness category. Because the two main hubs for haemodialysis services in the NT have different remoteness categories, relocation assignment was performed separately for Top End and Central Australia regions.

Dates of death, transplantation or other RRT modality change as reported to ANZDATA were used; kidney transplant operations are not performed in the NT. Both same day haemodialysis and non-same day hospitalisation admission dates were taken from NT public hospitals separation data.
**Statistical Analyses**

For each year after the start of treatment until censored, each patient was categorised according to the mean weekly haemodialysis attendance into three clinically relevant groups: ≤2.0 sessions/week (missing one or more of three prescribed sessions a week on average), 2.01–2.75 sessions/week and >2.75 sessions/week (missing less than one prescribed session a month on average). Attendance categories of uncensored patients were compared using the Kruskal-Wallis test for all categorical variables, and one way ANOVA for the continuous variables, age at start of year of follow-up and log-transformed eGFR at baseline.

The association between first year and subsequent years’ attendance was graphed and correlation assessed using simple linear regression.

Associations of demographic and clinical variables with each year’s average weekly attendance as a continuous outcome were assessed using multiple linear regression, weighted for the time-at-risk during the first year of follow-up (for those censored during the year).

Patients who transferred to the NT after commencing treatment interstate were excluded to avoid immortal time bias. To minimise potentially informative censoring, competing risks methods were used as they do not assume that those censored for treatment modality change,
death, loss to follow-up or recovery of renal function have the same subsequent theoretical risk of other events (Teixeira et al. 2013).

The cumulative incidences of death and transplantation to five years of follow-up were calculated and graphed by category of first year mean weekly attendance (Coviello & Boggess 2004), with the cumulative weighted differences between groups compared (Pepe & Mori 1993). Attendance category in the first year after starting treatment was used to balance a reasonable amount of time to observe and classify attendance with enough uncensored patients remaining to allow generalisable conclusions to be drawn.

For each year after start of treatment, Fine and Gray competing risks proportional hazards (CR-PH) models were used to examine the hazard for death or hospitalisation by category of the previous years’ attendance (Fine & Gray 1999). Similarly, negative binomial regression was used to model the relationship between attendance category and rates of overnight (that is, not same-day) hospitalisation by category of the previous years’ attendance. Variables were added to these models to determine which contributed most to the outcome of the final model. Explanatory variables included Indigenous status, gender, late referral and relocation at start of treatment and age, comorbidities, and BMI category at the start of year of interest.
All analyses were conducted using Stata/MP4 12.1 (StataCorp, College Station, Texas, USA). Approval for the study was granted by the combined Human Research Ethics Committee of the NT Department of Health and Menzies School of Health Research (HREC-2011-1567); this process included an assessment by an Aboriginal Ethics Sub Committee with veto powers.

5.5 Results

Separate, unlinked data from ANZDATA suggests that only seven NT patients started RRT with a kidney transplant and 85 started with peritoneal dialysis during the period of interest. The remaining 91.7% of the total NT patient population starting RRT commenced with satellite or hospital haemodialysis and were therefore included in this study. Of note in this population was the relatively low rate of censoring due to moving to other modalities. Figure 5.1 shows a flow chart of the study population including excluded and censored individuals.
Figure 5.1: Study composition, including those leaving study over time

1746 patients in NT public hospitals dataset from 01/01/1995 to 31/12/2011 with ICD-9/ICD-10 haemodialysis procedure codes and/or same day dialysis diagnosis codes

1088 patients recorded in ANZDATA as having haemodialysis at some stage in the NT

(341 patients taking 668 subsidised trips interstate for medical reasons)

1088 patients recorded in both ANZDATA and NT public hospitals as having haemodialysis at some stage

- 36 transferred to NT after starting treatment interstate
- 43 started treatment with peritoneal dialysis (PD) first
- 0 started treatment with home haemodialysis (HHD) first
- 0 started treatment with transplantation (Tx) first
- 56 missing creatinine at baseline
- 4 missing late referral information
- 8 missing height
- 2 missing weight at baseline
- 2 missing residence of origin remoteness information

937 patients starting haemodialysis in NT included in study

- 133 censored by 3 months (30 deaths, 5 Tx, 41 PD, 0 HHD, 23 left NT, 10 recovered, 2 lost to follow-up)
- 804 completed three months’ follow-up

- 186 censored by one year (64 deaths, 14 Tx, 41 PD, 4 HHD, 18 left NT, 10 recovered)
- 618 completed one year’s follow-up

- 136 censored by two years (63 deaths, 13 Tx, 10 PD, 4 HHD, 3 left NT)
- 482 completed two years’ follow-up

- 106 censored by three years (37 deaths, 13 Tx, 4 PD, 7 HHD, 5 left NT)
- 376 completed three years’ follow-up

- 109 censored by four years (44 deaths, 14 Tx, 2 PD, 2 HHD, 5 left NT)
- 267 completed four years’ follow-up

- 73 censored by five years (29 deaths, 8 Tx, 2 HHD)
- 194 completing five years’ follow-up

194
The characteristics of the population continuing haemodialysis for more than one year are outlined in Table 5.1, separated by categories of mean weekly attendance for the first year. Patients with lower mean weekly haemodialysis attendance were more likely to be Indigenous, be treated...
in Central Australia, have relocated to start treatment and have lower levels of endogenous kidney function; they were less likely to have coronary artery disease. Patients starting treatment in more recent years had a similar median of mean weekly attendance overall to earlier years. The proportion with mean weekly attendance ≤2.0 sessions/week in the first year of treatment for each starting time period varied somewhat: 1995–1999, 21.1%; 2000–2004, 31.7%; 2005–2009, 31.3%; 2010–2011, 27.9%.

Patterns of haemodialysis attendance are shown in Figure 5.2. Mean weekly attendance was skewed from the commonly prescribed three times a week towards fewer attendances for each year after starting treatment; there was a non-significant rise in the median of mean weekly attendance and fall in interquartile range in subsequent years. Figure 5.3 highlights the correlation between mean weekly attendance in the first year and subsequent years after starting treatment; this relationship, although present, was less pronounced over time.
Figure 5.2: Mean weekly attendance for each year after commencement of haemodialysis treatment

Includes all until recovery/loss to follow-up or transfer to PD/home HD/transplant/interstate
Figure 5.4 demonstrates the correlates of mean attendance during the first year with demographic and clinical variables within the dataset adjusted for all available demographic and clinical variables. Of the demographic variables, being Indigenous was associated with much lower mean weekly first year attendance; receiving dialysis in the Top End was associated with higher attendance. Of note, unadjusted analysis showed that needing to relocate to start dialysis was associated with a lower mean weekly first year attendance; the log-transformed eGFR at dialysis start was not. After adjusting for other variables (particularly Indigenous status) neither needing to relocate to start dialysis nor the log-transformed eGFR at dialysis start were associated with reductions in
mean weekly first year attendance. Of all comorbidities only having a BMI>30 was associated with a significantly higher dialysis attendance.

Figure 5.4: Correlates with dialysis attendance in first year after start of treatment

The unadjusted cumulative likelihoods of death or transplantation are shown in Figure 5.5, divided by categories of first year mean weekly haemodialysis attendance. The unadjusted likelihoods for the 2.01–2.75 group were not significantly different from the >2.75 group. Those attending ≤2.0 per week had a greater risk of death than those with higher attendance, most evident after two years of treatment (p=0.005);
there were no kidney transplants at all at this attendance level for those surviving at least a year (p=0.004 compared to higher attendance categories).

Figure 5.5: Cumulative incidence of death or transplantation, by attendance category (unadjusted)
Death

Table 5.2 shows the main effects of the risk of death using Fine and Gray CR-PH models with various levels of adjustment, for different time periods after starting treatment stratified by the previous period (generally the previous year's) mean weekly haemodialysis attendance. In general, these show that mean attendance at ≤2.0 sessions/week was associated with a significant and sizeable increase in the risk of death even after adjusting for age, sex and Indigenous status, or these variables together with the other available demographic variables (relocation, treatment centre at start, starting cohort, log eGFR and late referral) and comorbidities (diabetes, coronary artery disease, peripheral vascular disease, cerebrovascular disease, lung disease, a BMI<18.5 or >30 kg/m²).

For those with mean weekly attendance at 2.01–2.75 sessions/week there was a consistent but generally non-significant trend to an increased risk of death that was also similar with and without covariate adjustments.

For the fourth and fifth years of treatment increases in the risk of death for those with mean weekly attendance ≤2.0 sessions/week were seen progressively with adjustment for basic demographic variables and subsequently for other demographic and comorbidity variables; confidence intervals were wide.
Table 5.2: Risk of death in subsequent year by attendance category (Fine and Gray CR-PH models) with various adjustments

<table>
<thead>
<tr>
<th>Mean attendance per week</th>
<th>Completing 1st 3 months (n=806)</th>
<th>Completing 1st year (n=618)</th>
<th>Completing 2nd year (n=482)</th>
<th>Completing 3rd year (n=376)</th>
<th>Completing 4th year (n=267)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>HR</td>
<td>95% CI</td>
<td>HR</td>
</tr>
<tr>
<td>Unadjusted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2.0</td>
<td>3.09</td>
<td>1.38–6.92</td>
<td>3.04</td>
<td>1.33–6.95</td>
<td>2.01</td>
</tr>
<tr>
<td>2.01–2.75</td>
<td>1.73</td>
<td>0.74–4.05</td>
<td>1.60</td>
<td>0.69–3.67</td>
<td>1.78</td>
</tr>
<tr>
<td>&gt;2.75</td>
<td>1(ref.)</td>
<td></td>
<td>1 (ref.)</td>
<td></td>
<td>1(ref.)</td>
</tr>
<tr>
<td>Adjusted for sex, Indigenous status and age at start of year only</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2.0</td>
<td>3.25</td>
<td>1.43–7.40</td>
<td>3.99</td>
<td>1.74–9.11</td>
<td>2.52</td>
</tr>
<tr>
<td>2.01–2.75</td>
<td>1.67</td>
<td>0.70–3.96</td>
<td>1.95</td>
<td>0.84–4.50</td>
<td>2.15</td>
</tr>
<tr>
<td>&gt;2.75</td>
<td>1(ref.)</td>
<td></td>
<td>1 (ref.)</td>
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<td>1(ref.)</td>
</tr>
<tr>
<td>Adjusted for sex, Indigenous status, log eGFR, cohort, treatment centre, late referral and relocation at baseline and age, comorbidities and BMI category at start of year</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2.0</td>
<td>3.18</td>
<td>1.31–7.73</td>
<td>3.66</td>
<td>1.53–8.76</td>
<td>2.14</td>
</tr>
<tr>
<td>2.01–2.75</td>
<td>1.66</td>
<td>0.66–4.17</td>
<td>1.79</td>
<td>0.76–4.20</td>
<td>1.91</td>
</tr>
<tr>
<td>&gt;2.75</td>
<td>1(ref.)</td>
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<td>1 (ref.)</td>
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<td>1(ref.)</td>
</tr>
</tbody>
</table>
Transplantation

Table 5.3 shows the likelihood of transplantation using CR-PH models with various levels of adjustment, for different years after starting treatment stratified by the previous time period (usually the previous year) mean weekly haemodialysis attendance. No-one attending ≤2.0 sessions/week in the first or subsequent years after starting treatment received a transplant. Those with a mean weekly attendance of 2.01–2.75 sessions/week consistently had a lower subsequent likelihood of transplantation, although this was not always statistically significant. Adding demographic and clinical covariate adjustments did not alter second or later years’ estimates of the likelihood of transplantation.
Table 5.3: Likelihood of transplant in subsequent year by attendance category (Fine and Gray CR-PH models) with various adjustments

<table>
<thead>
<tr>
<th>Mean attendance per week</th>
<th>Completing 1st 3 months (n=806)</th>
<th>Completing 1st year (n=618)</th>
<th>Completing 2nd year (n=482)</th>
<th>Completing 3rd year (n=376)</th>
<th>Completing 4th year (n=267)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>HR</td>
<td>95% CI</td>
<td>HR</td>
</tr>
<tr>
<td>≤2.0</td>
<td>0.16</td>
<td>0.03–0.77</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2.01–2.75</td>
<td>0.16</td>
<td>0.03–0.77</td>
<td>0.40</td>
<td>0.13–1.25</td>
<td>0.38</td>
</tr>
<tr>
<td>&gt;2.75</td>
<td>1(ref.)</td>
<td>1 (ref.)</td>
<td>1(ref.)</td>
<td>1(ref.)</td>
<td>1(ref.)</td>
</tr>
</tbody>
</table>

**Unadjusted**

| ≤2.0                     | 0.36   | 0.07–1.78  | 0      | 0          | 0      | 0          | 0      | 0          | 0      | 0          |
| 2.01–2.75                | 0.35   | 0.06–2.05  | 0.49   | 0.16–1.46  | 0.26   | 0.09–0.71  | 0.47   | 0.15–1.41  | 0      | 0          |
| >2.75                    | 1(ref.)| 1 (ref.)   | 1(ref.)| 1(ref.)    | 1(ref.)| 1(ref.)    | 1(ref.)| 1(ref.)    | 1(ref.)| 1(ref.)    |

**Adjusted for sex, Indigenous status and age at start of year only**

| ≤2.0                     | 3.18   | 0.08–120.11| 0      | 0          | 0      | 0          | 0      | 0          | 0      | 0          |
| 2.01–2.75                | 0.52   | 0.04–7.15  | 0.44   | 0.08–2.43  | 0.31   | 0.07–1.28  | 0.48   | 0.20–1.80  | 0      | 0          |
| >2.75                    | 1(ref.)| 1 (ref.)   | 1(ref.)| 1(ref.)    | 1(ref.)| 1(ref.)    | 1(ref.)| 1(ref.)    | 1(ref.)| 1(ref.)    |

**Adjusted for sex, Indigenous status, log eGFR, cohort, treatment centre, late referral and relocation at baseline and age, comorbidities and BMI category at start of year**
Overnight hospitalisation

Table 5.4 shows the risk of any overnight hospital admission using CR-PH models with various levels of adjustment, for different years after starting treatment stratified by the previous time period (usually the previous year) mean weekly attendance. There were only relatively small and generally non-significant increases in the risk of hospitalisation with and without various demographic and clinical covariate adjustments.
Table 5.4: Risk of overnight hospitalisation in subsequent year by attendance category (Fine and Gray CR-PH models) with various adjustments

<table>
<thead>
<tr>
<th>Mean attendance per week</th>
<th>Completing 1st 3 months (n=806)</th>
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<tbody>
<tr>
<td></td>
<td>Completing 1st year (n=618)</td>
</tr>
<tr>
<td></td>
<td>HR</td>
</tr>
<tr>
<td>Unadjusted</td>
<td></td>
</tr>
<tr>
<td>≤2.0</td>
<td>1.30</td>
</tr>
<tr>
<td>2.01–2.75</td>
<td>1.08</td>
</tr>
<tr>
<td>&gt;2.75</td>
<td>1(ref.)</td>
</tr>
<tr>
<td>Adjusted for sex, Indigenous status and age at start of year only</td>
<td></td>
</tr>
<tr>
<td>≤2.0</td>
<td>1.26</td>
</tr>
<tr>
<td>2.01–2.75</td>
<td>1.05</td>
</tr>
<tr>
<td>&gt;2.75</td>
<td>1(ref.)</td>
</tr>
<tr>
<td>Adjusted for sex, Indigenous status, log eGFR, cohort, treatment centre, late referral and relocation at baseline and age, comorbidities and BMI category at start of year</td>
<td></td>
</tr>
<tr>
<td>≤2.0</td>
<td>1.21</td>
</tr>
<tr>
<td>2.01–2.75</td>
<td>1.04</td>
</tr>
<tr>
<td>&gt;2.75</td>
<td>1(ref.)</td>
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</tbody>
</table>
In contrast, Table 5.5 uses negative binomial regression to show the proportional change in the number of overnight hospital admissions with various levels of adjustment for different years, by the previous time period (usually previous year) mean weekly attendance category. Hospitalisation rates were increased consistently and significantly for those with mean weekly attendance ≤2.0 sessions/week for all time periods after commencing treatment. Estimates for those with mean weekly attendance between 2.01–2.75 sessions/week were intermediate between groups, suggesting a dose-response-effect. These estimates were not changed greatly with the addition of simple or more complex demographic and clinical covariate adjustments.
Table 5.5: Proportional change in the number of overnight hospitalisations in subsequent year by attendance category using negative binomial regression models with various adjustments

<table>
<thead>
<tr>
<th>Mean attendance per week</th>
<th>Completing 1st 3 months (n=806)</th>
<th>Completing 1st year (n=618)</th>
<th>Completing 2nd year (n=482)</th>
<th>Completing 3rd year (n=376)</th>
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<tbody>
<tr>
<td></td>
<td>IRR</td>
<td>95% CI</td>
<td>IRR</td>
<td>95% CI</td>
<td>IRR</td>
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<tr>
<td>Unadjusted</td>
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<td></td>
</tr>
<tr>
<td>≤2.0</td>
<td>1.48</td>
<td>1.20–1.83</td>
<td>2.07</td>
<td>1.62–2.64</td>
<td>2.21</td>
</tr>
<tr>
<td>2.01–2.75</td>
<td>1.18</td>
<td>0.96–1.47</td>
<td>1.39</td>
<td>1.11–1.75</td>
<td>1.30</td>
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<tr>
<td>&gt;2.75</td>
<td>1(ref.)</td>
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<tr>
<td>Adjusted for sex, Indigenous status and age at start of year only</td>
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</tr>
<tr>
<td>≤2.0</td>
<td>1.42</td>
<td>1.15–1.76</td>
<td>1.90</td>
<td>1.47–2.46</td>
<td>2.05</td>
</tr>
<tr>
<td>2.01–2.75</td>
<td>1.16</td>
<td>0.93–1.43</td>
<td>1.31</td>
<td>1.03–1.65</td>
<td>1.23</td>
</tr>
<tr>
<td>&gt;2.75</td>
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<tr>
<td>Adjusted for sex, Indigenous status, log eGFR, cohort, treatment centre, late referral and relocation at baseline and age, comorbidities and BMI category at start of year</td>
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</tr>
<tr>
<td>≤2.0</td>
<td>1.40</td>
<td>1.13–1.74</td>
<td>1.76</td>
<td>1.36–2.27</td>
<td>1.92</td>
</tr>
<tr>
<td>2.01–2.75</td>
<td>1.16</td>
<td>0.94–1.44</td>
<td>1.19</td>
<td>0.94–1.50</td>
<td>1.17</td>
</tr>
<tr>
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<td>1(ref.)</td>
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</tr>
</tbody>
</table>
Changes in Attendance

Those with lower levels of attendance in the first three months of treatment who subsequently improved attendance in the first year of treatment had non-significant trends to only about half the risk of death in the second year of treatment of those continuing lower mean weekly attendance (increasing attendance sub-hazard ratio [SHR] 0.53 [95% CI 0.15–1.85] compared to continuing ≤2.0 sessions/week); increasing attendance SHR 0.51 (95% CI 0.17–1.48) compared to continuing 2.01–2.75 sessions/week). The likelihood of transplant was also non-significantly higher for those increasing attendance (increasing attendance SHR 4.81 [95% CI 0.36–64.73] compared to continuing 2.01–2.75 sessions/week). As noted above, there were no transplants in those continuing to attend ≤2.0 sessions/week; of the 11 people who increased attendance from ≤2.0 sessions/week within the first year of treatment, two received a transplant in the second year.

The incidence of hospitalisation in the second year of treatment for those increasing attendance in the first year of treatment from mean levels <2.0 sessions/week in the first three months was lower (Incidence Rate Ratio [IRR] 0.55 [95% CI 0.37–0.84], compared to continuing <2.0 sessions/week), but there was little change for those with initial mean attendance 2.01–2.75 sessions/week who subsequently increased
attendance (IRR 0.96 [95% CI 0.71–1.30] compared to continuing 2.01–2.75 sessions/week).

Most patients who increased attendance in the first year of treatment were Indigenous: they had better survival, transplant and hospitalisation outcomes in the second year than those continuing lower mean weekly attendance. Non-Indigenous patients had better outcomes in the first two years of treatment (regardless of their attendance pattern) than Indigenous patients with continued lower mean weekly attendance (data not shown).

5.6 Discussion

In this analysis of patients receiving facility-based haemodialysis treatment in the NT, lower mean weekly attendance was associated with being Indigenous, treatment in Central Australia and a BMI over 30 kg/m², although the model could only explain 9% of variation (Figure 5.4). Although it was associated with the need to relocate, it was not associated with the need to relocate to start haemodialysis after adjustment for Indigenous status. Lower mean weekly attendance for treatment in the first year after starting treatment was associated with later lower mean attendance. Lower mean weekly attendance in any year after starting treatment was associated with an increased risk of death.
and overnight hospital admission and a reduced chance of receiving a transplant.

The inclusion of demographic variables and comorbidities into regression models did not increase markedly the risk of death associated with lower mean attendance in the first couple of years of treatment, indicating that lower mean attendance may be an independent predictor of death. The smaller number of patients continuing satellite haemodialysis with low mean weekly attendance into the fourth and fifth year after starting treatment in this study creates uncertainty around the estimates of the likelihood of both death and transplantation.

Also of note, proportional changes in rates of hospitalisation were not altered substantially by the inclusion of comorbidities in regression models for any time period from the start of treatment: mean weekly attendance was a much more important determinant of subsequent rates of hospitalisation than comorbidities.

Even when attendance only for the first three months of treatment was used, the subsequent impact of lower mean weekly attendance on the risk of death or hospitalisation or the likelihood of transplantation was evident. The first three months of treatment is a time when residual
kidney function may “protect” patients from adverse events associated with lower haemodialysis attendance rates. However, estimates of endogenous residual kidney function at start of treatment (eGFR) were not associated with lower mean weekly attendance in the first three months. Including eGFR in models examining the risk of death, likelihood of transplantation or rates of hospitalisation did not alter these risks appreciably. This may be because eGFR values were low by national standards, or because other factors besides residual kidney function were more important.

Recently there has been renewed interest in twice weekly haemodialysis schedules at the start of RRT (Kalantar-Zadeh & Casino 2014; Kalantar-Zadeh et al. 2014; Rhee et al. 2013; Vanholder, Van Biesen & Lameire 2014; Zhang et al. 2014), with the suggestion that endogenous kidney function may be preserved enough to ensure good outcomes. These data suggest that if such a strategy is attempted, residual endogenous kidney function should be higher than that seen here and outcomes followed carefully. Similarly, twice weekly haemodialysis is often used in resource poor settings (Bello et al. 2013; Bieber et al. 2014; Elamin & Abu-Aisha 2012; Lin et al. 2012; Stankuviene et al. 2010; Sultania, Acharya & Sharma 2009); this study suggests that this may be at the cost of worse clinical outcomes.
Although initial attendance was clearly important, lower initial attendance did not irrevocably damage long-term outcomes: those who increased attendance had better subsequent outcomes than those continuing to have lower attendance, although confidence intervals were very broad and more work with a larger sample would be needed to confirm this definitively.

Previous literature demonstrated a less pronounced difference in survival with varying haemodialysis attendance (Bander & Walters 1998; Kimmel et al. 1998; Leggat et al. 1998; O’Brien 1990; Rahman et al. 2000; Saran et al. 2003). This may be because other studies had smaller numbers with lower attendance (≤2 sessions/week), did not separate lower (≤2 sessions/week) from intermediate attendance (2.01-2.75 sessions/week) or examined outcomes having measured attendance for only one month. It may also be that haemodialysis techniques and survival have improved significantly over the past 20 years (Lawton et al. 2015), so that survival differences between those attending more and those less appear greater in more recent periods. Missing less than once a month (a mean weekly haemodialysis attendance of >2.75 but <3 sessions/week) may not be associated with an increased risk of adverse events, but would require a study with greater power.
Both Indigenous status and relocation from more remote areas to start treatment were associated with lower mean weekly attendance at any time after starting treatment, but being Indigenous appeared to be more important once all measured factors were taken into account (Figure 5.4). This further illuminates the understanding that the need for relocation to access treatment is associated with lower treatment attendance for Indigenous Australians, who often have strong family and cultural ties to their remote community of origin (Anderson et al. 2012; Burnette & Kickett 2009). Instead, this evidence suggests that other factors associated with being Indigenous and receiving dialysis treatment in the NT are important, such as a lack of knowledge about their condition and its treatment (Anderson et al. 2008; Rix et al. 2014), a first language other than English and low levels of income and formal education (Biddle 2009). Perceptions of a lack of control and lack of trust in caring health professionals are also well-described in Indigenous patients receiving RRT (Anderson et al. 2008; Burnette & Kickett 2009), and these may exacerbate “non-compliant” behavior (Allen, Wainwright & Hutchinson 2011).
Strengths and Limitations of this Study

The use of hospital data to determine the remoteness of patients’ residence at the start of treatment provides greater accuracy than that available through ANZDATA, which records only postcode of residence. However, this may still be inaccurate (Cass et al. 2001), as some patients from remote areas may have an urban address recorded due to prior relocation in preparation for the start of treatment (Zhao et al. 2013). ARIA+ remains a blunt tool in the NT, with only three of five remoteness areas present. Only the residence at the start of treatment was used to determine the need for relocation; the return of patients to regional satellite centres closer to home was not examined, and patients starting self-care modalities (19.6% of the 937 included in the study, to home haemodialysis, peritoneal dialysis or transplantation) were censored from their date of treatment change, as their treatment pattern would no longer be captured in hospital administrative data. Further detailed analysis of the distance travelled to access treatment and its associations will be required; in addition, examination of the rates of hospitalisation, transplantation and death amongst those returning home to remote communities or small regional centres is planned (although numbers are small).
Hospital administrative data was used in this study as the record of attendance for haemodialysis treatment. Clearly this is not perfect, as illustrated by those with absent administrative records despite an ANZDATA registry record indicating centre- or satellite-based haemodialysis, as seen in the small number with zero mean weekly attendance in Figures 5.2 and 5.3. There is no evidence that either non-reporting or under-reporting of haemodialysis attendance is anything other than non-differential, but it cannot be ruled out.

Comorbidity data used in this study were reported through ANZDATA, as recent audits in other jurisdictions have recommended (Gray et al. 2013; Kotwal et al. 2014). Neither dataset includes information about comorbidity severity. Similarly, neither hospital administrative data nor ANZDATA contain data about pre-dialysis potassium or inter-dialytic weight gain: further analyses using additional linked clinical data are possible to provide further insights into the reasons for higher mortality and hospitalization rates among those attending fewer than prescribed haemodialysis sessions. Understanding the reasons why patients attend fewer than the prescribed number of sessions is obviously needed if interventions are planned to increase attendance (and perhaps improve outcomes), but requires further qualitative work outside the scope of this analysis.
The particular circumstances of the haemodialysis population in the NT lend themselves to this study, not only because of the great variation in weekly haemodialysis attendance. Because the proportion changing treatment modalities is lower than nationally, there is less exposure to bias. In addition, this study’s methods minimise immortal time bias by excluding those starting treatment with other modalities or interstate and addresses informative censoring by using competing risks methods. However, as an observational study it provides evidence of association, not causation: there may be upstream factors contributing both to the pattern of attendance and the likelihood of hospital admission, transplantation and/or death.

This study adds to the limited existing literature about the outcomes and associations of lower haemodialysis attendance in a number of ways. It excludes any potential protective effect of residual kidney function on the risks associated with lower attendance, although perhaps higher levels of residual kidney function at commencement of treatment than seen here may be protective. Although a small study, it shows that lower attendance is consistently associated with an increased risk of serious adverse events, and that there is an apparent “dose response” with levels of attendance <2.0 sessions/week being at particularly high risk. It
demonstrates that modern, first-world haemodialysis techniques do not protect against the effects of lower attendance, but may accentuate them: “membrane contact time” appears to be important in reducing risks of adverse events. This study provides data for the first time examining the relationships between relocation from a remote area, dialysis attendance and outcomes in this setting — and finds that this is more complicated, largely explained by Indigenous status. Finally, it provides important data about the scope of the problem of maintaining the dialysis regimen among a predominantly Indigenous regional and remote Australian patient population. This is an important step in identifying reasons for an increased risk of death on RRT for Indigenous compared to non-Indigenous Australians and highlighting/understanding the barriers to transplantation for Indigenous Australians.

Centre-based haemodialysis presents distinct — and particularly complex — challenges for Indigenous patients. Other work has revealed “how feelings of alienation and isolation substantially increase the challenge of coping with an already demanding treatment” and affirmed “the stress [Indigenous patients face] reconciling family and cultural responsibilities with treatment requirements” (Anderson et al. 2012a). Language differences and the use of medical jargon by staff, combined with low levels of literacy and education, lead to ineffective communication and a large number of patients lacking an understanding of their situation,
treatment and options (Anderson et al. 2012; Anderson et al. 2008; Green et al. 2013; Rix et al. 2014). A key finding of this study is that these challenges may not be limited to those facing the social dislocation of having to move from their remote community home to an urban centre for dialysis treatment. Indigenous patients already living in urban centres may also face challenges in completing treatment due in part to factors such as limited education, miscommunication, marginalisation, racial discrimination and poverty.

The association of lower attendance with poorer outcomes does not necessarily mean that higher attendance in and of itself is associated with an optimal outcome, particularly for Indigenous patients. There is a large and growing body of literature describing the problems that Indigenous Australians requiring RRT face (Anderson et al. 2008, 2012; Burnette & Kickett 2009; Devitt & McMasters 1998a; Preece 2010; Rix et al. 2014, 2015). This literature strongly suggests that better patient-centred care is required to improve Indigenous RRT patients’ health literacy, experience of and confidence in the health system.

Identifying and improving such unmeasured patient-level and service-related factors is likely to be important to promote regular and frequent haemodialysis treatment, which appears to be necessary to improve
survival and transplantation rates. This study confirms that increases in haemodialysis treatment patterns are one reasonable surrogate for improved service delivery for Indigenous Australians requiring RRT. These data, building on previous work, suggest that more attention should be directed to the design and implementation of services that promote haemodialysis attendance through better patient-centred care for patients in the NT, regardless of the location of these services.
Chapter 6: Chronic Kidney Disease in the Top End of the Northern Territory of Australia, 2002–2011: a Retrospective Cohort Study Using Existing Laboratory Data

6.1 Chapter Overview

This chapter comprises a reprint of a paper published in *BMC Nephrology* on 22nd October, 2015, as well as two supplementary tables.

6.2 Declaration of Authorship

Paul Lawton conceived of and designed the study, performed the statistical analyses and drafted the manuscript. Joan Cunningham contributed to the design, analysis and interpretation of the study and helped draft the manuscript. Narelle Hadlow contributed to the design of the study, contributed data and critically reviewed the manuscript. Yuejen Zhao participated in the analysis of the study. Matthew Jose contributed to the design of the study, the interpretation of results and drafting of the manuscript. Although Paul Lawton takes overall responsibility, all authors read and approved the final manuscript before publication.
Chronic kidney disease in the Top End of the Northern Territory of Australia, 2002–2011: a retrospective cohort study using existing laboratory data

Paul D. Lawton, Joan Cunningham, Narelle Hadlow, Yuejen Zhao and Matthew D. Jose

Abstract

Background: The Northern Territory of Australia has a very high incidence of treated end-stage kidney disease (ESKD), largely confined to Indigenous Australians living in remote, under-resourced areas. Surveillance of chronic kidney disease (CKD) is still in its infancy in Australia. We estimate the prevalence and rate of progression of measured CKD across a region using inexpensive readily available laboratory information.

Methods: Using a retrospective de-identified extraction of all records with a serum creatinine or urinary albumin-to-creatinine ratio from the single largest ambulatory pathology provider to the Top End of the Northern Territory of Australia between 1st February 2002 and 31st December 2011, the yearly total and age-specific prevalence of measured microalbuminuria, overt albuminuria and estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m², and the prevalence of progressive CKD, were calculated.

Results: There was a steady increase in the proportion tested across all health districts in the region, more prominent in non-urban districts. In 2009, the regional adult prevalence of measured microalbuminuria and overt albuminuria was as high as 8.1%, overt albuminuria alone up to 3.0% and eGFR < 60 up to 2.3%. Rates of progressive disease were extremely high, particularly for those with albuminuria (53.1–100% for those with urinary albumin-creatinine ratio > 300 mg/mmol).

Conclusions: The rates of testing, particularly in districts of high measured prevalence of markers of CKD, are encouraging. However, extremely high rates of progressive CKD are troubling. Further describing the outcomes of CKD in this population would require analysis of linked datasets.

Keywords: Chronic kidney disease, Estimated glomerular filtration rate, Creatinine, Urinary albumin-creatinine ratio, Public health surveillance

Background

The Top End of the Northern Territory (NT) of Australia is a large geographical area of over 500,000 square kilometres with a relatively small population comprised of a largely urban centralised non-Indigenous population and a smaller, largely remote, de-centralised and disadvantaged Indigenous population (Fig. 1) that is under-enumerated and culturally and linguistically heterogeneous [1]. The poor health status of its Indigenous population with high rates of chronic kidney disease (CKD) is a public health concern in the NT [2]. There is a single tertiary referral centre staffed by nephrologists in Darwin.

The incidence of treated end-stage kidney disease (ESKD) in the NT is 3–4 times national Australian figures, and is largely confined to the Indigenous community that comprises a third of the NT’s population [3]. At least one individual community has a reported ESKD incidence up to 25 times the national rate [4], amongst the highest in the world. Reports from cross-
sectional surveys of a few individual Top End Indigenous communities have shown a very high prevalence of albuminuria [5–8]. However, it is not clear if this means that the high incidence of treated ESKD is a result of a large burden of earlier stages of CKD, a rapid rate of progression or a higher survival rate of those with CKD to end-stage.

The recent validation of the CKD-EPI equation for Indigenous Australians [9], the publication of position papers regarding the use of the CKD-EPI formula for all Australians [10] and the classification and risk stratification of CKD [11] support a population-based approach to determining CKD prevalence.

A few studies have examined clinical laboratory results to determine the prevalence of measured CKD across regions [12, 13], including one in the Australian state of Tasmania [14]. While this method cannot take the place of a population-based random sample, it can be an important adjunct if the population is hard to reach due to remoteness, health service limitations or cross-cultural and linguistic challenges. It can be particularly useful in areas where there is heightened awareness of CKD and strategies to detect and manage it that lead to a substantial proportion of the population at risk to be tested as part of routine clinical care. All of these circumstances apply in the Top End of the NT [2]. For the time of this study the Top End region of the NT was served by one dominant provider of ambulatory pathology services, Western Diagnostic Pathology (WDP, Myaree, Western Australia, a private laboratory providing pathology services across the NT and WA); almost all services for dialysis and transplant patients were provided through an alternative, NT Department of Health hospitals pathology. This allowed calculation of the prevalence of measured CKD that largely excluded those with treated ESKD without the need for data linkage, which has particular ethical and technical challenges for Indigenous Australians [15] and is time consuming, expensive and still in a capacity building phase in Australia.

The aim of this study was to examine CKD prevalence and rate of progression over a 10 year period in a geographical area with a high incidence and prevalence of treated ESKD using inexpensive readily available information.
Methods

Study design and population
A retrospective cohort study was performed using de-identified pathology records with NT postcodes from 1st February 2002 to 31st December 2011 from a single pathology provider. The population included all those with records of a serum creatinine or urinary albumin-to-creatinine ratio (UACR) analysed by WDP.

All records were identifiable only by a laboratory unique identifier for each individual: linkage of records to an individual was performed for clinical purposes at the laboratory level and no other linkage was performed. Records were matched to health districts within the Top End region using the individual’s postcode recorded at the time of testing and 2006 postal area concordance files available from the Australian Bureau of Statistics (ABS) [16] and the NT Health Department’s Health Gains Planning Branch (HGP) [17].

Laboratory measures
All serum samples were collected into Becton Dickinson serum separator tubes (BD SST II, Becton Dickinson, North Ryde, NSW, Australia). Serum and urine creatinine were measured using the Siemens ADVIA 2400 iaffe creatinine assay (Siemens Ltd. Australia and New Zealand—Diagnostics Division, Tarrytown, NY, USA), an alkaline picrate kinetic method with blank correction. Creatinine was standardised to isotope dilution mass spectrometry (IDMS) standards on 1st February 2002. Percentage coefficients of variation (CVs) within run for quality control material over an indicative 12 month period were: Level 1 (serum creatinine 74.5 umol/L) 1.57–2.1 % CV, Level 2 (serum creatinine 523.9 umol/L) 1.32–6.91 % CV. Urine albumin was measured using the Advia Chemistry 2400 method, and percentage CVs between runs were: Level 1 (urine albumin 13.22 mg/L) 5.7 % CV, Level 2 (urine albumin 63.27 mg/L) 2.54 % CV. UACR was reported in mg/mmol.

Outcome measures
The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation, as recommended and validated for both Indigenous and non-Indigenous Australians [9, 10]. Mean eGFR was calculated for each year with available data, similar to previous work [14]; mean UACR was calculated similarly. Individuals were then grouped based on their mean eGFR and UACR levels into strata chosen to enable comparison with previous literature. Gender-specific cut-offs were used to define microalbuminuria: for men ≥ 2.5 mg/mmol, for women ≥ 3.5 mg/mmol.

Statistical analysis
Those with results in years before and after the year of interest, but not in the year of interest, could reasonably be assumed to be still alive in the Top End and were eligible to be counted towards the prevalence numerator for that year. Their result for the year of interest was assumed to be the same as their previous measured result until a new value supplanted it. For example, a person with a mean eGFR in 2002, but no further results until 2005, was assumed to be alive in the Top End and have the same eGFR in 2003 & 2004 until the new mean result in 2005; their 2002 mean eGFR counted for the first 3 years to the numerator of the relevant eGFR category.
Population figures for the region were for the prevalence denominator, taken from yearly ABS Estimated Resident Population (ERP) figures [18] and mapped to NT health districts using HGP population concordance files [17]. All prevalence was expressed in percentages. The total adult population (15 years or greater) was taken as the denominator to account in part for confounding by indication, in that those having tests performed presumably had a clinical indication for them (and were therefore more likely to have disease than those not tested). In addition, using the total population as the denominator ensured that the prevalence expressed would be more reliable as a minimum estimate. Since all available results from the whole population were used and the population was not assumed to be a random sample, confidence intervals were not calculated.

To examine disease progression, only data from those with two or more serum creatinine measurements at least 2 years apart was used. Progressive CKD was defined as an average annual decline in eGFR during follow-up of ≥2.5 ml/min/1.73 m² per year and a last eGFR value < 45 ml/min/1.73 m², independent of baseline eGFR level [11]. Average annual decline in eGFR was calculated as last available eGFR minus baseline eGFR divided by follow-up time (in years, minimum two) between the two observations [11]. The prevalence of progressive CKD was expressed as a percentage of the tested population.

Ethical approval was given by the combined Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research (HREC-2011-1566).

Results
Those with interstate or overseas postcodes were excluded (15,307 tests), as were those aged <15 years (13,340 tests about 9605 individuals), as the CKD-EPI formula performs poorly in children and adolescents [19]. Those with serum creatinine <25 micromol/L were also excluded as in other studies (249 tests about 146
individuals) [13, 14]. Another 8017 tests about 1829 individuals did not match to a valid postcode, and were excluded. The remaining 495,672 tests about 127,526 individuals were included for analysis.

Population characteristics are outlined in Table 1. Over most of the period, there was an increase in the number of people being tested with either a serum creatinine or UACR; this was consistently weighted towards the major population centre, the Darwin Urban district. However, the proportion of the regional population tested was highest in the Darwin Rural district and lowest in the East Arnhem district over the period (Fig. 2).

In each region, there was a rise in proportion tested with increasing age for age groups up to 74 years. In every age group 4–6% more women than men were tested. In any year, most people tested had only one test. For example, in 2009, 95.2% of those with a serum creatinine and 99.9% of those with a UACR had only one test.

A sharp rise in absolute numbers tested (Table 1) and in the proportion of the total population tested was noted from 2002 to 2004, with subsequent smaller yearly rises to 2008–9 and then a plateau, with similar patterns in each region (Fig. 2) and for both serum creatinine and UACR tests (data not shown).

The prevalence of measured moderate to severe CKD (eGFR ≤ 60 mL/min/1.73 m²) increased markedly with age (Fig. 3). Overall the prevalence (up to 2.3%) was 1.5–2 times higher in health districts outside Darwin Urban (Table 2).

In general, the prevalence of measured microalbuminuria and overt albuminuria (Fig. 4) increased with age after 2004; the considerable volatility in older age groups was consistent with relatively small absolute numbers. Overall the prevalence of those with a UACR ≥ 2.5/3.5 (up to 8.1%) or a UACR ≥ 30 (up to 3.0%) was four to six times higher in districts outside Darwin Urban (Table 2).

Over the whole study period, 39,850 people had ≥2 serum creatinine levels separated by at least 2 years; median follow-up was 6.8 years with a maximum of 9.9 years. Of these, 1159 people (2.9% of those assessed) met the definition for progressive CKD. Table 3 outlines the risk of progression according to initial CKD stage, and shows the importance of the initial degree of albuminuria and (to a lesser extent) level of eGFR to the risk of progression.

### Discussion

This study describes the overall prevalence of measured CKD in a region with very high incidence of treated ESKD and a single dominant (albeit not exclusive) pathology service provider. Previous cross-sectional studies in the region (Additional file 1: Table S1) have described a very high prevalence of markers of kidney disease in individual remote communities largely populated by Indigenous Australians [3–5] and a somewhat lower prevalence amongst Indigenous people of the Darwin Urban region [8]. This study, using existing clinical pathology data rather than community-wide screening or a population-based random or weighted sample, has demonstrated a still lower prevalence of CKD, although this is likely to represent a minimum figure that is still higher than national estimates.

This lower prevalence could be explained partly by the "whole of population" approach, which includes a large number of non-Indigenous people at lower risk of kidney disease. The CKD-EPI formula used in this study will more correctly estimate a lower proportion with moderate to severe CKD than the MDRD formula used in previous studies [9, 20]. In addition, the relatively high proportion missing UACR tests underestimates the tabulated prevalence of those with CKD and higher (that is, normal or "near-normal") eGFRs. These individuals

### Table 1 Baseline characteristics by year

<table>
<thead>
<tr>
<th>Year</th>
<th>Individuals tested with eGFR</th>
<th>Individuals tested with UACR</th>
<th>Mean Age</th>
<th>Male (%)</th>
<th>Darwin Urban (%)</th>
<th>Darwin Rural (%)</th>
<th>East Arnhem (%)</th>
<th>Katherine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>10,059</td>
<td>1,141</td>
<td>47.3</td>
<td>48.3</td>
<td>66.9</td>
<td>7.2</td>
<td>10.4</td>
<td>15.5</td>
</tr>
<tr>
<td>2003</td>
<td>18,223</td>
<td>1,968</td>
<td>46.7</td>
<td>48.6</td>
<td>65.1</td>
<td>9.7</td>
<td>9.7</td>
<td>15.5</td>
</tr>
<tr>
<td>2004</td>
<td>20,126</td>
<td>2,813</td>
<td>46.5</td>
<td>49.4</td>
<td>63.6</td>
<td>10.2</td>
<td>10.4</td>
<td>15.8</td>
</tr>
<tr>
<td>2005</td>
<td>21,764</td>
<td>3,562</td>
<td>46.1</td>
<td>47.7</td>
<td>64.1</td>
<td>10.6</td>
<td>10.5</td>
<td>14.7</td>
</tr>
<tr>
<td>2006</td>
<td>23,095</td>
<td>3,128</td>
<td>46.8</td>
<td>47.6</td>
<td>64.2</td>
<td>10.4</td>
<td>10.6</td>
<td>14.8</td>
</tr>
<tr>
<td>2007</td>
<td>27,247</td>
<td>3,231</td>
<td>46.4</td>
<td>47.7</td>
<td>63.1</td>
<td>10.3</td>
<td>10.7</td>
<td>15.9</td>
</tr>
<tr>
<td>2008</td>
<td>29,709</td>
<td>3,942</td>
<td>46.0</td>
<td>48.2</td>
<td>63.6</td>
<td>10.5</td>
<td>10.7</td>
<td>15.2</td>
</tr>
<tr>
<td>2009</td>
<td>31,788</td>
<td>3,881</td>
<td>46.2</td>
<td>47.2</td>
<td>64.3</td>
<td>10.3</td>
<td>11.0</td>
<td>14.5</td>
</tr>
<tr>
<td>2010</td>
<td>30,507</td>
<td>3,535</td>
<td>46.4</td>
<td>47.1</td>
<td>62.8</td>
<td>10.6</td>
<td>10.8</td>
<td>15.8</td>
</tr>
<tr>
<td>2011</td>
<td>30,246</td>
<td>3,616</td>
<td>45.6</td>
<td>47.0</td>
<td>60.3</td>
<td>11.8</td>
<td>11.1</td>
<td>16.8</td>
</tr>
</tbody>
</table>
appears to behave more like those with normal or "near-normal" UACRs when progression is examined.

This is the first study to demonstrate the rate of CKD progression in the region, which appears to be much higher than that demonstrated in "high-risk population" studies elsewhere [21]. The degree of proteinuria is a potent predictor of CKD progression, as widely described elsewhere [21, 22].

There was an initial and substantial rise in the numbers tested and in the measured prevalence of CKD markers from 2002 to 2004. This is well beyond that expected from an initial incomplete year (2002 results only are from 1st February due to the commencement of IDMS standardisation). Although there were changes in reimbursement for health checks for Indigenous adults (introduced in 1999 for those over 55, and 2004 for those aged 15–55 years), these changes are unlikely to be the main reason for the increase because of the low uptake of these services [23]. Rather, it is probably best explained by increased testing as a result of the implementation of changes in non-communicable chronic disease care in the Top End in 2002, including increased funding and resources from changes to pharmaceutical funding (fully reimbursing costs of medications used in remote communities) [24] and the commencement and expansion of remote primary care based chronic disease quality improvement research [25].

There was a subsequent steady fall in the prevalence of measured moderate to severe CKD (eGFR < 60 ml/min/1.73 m²) as the population size grew and the proportion of the population tested slowly increased, despite the prevalence of albuminuria increasing. This suggests that those with more severe kidney disease were identified by health services early in the time period studied. It also suggests that either there are many with earlier stage CKD (particularly with albuminuria alone) who are still to be identified, or alternatively that in aggregate across the region the prevalence of markers of earlier stage CKD is lower than the individual community data previously published.

There were large differences between the age-specific prevalence rates in this study and those reported in the recently released Australian National Health Measures Survey (NHMS), although such comparisons must be made with extreme caution as remote areas were excluded from the NHMS and the proportion of Indigenous respondents was very small [26]. Whilst the prevalence of moderate to severe CKD (eGFR < 60 ml/min/1.73 m²) in those over 65 years was similar in this study and in the NHMS, rates for those between 35 and 65 years in the Top End of the NT were double national rates. In contrast rates of albuminuria in the Top End were significantly lower than national rates at every age group. This also suggests either that there are many more people with albuminuria yet to be identified in the Top End of the NT or that they were tested using point-of-care technology rather than laboratory testing [27].

Also relevant are comparisons with data from the recently released National Aboriginal and Torres Strait Islander Health Measures Survey (NATSIHMS), which aimed to be a representative sample of Indigenous Australians from 2012–13 [28]. The prevalence of those with eGFR < 60 ml/min/1.73 m² in non-urban health districts was slightly lower in these Top End data than in
the NATSHIMS; again, rates of albuminuria in these Top End data were significantly lower than national Indigenous rates. Unfortunately, NATSHIMS rates by age groups have not been released for comparison.

To our knowledge, this is the first study to use methodology that includes cases known to be alive, despite not being tested, in interval years to calculate prevalence. This “carrying forward” approach may underestimate fluctuations in kidney function and albuminuria over time. This approach also assumes that the Top End’s population does not leave and then return to the Top End after long periods of time. Whilst an estimate of those returning to the NT is not available, 2001 ABS census data estimated that 89.4% of Indigenous Top End residents and 67.0% of non-Indigenous Top End residents lived in the same Health District 5 years before [29].

In the vast majority of individuals, calculation of mean eGFR and mean UACR relied upon one test only, and this might result in an overestimate in prevalence of CKD markers, particularly low-level albuminuria [30, 31]. The collection of these data predated revisions to the definition of CKD that now incorporate both eGFR and UACR simultaneously; during the time of this study testing was sequential (based on local guidelines) and eGFR-UACR “paired” samples uncommon.

Data about the proportion of tests processed by individual pathology providers in Australia are closely held by government and thought “commercially sensitive”; as a result, it is not possible to document the extent of Western Diagnostic Pathology’s dominance in the region over the time of study. Replicating this work for the whole of the NT or for other Australia states would require linking records from more than one pathology.

<table>
<thead>
<tr>
<th>District</th>
<th>Number UACR tests</th>
<th>Percent ERP(^a) tested</th>
<th>Percent with UACR ≥ 2.5/3.5</th>
<th>Percent with Mean UACR ≥ 30</th>
<th>Percent with Mean UACR ≥ 50</th>
<th>Number eGFR tests</th>
<th>Percent ERP(^a) tested</th>
<th>Percent with eGFR</th>
<th>Percent with Mean eGFR ≤ 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darwin Urban</td>
<td>7070</td>
<td>7.2</td>
<td>1.6</td>
<td>0.5</td>
<td>28,790</td>
<td>29.2</td>
<td>1.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Darwin Rural</td>
<td>2295</td>
<td>19.5</td>
<td>8.1</td>
<td>2.8</td>
<td>4147</td>
<td>35.2</td>
<td>1.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>East Arnhem</td>
<td>2223</td>
<td>18.5</td>
<td>8.9</td>
<td>2.4</td>
<td>4458</td>
<td>37.1</td>
<td>1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Katherine</td>
<td>2974</td>
<td>20.9</td>
<td>8.1</td>
<td>3.0</td>
<td>6132</td>
<td>43.2</td>
<td>2.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Represents 2009 results as well as results prior to 2009 carried forward if there were no 2009 results but both pre-2009 and post-2009 data were available (see Methods)

\(^b\) Estimated Resident Population 15 years and over
provider. Because Indigenous status is not recorded in pathology data, calculating separate Indigenous and non-Indigenous estimates of CKD prevalence would require linkage with other datasets that include an Indigenous identifier (such as hospitalisation data). Linkage would also reduce the chances of multiple identifiers leading to an overestimate of prevalence, particularly for Indigenous Territorians.

The absence of dataset linkage also means that this study is unable to determine accurately the total number of ESKD cases not receiving treatment, as it is possible that some of those receiving RRT had some blood tests through Western Diagnostic Pathology even though the dominant pathology provider for these individuals would have been the public hospital based pathology service.

This study used existing clinical pathology data rather than a population-based random sample or community-wide screening as attempted in other studies summarised in the Additional file 1: Table S1. As a result, inferences drawn about those not tested, and the population as a whole, are limited. Different approaches to testing for CKD in urban and remote areas of the Top End of the NT are likely to limit the validity of comparisons between them, given specific guidelines [32] and awareness of the heightened ESKD risk for Indigenous people in remote areas of the NT. The prevalence

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**Table 3** Percentage with progressive CKD, whole time period

<table>
<thead>
<tr>
<th>Initial eGFR group</th>
<th>Initial UACR &lt;3.4</th>
<th>Initial UACR 3.4–9.9</th>
<th>Initial UACR 10–29</th>
<th>Initial UACR 30–299</th>
<th>Initial UACR &gt;300</th>
<th>Missing UACR</th>
</tr>
</thead>
<tbody>
<tr>
<td>105+</td>
<td>0.3</td>
<td>1.9</td>
<td>1.7</td>
<td>7.9</td>
<td>53.1</td>
<td>0.2</td>
</tr>
<tr>
<td>90–104</td>
<td>0.6</td>
<td>2.5</td>
<td>3.7</td>
<td>13.9</td>
<td>66.6</td>
<td>0.3</td>
</tr>
<tr>
<td>75–89</td>
<td>1.7</td>
<td>3.6</td>
<td>4.3</td>
<td>23.0</td>
<td>61.7</td>
<td>1.3</td>
</tr>
<tr>
<td>60–74</td>
<td>3.6</td>
<td>13.4</td>
<td>22.5</td>
<td>40.1</td>
<td>71.8</td>
<td>5.7</td>
</tr>
<tr>
<td>45–59</td>
<td>6.4</td>
<td>10.6</td>
<td>20.9</td>
<td>42.2</td>
<td>95.6</td>
<td>1.4</td>
</tr>
<tr>
<td>30–44</td>
<td>4.9</td>
<td>7.8</td>
<td>25.6</td>
<td>57.6</td>
<td>84.3</td>
<td>26.1</td>
</tr>
<tr>
<td>15–29</td>
<td>0.0</td>
<td>1.0</td>
<td>19.2</td>
<td>56.2</td>
<td>55.0</td>
<td>34.9</td>
</tr>
<tr>
<td>0–14</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>13.8</td>
<td>100.0</td>
<td>9.9</td>
</tr>
</tbody>
</table>

*Percentage is of those with 2 or more creatinine measurements at least 2 years apart (N=19,890)

*Progressive CKD defined as average annual decline of >2.5 ml/min/1.73 m²/year, with final eGFR <45 ml/min/1.73 m², minimum follow-up 2 years [11]*
figures shown, however, do provide minimum estimates for the whole population; they are useful in the absence of a population based random sample of the region which is unlikely in the foreseeable future due to the competing demands and prohibitive expense of research in such a remote, culturally diverse environment.

The prevalence of measured CKD, even if the whole population were tested, is only one measure of the burden of disease. Because prevalence is related to both incidence and duration, substantial differences in the incidence of and survival from disease may be masked within similar prevalence figures between populations.

Conclusions
This study provides useful information for planning and policy development. Both the rate of testing and the minimum estimates of the prevalence of markers of CKD are much higher in non-urban health districts of the Top End, but still lower than previous community-based surveys. Rates of moderate to severe CKD in middle age in the Top End are double national figures. As testing rates have increased over the last decade, the prevalence of measured albuminuria has increased but moderate to severe CKD has not. The rate of CKD progression is much higher than that published for other high-risk populations. To determine better the incidence and outcomes of CKD across this or other regions, including its association with Indigenous status, studies using linked data from multiple sources will be required. Now that data linkage systems are developing in Australia, it should be possible to do this in the near future.

Additional file

Additional file 1: Table S1. Comparison of overall prevalence of markers of CKD in different studies in Top End NT region & nationally (DOCX 13 kb)

Abbreviations
NT: Northern Territory (of Australia); CKD: Chronic kidney disease; ESKD: End-stage kidney disease; ABS: Australian Bureau of Statistics; HGP: Health Gains Planning Branch (of the Northern Territory Department of Health); eGFR: Estimated glomerular filtration rate; CKD-EPI: Chronic kidney disease epidemiology collaboration; CV: Coefficient of variation; ERPF: Estimated renal plasma flow; UACR: Urine albumin-to-creatinine ratio; NHMRC: National Health Measurement Survey; NATSHMS: National Aboriginal and Torres Strait Islander Health Measures Survey; MODS: Modification of diet in renal disease.

Competing interests
PDL is supported by a National Health and Medical Research Council (NH&MRC) Postgraduate Scholarship (#1038721). JC is supported by a NH&MRC Senior Research Fellowship (#1005084). The views expressed in this publication are those of the authors and do not necessarily reflect the views of Western Diagnostic Pathology, PathWest, the NT Department of Health or the NHMRC.

Authors’ contributions
PDL conceived of and designed the study, performed the statistical analyses and drafted the manuscript. JC contributed to the design, analysis and interpretation of the study and helped draft the manuscript. NH contributed to the design of the study, contributed data and critically reviewed the manuscript. YZ participated in the analysis of the study. MDJ contributed to the design of the study, the interpretation of results and drafting of the manuscript. All authors read and approved the final manuscript.

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Acknowledgements
The authors wish to acknowledge the Western Diagnostic Pathology staff who analysed the samples providing data for this research, and the Health Gains Planning Branch of the Department of Health, Northern Territory.

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Received: 16 February 2015 Accepted: 14 October 2015
Published online: 22 October 2015

References


### 6.3 Supplementary Table S1

Comparison of overall prevalence of markers of CKD in different studies in Top End NT region & nationally

<table>
<thead>
<tr>
<th>Study</th>
<th>Number tested</th>
<th>Eligible population tested (%)</th>
<th>Ages</th>
<th>Micro-albuminuria (%)</th>
<th>Macro-albuminuria (%)</th>
<th>eGFR&lt;60 (%)</th>
<th>eGFR method</th>
<th>Ethnicity</th>
<th>Location</th>
<th>Sample</th>
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</thead>
<tbody>
<tr>
<td>Hoy et. al., 2001</td>
<td>956</td>
<td>76.2</td>
<td>20+</td>
<td>24</td>
<td>18.9</td>
<td>6</td>
<td>MDRD-186</td>
<td>Indigenous only</td>
<td>NT Remote</td>
<td>Community screening</td>
</tr>
<tr>
<td>McDonald et. al., 2003</td>
<td>237</td>
<td>58</td>
<td>18+</td>
<td>31</td>
<td>13</td>
<td>N/A</td>
<td>MDRD-186</td>
<td>Indigenous only</td>
<td>NT Remote</td>
<td>Community screening</td>
</tr>
<tr>
<td>Shemesh et. al., 2007</td>
<td>379</td>
<td>53.7</td>
<td>15+</td>
<td>23.7</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Indigenous only</td>
<td>NT Remote</td>
<td>Community screening</td>
</tr>
<tr>
<td>Maple-Brown et. al., 2011</td>
<td>860</td>
<td>14</td>
<td>15+</td>
<td>10.5</td>
<td>4.3</td>
<td>2.4</td>
<td>MDRD-186</td>
<td>Indigenous only</td>
<td>NT Urban</td>
<td>Regional volunteer survey</td>
</tr>
<tr>
<td>White et. al., 2010 (AusDiab)</td>
<td>11,247</td>
<td>55.3</td>
<td>25+</td>
<td>6.3</td>
<td>1.1</td>
<td>3.4</td>
<td>CKD-EPI</td>
<td>Mostly non-Indigenous</td>
<td>Australia Mostly urban</td>
<td>Nationally representative weighted survey</td>
</tr>
<tr>
<td>NHMS/AHS, 2013</td>
<td>11,248</td>
<td>37.1</td>
<td>12+</td>
<td>6.7</td>
<td>0.9</td>
<td>3.6</td>
<td>CKD-EPI</td>
<td>Mostly non-Indigenous</td>
<td>Australia Mostly urban</td>
<td>Nationally representative weighted survey</td>
</tr>
<tr>
<td>NATSIHMS, 2014</td>
<td>8,157</td>
<td>40.4</td>
<td>18+</td>
<td>12.5</td>
<td>4.1</td>
<td>2.5</td>
<td>CKD-EPI</td>
<td>Indigenous only</td>
<td>Australia Urban &amp; Remote</td>
<td>Nationally representative weighted survey</td>
</tr>
</tbody>
</table>
Chapter 7: Conclusion

7.1 Chapter Overview

This chapter summarises the key findings of the research program, describes contributions to the field of nephrology, discusses limitations of the research program and suggests directions for future research.

7.2 Summary of Main Findings

Previous work has well documented the disparity in the incidence of end stage kidney disease (ESKD) requiring renal replacement therapy (RRT) between Indigenous and non-Indigenous Australians, and the biological and socio-economic antecedents to ESKD. This thesis has extended previous work by exploring the disparities in outcomes of ESKD requiring RRT between Indigenous and non-Indigenous Australians, and examining the prevalence and progression of chronic kidney disease (CKD) in a region with a very high incidence of ESKD amongst Indigenous Australians.
7.2.1 Survival of Indigenous Australians Receiving RRT: Closing the Gap?

Encouraging initial findings were that (in unadjusted analysis) a disparity in survival between Indigenous and non-Indigenous patients in the late 1990s appeared to have closed and that (once covariate differences are accounted for) there had been a steady improvement in five-year survival for all Australians receiving RRT since 1995. However, Indigenous RRT patients consistently had around 40% higher death rates than non-Indigenous patients when population differences were considered, with this disparity most prominent in urban, not remote, areas of the country (Lawton et al. 2015). The urban-to-remote rising gradient in death rates, previously described in non-Indigenous patients (Gray, Dent & McDonald 2012) and confirmed in this study, was not seen in Indigenous patients. Amongst the reasons for improvement in survival after adjustment for demographic and clinical factors was the increasing age and comorbidity profile of those receiving RRT, evident for both Indigenous and non-Indigenous patients: the Australian renal community has got better at keeping older, sicker patients alive (Lawton et al. 2015).

This disparity in survival between Indigenous and non-Indigenous patients requires explanation. Similar comparisons overseas have shown better adjusted survival rates for those from minority groups (Frankenfield et al. 2009; Roderick et al. 2009) or at least equal survival
in the case of Aboriginal patients from the Prairie Provinces of Canada (Tonelli et al. 2004) or minority groups in the United States when numerous variables were considered (Robinson et al. 2006). Greater remoteness of origin for Indigenous Australian patients do not explain the disparity in survival, and greatly different patterns of referral for RRT compared to these overseas observations are unlikely. One possibility is that the much lower likelihood of Indigenous Australians receiving a kidney transplant than non-Indigenous patients accounted for some of this difference. However, established conventional methods for time-to-event analysis are inadequate when different treatment modalities are examined separately, due to the problem of “competing risks” (Noordzij et al. 2013; Teixeira et al. 2013; Verduijn et al. 2011).

7.2.2 What Are My Chances, Doc? The Competing Risks of Death and Transplantation for Indigenous Australian Dialysis Patients

The challenges of time-to-event analysis stratified by different RRT modalities can be overcome if competing risks methods are used. These methods take into account differing probabilities for more than one outcome for each individual (Fine & Gray 1999), and can overcome the problem of “informative censoring” that can occur if more conventional methods are used (such as the Kaplan-Meier method or Cox proportional hazard regression) (Verduijn et al. 2011). Once analysed in this way (and
adjusting for population differences), it becomes clear that the disparity in five-year survival between young and middle-aged Indigenous and non-Indigenous Australians receiving any form of dialysis therapy has narrowed, but that the likelihood of transplantation has fallen for Indigenous Australians receiving dialysis therapy even as it has risen for non-Indigenous patients since 2000. In other words, the “gap” in survival on dialysis has closed, but the “gap” in transplant rates has widened.

Of interest, non-Indigenous dialysis patients living more remotely were more likely to receive a kidney transplant than their urban equivalent, whereas Indigenous patients from more remote areas were less likely to receive one than their urban equivalent. Comorbidities accounted for only a small amount of the disparity in transplant rates. This raises important questions about equity of treatment, particularly because a much larger proportion (and higher absolute number) of Indigenous patients come from remote or very remote areas than non-Indigenous Australians.

7.2.3 They Don’t Do Well, Do They? Survival of Propensity Matched Indigenous Transplant and Dialysis Patients

These concerns about the equity of treatment choices are of particular interest when the utility of transplantation is considered. Although previous published work has demonstrated that non-Indigenous transplanted patients have superior survival to Indigenous patients (Jose
et al. 2008; McDonald 2004; Rogers, Lawton & Jose 2006), the question of whether Indigenous patients are likely to benefit from receiving a kidney transplant has not been examined adequately due to small numbers (McDonald 2004).

The five-year survival of patients receiving kidney transplants was compared to patients continuing dialysis treatment who had a similar propensity for transplantation based on baseline variables available within the ANZDATA Registry. Both non-Indigenous and Indigenous patients had substantially better five-year survival than similar patients continuing with dialysis treatment; the magnitude of benefit was larger for non-Indigenous than Indigenous patients and most readily apparent for Indigenous patients from urban areas. Relatively fewer potentially suitable Indigenous patients were transplanted than non-Indigenous patients.

This method of comparison (between transplant and dialysis within each ethnicity group) is more clinically and individually relevant than previous comparisons between Indigenous and non-Indigenous transplant recipients. Being an Indigenous Australian is not a treatment decision; transplantation is.

The findings from this work raise important questions about the equity-utility balance in kidney transplantation in Australia, and suggest that
excessive pessimism about kidney transplantation for Indigenous patients may be due to comparison of outcomes with non-Indigenous patients, rather than considering what may be in the best interests of individual Indigenous patients themselves (Lowe, Kerridge & Mitchell 1995).

7.2.4 What’s Wrong With Missing Dialysis? Pattern and Outcomes of Haemodialysis Attendance in the Northern Territory of Australia, 1995–2011

One often discussed reason for the disparity in transplant rates between Indigenous and non-Indigenous dialysis patients is the concern among nephrologists about “compliance” (Anderson et al. 2012; Bennett et al. 1995; Lowe, Kerridge & Mitchell 1995). Compliance with dialysis therapy may often be used as an indicator of post-transplant medication and appointment attendance compliance (Anderson et al. 2007, 2012), despite a lack of evidence for this association.

The relationship of haemodialysis attendance compliance to outcomes such as death, transplantation or hospitalisation cannot be examined using ANZDATA Registry data alone. In the Northern Territory of Australia, where approximately 40% of all Indigenous Australian RRT patients live (ANZDATA Registry 2015b), most dialysis treatments are given in haemodialysis “satellite units” by registered nurses and recorded
administratively as “same-day” inpatient public hospital admissions. This means that data linkage of RRT registry data to other datasets such as administrative hospitalisation and haemodialysis treatment data allows dialysis attendance patterns (and their relationship to outcome) to be examined.

Analysis of these linked ANZDATA registry and hospital administrative records reveals that attendance for fewer than three haemodialysis sessions a week in the Northern Territory was common. After adjustment it correlated much more with being Indigenous than with needing to relocate from remote to regional centres for treatment (the previously widely accepted reason given for lower haemodialysis treatment attendance). Using appropriate competing risks time-to-event methods once again, it is clear that lower attendance was associated with both higher death rates and lower transplant rates in a “dose-dependent” fashion. Indeed, after attendance during the first year of treatment at or below an average of two sessions a week, no surviving patients received a transplant at all in the subsequent four years. Rates of hospitalisation requiring overnight admission were also associated with lower haemodialysis attendance.

These findings show the importance of extending beyond limited registry data to understand possible reasons for treatment choices, particularly
when there appears to be disparity based on the information collected within the registry alone. These data also highlight the shortcomings of using health-related data alone: being Indigenous is more likely to be a surrogate for factors such as poorer living circumstances, lower levels of health literacy, marginalisation and racial discrimination than a determinant of behavioural patterns around haemodialysis attendance itself.

However, these data complement and confirm recent extensive qualitative research into the experience of Indigenous Australian dialysis patients and the decision-making processes around transplantation amongst Australian nephrologists (Anderson et al. 2007, 2012; Cass et al. 2007). “Compliance” with the onerous dialysis treatment program is particularly difficult for Indigenous Australians; struggling with it has serious adverse health consequences for patients (Anderson et al. 2012a). Included amongst these is a reduction in the likelihood of receiving a kidney transplant: nephrologists actually do consider at least one measure of dialysis “compliance” when deciding on kidney transplantation (Cass et al. 2007).
In the absence of a registry for those with earlier stage CKD, examining survival outcomes is more difficult. Nevertheless, it remains important to attempt to understand the drivers of the high incidence rates of ESKD requiring RRT amongst Indigenous Australians, particularly from regional and remote areas in northern Australia. Unlinked ambulatory care pathology data can give some indication of rates of progressive CKD and minimum estimates of rates of prevalence of CKD, particularly if most testing is done through one dominant service provider.

These data from the Top End of the Northern Territory demonstrate a high prevalence of moderate to severe CKD amongst middle aged people, particularly from remote districts. When compared to national population-based (Australian Bureau of Statistics 2013, 2014; Chadban et al. 2003) or local community-wide cross-sectional samples (Hoy et al. 2001; Maple-Brown et al. 2011; McDonald 2003; Shemesh et al. 2007), they also suggest that people with earlier stages of CKD are not being tested and identified. They show that those who are tested have an extremely high prevalence of progressive CKD, most notable amongst those with overt albuminuria.
These data explain and extend previous observations. Recent national prevalence studies have also demonstrated an increased risk of markers of CKD in middle age for Indigenous compared to non-Indigenous Australians, which is most apparent in remote and very remote areas and highest in the Northern Territory (Australian Bureau of Statistics 2013, 2014). Previous local cross-sectional work has identified relatively few patients with moderate or severe CKD (Hoy et al. 2001; Maple-Brown et al. 2011): the data in this thesis suggest that the reasons for this include a rapid rate of progression. Because the data were unlinked to any other outcome data, it was not possible to explore the competing risks of death and ESKD in this analysis, as with other recent work overseas (Dyck, Jiang & Osgood 2014; Jiang et al. 2014; Lim et al. 2010). Indigenous status is not recorded in Australian pathology testing data, limiting the ability to compare with other national population-based samples separated by ethnicity: by their nature, pathology testing data have limited demographic and no other clinical information about patients. For all these reasons, this work should be confirmed and continued with analysis of primary care data linked to hospital and death data.

This work is also an example of a method to gather data about the minimum prevalence estimates and (indirectly, and in part) the quality of care of CKD in a resource-poor and/or remote setting. This approach
cannot supplant a population-based random survey, but these are time-
consuming and very costly, particularly in remote areas.

7.3 *Synthesis of Findings: They Don’t Do Very Well, Do They?*

Together, this body of work clarifies several outstanding issues in the
treatment of CKD and ESKD amongst Indigenous Australians.

Firstly, it confirms that rapid progression of CKD, as well as a higher
prevalence in middle age and under-identification of earlier stage CKD,
remains an important problem in the Northern Territory despite health
system-wide strategies to identify and manage CKD and associated
conditions like diabetes mellitus over the past twenty years (Bailie et al.
2007, 2008, 2010; Central Australian Remote Practitioners Association
2014; Department of Health and Families Preventable Chronic Disease

Secondly, it highlights a disparity in RRT survival between Indigenous
and non-Indigenous patients that continues despite overall survival
improvements. This current disparity is not obviously due to differences
in survival on dialysis treatment (although the disparity in transplant
rates creates dialysis population differences not easily captured in the
data). Disparities in rates of transplantation are a major contributor to
RRT survival differences, particularly since it is now clear that Indigenous patients benefit from receiving a kidney transplant just as non-Indigenous patients do.

Thirdly, it demonstrates that (at least in the Northern Territory) lower levels of attendance for haemodialysis treatments are more powerful than recorded comorbidities as a predictor of the subsequent risk of death or hospitalisation and the likelihood of transplantation.

Fourthly, it shows that these disparities in survival and transplantation are not wholly associated with remoteness of residence even though Indigenous patients account for the majority living in remote or very remote areas; rather, they are more strongly associated with being Indigenous, regardless of where patients come from.

These findings reveal further insights into the life course of disadvantage already characterised and described for Indigenous patients leading to the onset of CKD (Cass et al. 2004). They suggest a pathway of disadvantage that continues even as CKD becomes established: under-identification of early CKD in early to mid-adulthood, rapid progression of moderate to severe CKD towards ESKD in middle age, well-documented higher rates of “late presentation” to nephrologists (ANZDATA Registry 2015b) at a later stage of disease (ANZDATA 196
Registry 2015b), higher rates of comorbidity (Lawton et al. 2015), lower levels of haemodialysis treatment attendance, higher rates of hospitalisation and death as a result and very low rates of transplantation.

Importantly, this work suggests that substantial improvements in life expectancy are possible for Indigenous patients, both for those with early to moderate CKD and those with advanced CKD or receiving RRT.

It suggests a role for continued efforts to increase the proportion of the population tested for markers of CKD especially in remote areas of the Northern Territory, coupled with renewed efforts to delay progression (even a little) in those with diagnosed CKD and albuminuria at demonstrably high risk for progression. The high prevalence rates of CKD and consequential ESKD receiving RRT make this approach much more likely to be cost-effective in the Northern Territory than for the general Australian population (Howard et al. 2010). Given the poor overall survival of patients receiving RRT, avoiding or even delaying the need for it is likely to lead to gains in life expectancy for those with CKD.

For those needing RRT, if haemodialysis treatments can be delivered to patients at a minimally effective and near-prescribed rate, it is plausible that a fall in dialysis-associated death rates will occur and kidney
transplantation becomes a realistic possibility for more potentially suitable dialysis patients. Increasing transplant rates for potentially suitable Indigenous patients will lead to further improvements in Indigenous RRT survival overall.

### 7.3.1 What These Findings Cannot Suggest, But Other Work Can

None of the findings in this body of work explain what it is about being an Indigenous Australian patient with CKD or ESKD that exposes them to worse outcomes than non-Indigenous Australian patients. Several theories are possible:

i) cultural practices and normative behaviours amongst Indigenous Australian patients that are different to non-Indigenous patients

ii) greater language barriers and less effective communication between Indigenous Australian patients and health care providers than for non-Indigenous patients

iii) biological differences (such as different patterns of blood groups and HLA haplotypes to the prevailing Australian transplant donor pool)

iv) disadvantage-related entrenched excess mortality risk amongst Indigenous Australians that pre-exists CKD or ESKD

v) individual-level and/or institutional- and structural-level systematic bias (that is, racism) within the health system against Indigenous patients.
Work published within the last 15 years provides a considerable body of evidence that sheds light on several of these theories.

7.3.2 Cultural Differences

It is true that many Indigenous Australians have different values and traditions and pursue distinctive cultural practices to those of mainstream, non-Indigenous Australia. However, these differences are more apparent in remote and very remote Australia, where the connection to country and culture has been disturbed less than in urban and regional Australia (Australian Institute of Health and Welfare 2015; Biddle 2009). Almost two-thirds of Indigenous Australian adults identify with a regional, tribal, language or clan group; rates of identification are higher with increasing remoteness (Australian Institute of Health and Welfare 2015). However, cultural factors are unlikely to explain the differences in outcome for Indigenous patients with ESKD generally: these outcomes are similar across all categories of remoteness.

In addition, when asked about the cause of their kidney disease, few Indigenous ESKD patients attributed their kidney disease to “spiritual “ or “religious” reasons: most reported well-described biomedical risk factors (Anderson et al. 2008). It is also worth bearing in mind a different sort of cultural divide: that between Indigenous patients, who emphasise the importance of family and relationships, and health care professionals
who view treatment and “practical” issues as paramount (Anderson et al. 2012a, 2012b; Rix et al. 2015).

### 7.3.3 Language and Communication Barriers

Language and communication barriers between Indigenous ESKD patients and health care providers have been described repeatedly (Anderson et al. 2008; Cass et al. 2002; Rix et al. 2014). The extent, importance, effect and implications of these difficulties are now much better understood. However, what has not often been made explicitly clear is that these communication difficulties are often not due to patients’ lack of English language proficiency: 90% of Indigenous Australians speak English at home (although in the Northern Territory only 40% do) (Australian Institute of Health and Welfare 2015). Amongst the minority speaking an Indigenous language at home, only 17% reported not speaking English well or at all (Australian Bureau of Statistics 2012a). Rather, miscommunication appears to be the result of:

(i) the use of jargon or non-plain English by health care providers when explaining concepts to patients (Rix et al. 2014)

(ii) perceived exclusion from information in the context of perceptions that it is the role of health professionals to provide information rather than the patient’s role to seek it (Anderson et al. 2008, 2012)

(iii) a longstanding mistrust of the mainstream health system and
health professionals, arising from a history of marginalisation, exclusion, frustration, discrimination and (at times) abuse (Anderson et al. 2008; Rix et al. 2013, 2014, 2015)

(iv) a lack of cultural awareness amongst non-Indigenous health service providers, the absence of tailored cultural awareness programs and a scarcity of Indigenous support staff or health professionals (Anderson et al. 2008; Rix et al. 2013, 2014, 2015).

As Anderson and colleagues have suggested, “merely providing information is not effective education; the quality of the communication and the appropriateness of the information are crucial to their efficacy.” (Anderson et al. 2008).

7.3.4 Biological Differences

Biological explanations for Indigenous: non-Indigenous disparities in outcome should be considered. Genetic explanations for a predisposition to CKD amongst Indigenous Australians have little evidence to support them currently (McDonald et al. 2002). However, Indigenous patients with CKD may have more rapid progression than non-Indigenous patients if their kidneys have fewer nephrons (due to intra-uterine and epigenetic influences) (Luyckx et al. 2013; Luyckx & Brenner 2005, 2010) or their disease process is characterised by additional insults, such as episodes of post-infectious glomerulonephritis in young life (Hoy et al. 201...
2012; White, Hoy & McCredie 2001) or a greater burden of comorbidities such as diabetes (Australian Bureau of Statistics 2014).

It may also be superficially plausible that poorer Indigenous outcomes once on RRT have biological explanations. Differences in body shape and size between Indigenous and non-Indigenous patients with CKD have been described (Hughes et al. 2015) that could conceivably lead to differences in dialysis solute clearance and recognition of volume overload, leading to less than optimal treatment for Indigenous patients on dialysis and subsequent poor outcomes (as has been hypothesised in minority groups in the United States (Wang et al. 2015). Concerns about the high rates of co-morbidities at a younger age for Indigenous compared to non-Indigenous dialysis patients (particularly in rates of diabetes) raise the possibility of these becoming barriers to kidney transplantation. Unpublished work using national ANZDATA registry data demonstrates that the spectrum of human leukocyte antigen (HLA) haplotypes amongst non-Indigenous patients correlates well with the HLA spectrum of kidney donors. However, Indigenous patients have a very different spread of HLA haplotypes to the Australian deceased donor pool (Jose, personal communication).

However, biological explanations do not explain the disparity in outcomes adequately. This thesis demonstrates that more recent dialysis treatment
outcomes are not significantly different between Indigenous and non-Indigenous patients, suggesting that the issue of differential treatment (through, for example, different dialysis clearance when having dialysis) is moot. Recently presented work shows that Indigenous Australians have lower transplant rates because they are less likely to be wait-listed for deceased donor transplantation (Khanal et al. 2015), not because they have more HLA mismatches. This thesis confirms previous work suggesting that they are not listed for transplantation primarily because of concerns about “compliance” with dialysis treatment regimes, not because of the presence of co-morbidities.

Biological explanations for higher rates of rapid progression of CKD are also plausible and have been discussed by previous authors (Cass et al. 2004). However, these explanations suggest neither a disease model uniquely different from “classical” pathology-based explanations, nor a deterministic one. Instead, the evidence supports a hypothesis that encompasses a life-time of disadvantage for Australian Indigenous people and a “multi-hit” theory of insults to their kidneys (Cass et al. 2004; Hoy et al. 2014; Luyckx et al. 2013). Rapid progression of CKD may plausibly be the result of multiple further “hits” to the kidney, as well as less-than-optimal control of individual progression risk factors (such as tobacco smoking, blood pressure and glycaemic control), mediating disadvantage that is both structural (economic disadvantage, low educational
attainment, poor health literacy, reduced access to primary and specialist health care) and ultimately personal.

7.3.5 Pre-existing Excess Mortality Risk Amongst Indigenous Australians

The disparity in outcomes across the spectrum of CKD and ESKD may be a demonstration of the difference in outcomes between Indigenous and non-Indigenous Australians in society broadly. Indigenous Australian men are estimated to die 10.6 years earlier than non-Indigenous men; women, 9.5 years earlier (Australian Institute of Health and Welfare 2015). “Only” 5% of the national disparity between Indigenous and non-Indigenous mortality from 2008 to 2012 was thought attributable to kidney disease (underlying causes only) (Australian Institute of Health and Welfare 2014b). This raises the possibility that other disease processes, such as cardiovascular disease or cancer, will manifest themselves in higher death rates in the Indigenous population receiving RRT just as in the general population.

There is some indirect evidence to support this hypothesis. Recent analyses of ANZDATA registry data have revealed that Indigenous dialysis patients were less likely than non-Indigenous patients to have “dialysis withdrawal” recorded as the cause of death (Chan et al. 2012); McKercher and colleagues have since shown that Indigenous dialysis
patients over 64 years of age had worse survival than similar non-Indigenous patients, with cardiac causes more common than withdrawal for Indigenous patients in contrast to non-Indigenous patients (McKercher et al. 2014). As for their counterparts without CKD or ESKD, Indigenous ESKD patients appear to have a higher mortality from cardiovascular causes at an earlier age than non-Indigenous patients.

This area of research would be amenable to further study using competing risks methods to analyse existing ANZDATA registry data. Work examining this possibility for patients with CKD in Australia would require the collation of data from primary care based data systems and linkage to hospitalisation and mortality data: capacity to do this sort of research work in Australia has lagged behind other countries (notably Canada and New Zealand) but is building now (2012).

This thesis shows that disparities in survival between Indigenous and non-Indigenous Australian ESKD dialysis patients have narrowed over time, even as transplantation rate disparities have widened. Despite Indigenous Australians in the general population surviving 10–15 years less than non-Indigenous Australians, and Indigenous Australians being over-represented in the number with ESKD receiving RRT, their survival on dialysis is not significantly proportionally less than non-Indigenous patients. This suggests that the overarching and/or pre-existing disadvantage experienced by Indigenous people in contemporary
Australian society can be effectively overcome within the health system to deliver equitable outcomes, at least in one respect.

### 7.3.6 Racism in the Health System

Could the disparity in outcomes measured in this thesis (particularly transplantation rates) be explained by biases against Indigenous patients at the system, service or interpersonal level?

Evidence suggests that bias in treatment against Indigenous patients exists within the Australian hospital system. As early as 1962, comment was made about different treatment patterns for Indigenous and non-Indigenous patients with anaemia in the Northern Territory (Christophers 1962). In 2002, Cunningham (2002) showed that:

> “patients identified as Indigenous are less likely than other patients to have a principal procedure recorded, at least in public hospitals. This disparity is partly explained by characteristics of the patient, the episode and, to a larger extent, the hospital, but a considerable difference remains.”

More recent analysis using similar methodology has shown that this disparity in procedure rates has narrowed but not closed (Australian Health Ministers’ Advisory Council 2015). Staff perceptions from Aboriginal and Torres Strait Islander community-controlled primary health care organisations are that discriminatory practices towards Indigenous patients persist.
Indigenous patients continue in Australian hospitals (Peiris et al. 2012). In the representative 2008–2009 National Aboriginal and Torres Strait Islander Social Survey, 4.0% (95% CI 3.3–4.7) of 7,823 people reported having experienced racial discrimination in the previous 12 months (Cunningham & Paradies 2013). A cross-sectional survey of 755 Aboriginal Australians in Victoria in 2011 found that experiences of racism in health settings were common and associated with considerable distress (Kelaher, Ferdinand & Paradies 2014). Most other work on racism in health services comes from the United States (Paradies, Truong & Priest 2014).

In commentary about Cunningham’s observations, Fisher and Weeramanthri (2002) suggested the following that easily applies to the problems covered in this thesis:

“It seems implausible that such significant and Australia-wide differences could implicate large numbers of individual clinicians and result from purely personal biases based on race. The disparities are more likely a result of subtler systemic practices, not ill-intentioned but still discriminatory, and almost invisible within an individual patient-provider encounter.”

They went on to say:
“The uptake of services is more than ‘patient related’ and cannot be separated from the provision of services; societal and institutional practices also structure the doctor-patient encounter within which decisions are made.”

This is particularly relevant when considering the issue of widespread lower-than-prescribed haemodialysis treatment attendance, and its effect on transplantation rates uncovered in this thesis. The scope of the issue again suggests either that individual-level racism is pervasive within renal services in the Northern Territory (unlikely), or that systemic issues within the organisation exist that do not take the needs of many Indigenous patients into account. This lack of responsiveness to the needs of a group of Indigenous individuals, so clustered as to be statistically significant, suggests strongly that renal services in the Northern Territory as a whole provide treatment that is systematically biased against Indigenous patients. This has been called “institutional racism” in other contexts (Henry, Houston & Mooney 2004; Macpherson 1999) and the poorer outcomes demonstrated are consistent with this.

Previous work examining the attitudes of Australian nephrologists to kidney transplant recipient assessment showed that dialysis treatment “non-compliance” was the most important factor considered, while Indigenous status was not at all important (Cass et al. 2007). This thesis
confirms that reduced haemodialysis attendance ("non-compliance") and being Indigenous are closely linked, even when other measured factors are accounted for, confirming the suspicion that these two factors are easily conflated as suggested (Cass et al. 2007).

Some have argued that discussing and measuring non-compliance concentrates attention unduly on the provider-patient dyad at the expense of the institutional, structural or broader socio-economic context, privileges providers’ perspectives over patients’, risks the maintenance of perjorative provider attitudes towards patients and itself does nothing to improve outcomes (Humphrey & Weeramanthri 2001). While these criticisms have some validity, there is also the possibility that measurement of patients’ non-compliance with providers’ prescriptions gauges the degree of “concordance” between patients and providers (including individuals and institutions). It can be useful in judging the success of interventions that aim to address institutional or organisational biases, and provide a way of measuring:

“the material consequences of particular models and practices of health service provision, undertaken within particular institutional, political, social and cultural contexts.” (Humphrey & Weeramanthri 2001)
A “one size fits all” approach to the provision of haemodialysis treatments is based on models of care designed and used by people from the dominant non-Indigenous culture in Australia and overseas. It is plausible, even likely, that these models of care do not suit Indigenous Australians (Anderson et al. 2012; Rix et al. 2014, 2015). The concept of the elimination of “difference blindness” is helpful here (Kelaher et al. 2012): it is no longer enough to believe all that is necessary is to treat everyone the same (equality); rather, people should receive treatment according to need (equity, or “equal consideration of interest”) (Cunningham, Cass & Arnold 2005; Singer 2011).

This has been codified in international convention. The rights of all peoples to health services appropriate to their circumstances and needs has been clarified by the United Nations’ Committee on Economic, Social and Cultural Rights in General Comment No. 14 (United Nations Committee on Economic, Social and Cultural Rights 2001). These rights to health include the elements of availability, acceptability, quality and accessibility (which includes the dimensions of non-discrimination, physical accessibility, economic accessibility [affordability] and information accessibility). Based on the evidence from this thesis of poorer outcomes for Indigenous ESKD patients tied to their pattern of haemodialysis attendance, it appears that there is a prima facie case that patients’ rights to acceptable, accessible and high quality integrated renal
services have been compromised. Further work should be pursued urgently to confirm and change this.

7.4 Delivering Better Outcomes for Indigenous Patients with CKD and ESKD: We Could do Better, Couldn’t We?

7.4.1 Yes, we can!

Substantial improvements in adjusted mortality rates for both Indigenous and non-Indigenous patients requiring RRT have occurred in Australia since 1995. This has been driven by both the improvement in survival for young and middle aged patients with minimal co-morbidity and the extension of treatment to older patients with more co-morbidities. This should be a cause for considerable optimism.

Inherent in this thesis is a paradox that should lead to further optimism:

(i) there is a higher mortality associated with lower levels of haemodialysis treatment attendance

(ii) lower levels of haemodialysis attendance are associated with being Indigenous and are common (at least in the Northern Territory, where 40% of all Indigenous Australian dialysis patients are treated, although they are perceived by health professionals to be a problem elsewhere too [Anderson et al. 2012; Rix et al. 2013])

(iii) an earlier sizeable disparity in mortality outcomes between
Indigenous and non-Indigenous dialysis patients has narrowed to become not significantly different most recently. This raises the possibility of substantial further improvements in mortality rates for Indigenous dialysis patients that may ultimately become better than non-Indigenous dialysis mortality rates, if methods can be developed and implemented to improve engagement between the health system and Indigenous patients. As argued elsewhere (14 years ago), there is a need:

“to comprehensively and successfully address the nexus between the provision and uptake of health services in a Northern Territory context.” (Humphrey & Weeramanthri 2001)

The possibility of better dialysis mortality rates has precedent in the United States, where (non-Indigenous) African-American dialysis patients have had significantly lower adjusted mortality rates than (non-Indigenous) “white” Caucasian American patients (Kalantar-Zadeh et al. 2007; Pugh, Tuley & Basu 1994; Rhee et al. 2014). Non-Indigenous minority RRT patients in England and Wales have had similar adjusted mortality rates to the majority white patient population (Roderick et al. 2009). In Canada, First Nations RRT patients have had similar adjusted mortality rates to non-Indigenous patients (Tonelli et al. 2004).
It is also clear that increases in rates of transplantation for Indigenous dialysis patients are needed to improve their outcomes in general, not just mortality rates. This thesis confirms that transplantation rates have fallen for Indigenous patients since 2000. It demonstrates clearly (for the first time) that Indigenous patients receiving a kidney transplant have much better survival than similar patients continuing on dialysis. It also provides (for the first time) quantitative data to support previous qualitative work linking dialysis treatment compliance with transplantation rates in Australia (Anderson et al. 2007, 2012). These findings confirm the importance of improving engagement between the health system and Indigenous patients: transplant rates are unlikely to improve without a focus on developing better concordance between Indigenous patients and (almost always non-Indigenous) health care providers during earlier stage CKD and dialysis treatment.

For those Indigenous Australian patients with earlier stages of CKD, there are fewer data but what exists suggests that engagement between the health system and patients could be improved and in doing so lead to better outcomes. Linked primary health care and hospital data from the Northern Territory demonstrates a “U-shaped curve” relationship between the number of primary health care interactions and the risk for hospitalisation for several non-communicable chronic diseases, particularly for those with CKD (Zhao et al. 2013).
7.4.2 How Can Better Outcomes Be Delivered?

How can better outcomes for Indigenous Australian patients with CKD and ESKD be delivered?

First, evidence from this thesis is consistent with the theory that better engagement with Indigenous patients with CKD and ESKD is necessary to improve outcomes, including death, hospitalisation and transplantation rates.

Second, measurement of the level of engagement with Indigenous patients is crucial, as is measurement to ensure that any model of better patient-provider engagement delivers better outcomes that are meaningful to both patients and health care providers (Breckenridge et al. 2015; Coulter et al. 2015; Flythe et al. 2015; Moss & Davison 2015; Naik, Hess & Unruh 2012).

Third, better systems of engagement with Indigenous patients with earlier-stage CKD have the potential to both reduce the need for dialysis or transplantation treatment (Howard et al. 2010) and improve outcomes for patients who develop ESKD despite risk-factor management (Cass et al. 2002).
What is meant by “better engagement?” Dillon and Westbury (2007) have defined engagement thus:

“Engagement by governments refers to policies, actions, programs and decisions which substantively project the broad panoply of formal and informal sovereignty of the nation state.” (p. 208)

For the majority of Indigenous Australians, health care practitioners (doctors, nurses and, to a lesser extent, Aboriginal health practitioners) are directly employees of national or state/Territory governments. In most circumstances, health care practitioners are therefore agents of government action.

In relation to Indigenous Australians, Dillon and Westbury have argued that:

“This lack of engagement [by government] has been the key factor that has contributed to the downward spiral of dysfunctionality and disadvantage which so perplexes government and others.” (p. 208)

They have suggested that:

“... engagement must be substantive, and cannot be merely rhetorical or ornamental. At the other end of the spectrum, engagement should not involve the imposition of excessive levels of authority and order which exclude the reciprocal and iterative
processes which are inherent in underpinning the legitimacy of government.” (p. 209)

When considered in the context of recent calls for more “patient-centred care” and “shared decision making” in the health system broadly, the concept of “better engagement” by governments proposed by Dillon and Westbury appears relevant and timely when considering how health care systems and professionals interact with Indigenous Australian patients.

These insights can and should inform health system changes and future research directions to improve outcomes for Indigenous Australians with kidney disease.

7.4.2.1 Increasing Haemodialysis Attendance

and improve non-compliance, usually (but not exclusively) from a dialysis nurse or social worker perspective (Bordelon 2002; Bruno 1999; Grefberg 1998; Hedman 1998; Kammerer et al. 2007; Molzahn 1989; Morgan 2000; Prescott 2004; Russell et al. 2011; Sehgal et al. 2002; Valdez 2003; Wells 2011; White 2004; Zrinyi 2001). In contrast, work about compliance generally in the Indigenous Australian health context has been more theoretical concentrated on the systemic issues that underpin patients’ experiences of health services, such as the broader societal context, the cultural safety or competence of a service, and the degree to which a service empowers patients (Anderson et al. 2012; Devitt & McMasters 1998a, 1998c; Humphrey & Weeramanthri 2001; Preece 2010; Rix et al. 2013, 2015).

These observations suggest that both interpersonal and systems-wide changes are desirable to “improve the nexus between service provision and uptake”, but that both have challenges. Interpersonal solutions are accessible to individual health service staff but have challenges with scalability and sustainability and do not address systemic issues. In contrast, larger-scale systemic changes can affect whole health systems and may prove more sustainable but are less amenable to change without managerial engagement (Gruen et al. 2008; Humphrey & Weeramanthri 2001).
Such system redesign is possible, but as Wong, LaVeist and Sharfstein (2015) have pointed out:

“To design services that promote health equity, there must be a clear focus on specific communities at risk, a commitment to listen and collect meaningful data to understand local needs and priorities, a conviction to make progress, and ongoing assessment of health outcomes.”

There are models of service re-design through community ownership in the care of Indigenous Australian dialysis patients. In the western Kimberley region of Western Australia a haemodialysis service has been community-run since late 2002, and has demonstrated survival outcomes comparable to age-adjusted national non-Indigenous levels (Marley et al. 2010). In Central Australia, the Western Desert Nganampa Walytja Palyantjaku Tjutaku Aboriginal Corporation (translated from the Pintupi as “Making All Our Families Well”) has provided support and services to some ESKD patients since 2000; early reports suggested improvement in outcomes (such as reduced remote community evacuations) and costs (Rivalland 2006). Whether these improvements in different parts of the country have been associated with changes in haemodialysis attendance (and subsequent changes in hospitalisation, survival or transplantation rates) has not yet been explored.
7.4.2.2 Increasing Transplantation Rates and Transplant Outcomes

Transplanting a larger number of “suitable” Indigenous patients would appear to be one obvious way to improve outcomes for Indigenous ESKD patients. However, there are important caveats:

1. The proportion of Indigenous patients deemed “suitable” by nephrologists is not known, since the proportion of Indigenous patients nationally who comply with dialysis prescriptions is not known.

2. Compliance with the dialysis prescription may not necessarily be a good measure of post-transplant success in any case (and thus a criterion for “suitability” [TSANZ 2011]), as this widely-held hypothesis has not been examined.

3. Given that demand for deceased kidney donors continues to outstrip supply in Australia despite recent increases in “marginal” donors (ANZOD Registry 2014), providing more kidney transplants to Indigenous patients would reduce the size of the pool available to non-Indigenous patients and lead to a reduction in overall survival for non-Indigenous patients.

4. Live related kidney donation has been shown to deliver poor long-term outcomes for Indigenous donors from the Northern Territory (Rogers, Lawton & Jose 2009).
As a result, nationally palatable and sustainable increases in Indigenous transplant rates are only likely to come once there are successful strategies both to engage meaningfully with Indigenous ESKD patients (leading to a better “match” between nephrologists’ expectations and patients’ needs) and increase deceased organ donor rates nationally.

Improving transplant outcomes for Indigenous ESKD patients is also obviously desirable, but may be more challenging. Major causes of poor outcomes are infection-related death and loss of a functioning graft through immunosuppression withdrawal in the setting of life-threatening infection, not non-compliance related acute transplant rejection (Rogers, Lawton & Jose 2006). The former have not so far been amenable to clinical solutions (such as broad spectrum antibiotic prophylaxis) (Davis et al. 2003). Underlying factors predisposing to these poorer outcomes may include:

(i) greater immunosuppression required to overcome greater HLA mis-matching (Rogers, Lawton & Jose 2006);

(ii) poorer quality housing and overcrowding, sometimes without basic “health-related infrastructure” in the house (Bailie, Carson & McDonald 2004; Bailie & Runcie 2001)

(iii) remoteness-related reduced access to timely specialist involvement in the diagnosis and management of serious infections.
A greater understanding of the antecedents to serious infection in Indigenous kidney transplant patients is clearly needed before changes are introduced that are likely to improve transplant and/or patient survival.

### 7.4.2.3 Slowing the Rate of Progression of CKD

Ultimately, given the challenges outlined above in the management of dialysis and transplantation, the least challenging answer available within the health system is to slow the rate of progression of CKD towards ESKD, thereby delaying (and perhaps preventing) the need for RRT.

Several necessary steps towards this goal are already in place, at least within the Northern Territory. Tools for the identification of CKD have been validated (Maple-Brown et al. 2012) and agreed upon (Johnson et al. 2012a, 2012b), leading to incorporation in local guidelines (Central Australian Remote Practitioners Association 2014). The widespread use of electronic medical records in the provision of primary health care to the population at risk (Indigenous Australians living more remotely) since 2010, along with information sharing with the hospital sector, make access to longitudinal information for patient care planning easier than ever before. Processes for random chart audit, feedback and reflection at a clinic level are well established (Bailie et al. 2008); prescription rates
for angiotensin converting enzyme inhibitors or receptor blockers in those with diabetes mellitus or identified proteinuria are high (NT Department of Health 2012). Whether these substantial advantages have led to improvements in other processes of care or outcomes has not yet been established.

7.4.3 Future Research

Further observational and interventional research is required to understand the scope and magnitude of issues facing Indigenous patients with kidney disease, lead change in health service processes and clinical practice, and measure (any) improvement in outcomes.

7.4.3.1 Use of Existing Data

In the first instance, existing administrative and registry data can be used more effectively in observational studies, as demonstrated in this thesis. Work is underway on a National Health and Medical Research Centre funded project to examine the “whole-of government” cost-effectiveness of different models of care for patients with ESKD in the Northern Territory using both prospective qualitative data and retrospective quantitative data (collated in a layered data linkage exercise novel to Australia) (Menzies School of Health Research 2015). Follow-up of at least one existing defined cohort is underway to establish
and validate established and “novel” risk factors for cardiovascular disease, ESKD and mortality (Barr et al. 2015).

Linkage prospectively of ANZDATA registry, hospital administrative and outpatient public health insurance billing data (from the Australian Medical Benefits Schedule and Pharmaceutical Benefits Scheme) with National Death Index data could examine untested hypotheses nationally about the health service utilisation and outcomes of Indigenous and non-Indigenous patients with kidney disease, including but not limited to dialysis attendance patterns.

It is now also time to create a registry of all patients identified with CKD in the Northern Territory, specifically because:

(i) CKD is definable - it can now be (relatively) easily diagnosed, classified and codified

(ii) data collection is feasible - there are a relatively small number of information sources from which to gather data (three laboratory networks and two primary health care networks, all computerised)

(iii) CKD is a local priority of major political and community concern

(iv) CKD has both a significant incidence and is an important cause of morbidity and mortality, particularly for the Indigenous community

(v) ESKD is amenable to control through the implementation of
effective clinical management (at earlier stages of identified CKD)
(vi) a registry of CKD would enable the evaluation and adjustment of programs to delay and (hopefully) prevent ESKD (Centre for Disease Control 2010).

A registry would also facilitate the development and implementation of further interventional research, including potentially through pragmatic registry-based trials using electronic health records (Staa et al. 2012). It would also enable more accurate prospective planning of ESKD services than currently used historical projections (You et al. 2015).

### 7.4.3.2 Augmenting Existing Data with Extra Data Collection

Collecting extra data in specific areas would greatly augment the use of existing data in the measurement of outcomes for Indigenous patients with kidney disease. This is particularly the case in the developing field of patient-reported experience measures (“PREMs”) and patient-reported outcome measures (“PROMs”), which have been recently suggested as one systematic way to measure patient-centred care (Bellgard et al. 2015; Breckenridge et al. 2015; Coulter et al. 2015).

In addition, as this thesis has demonstrated and alluded to, it remains important to collect and analyse extra qualitative and quantitative information to explain why outcomes are as they are. This is particularly important when considering interventions: demonstrating disparities
between Indigenous and non-Indigenous patients in kidney transplantation access from registry data alone is much less useful without the qualitative research exploring nephrologists’ attitudes to transplant assessment and suitability and without quantitative analysis of hospital administrative data. In the future, more attention needs to be paid to data outside registries (using data linkage techniques to link to registry data, as in this thesis).

7.5 “Closing the Gap Between Indigenous and Non-Indigenous Australians on Life Expectancy”

On Wednesday 13th February 2008, riding a wave of popular and bipartisan support, the Prime Minister of Australia apologised to Australia’s Indigenous Peoples for past government actions, and set an agenda for the nation that has been re-affirmed with subsequent leaders and governments. In part, he said:

“Our challenge for the future is to embrace a new partnership between Indigenous and non-Indigenous Australians. The core of this partnership for the future is closing the gap between Indigenous and non-Indigenous Australians on life expectancy, educational achievement and employment opportunities. This new partnership on closing the gap will set concrete targets for the future: within a decade to halve the widening gap in literacy, numeracy and employment outcomes and opportunities for
Indigenous children, within a decade to halve the appalling gap in infant mortality rates between Indigenous and non-Indigenous children and, within a generation, to close the equally appalling 17-year life gap between Indigenous and non-Indigenous when it comes to overall life expectancy.” (Hansard 2008)

Amongst many other initiatives, “closing the gap” in life expectancy needs efforts to address disparities in health care (Cunningham, Cass & Arnold 2005), including for those with CKD or ESKD (which were the underlying or associated cause of death for 15.8% of Indigenous deaths between 2008 and 2012 (Australian Institute of Health and Welfare 2015), and contributed 5% of the total disparity between Indigenous and non- Indigenous mortality between 2008 and 2012 using underlying causes only (Australian Institute of Health and Welfare 2014b). If we are to “close the gap”, modern methods (both quantitative and qualitative) are required to measure “the gap” in outcomes and the impact of our efforts to close it.
Chapter 8: Appended List of Related Papers
Published During PhD Candidature That Do Not Form a Direct Part of the Thesis


Maple-Brown, LJ, Hughes, JT, Chatfield, MD, Ward, LC, Piers, LS, Jones, GR, Lawton, PD, Ellis, AG, Cass, A, Hoy, WE, O'Dea, K,


Anderson, K, Devitt, J, Cunningham, J, Preece, C & Cass, A. 2008, "All they said was my kidneys were dead": Indigenous Australian patients' understanding of their chronic kidney disease', *Medical Journal of Australia*, vol. 189, no. 9, pp. 499-503.


Austin, PC. 2009, 'Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples', *Statistics in Medicine*, vol. 28, no. 25, pp. 3083-107.


——. 2014, 'The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments', *Statistics in Medicine*, vol. 33, no. 7, pp. 1242-58.


—— 2012a, *Census of Population and Housing: characteristics of Aboriginal and Torres Strait Islander Australians, 2011*, Cat. no. 2076.0, ABS, Canberra.
2012b, *Population Estimates by Age and Sex, Australia by Geographical Classification [ASGC 2011], 2001 to 2011, data cube: SuperTable*, Cat. no. 3235.0, ABS, Canberra.

2013, *Australian Health Survey: Biomedical Results for Chronic Diseases, 2011-12. data cube: Table 6: Kidney disease biomarkers*, Cat. no. 4364.0.55.005, ABS, Canberra.

2014, *Australian Aboriginal and Torres Strait Islander Health Survey: Biomedical Results, 2012-13. data cube: Table 10: Kidney disease biomarkers*, Cat. no. 4727.0.55.003, ABS, Canberra.


2014a, *Indigenous health check (MBS 715) data tool, 3rd Release*, AIHW, Canberra, viewed April 2015,
—— 2014b, *Mortality and life expectancy of Indigenous Australians: 2008 to 2012*, Cat. no. IHW 140, AIHW, Canberra,

—— 2015, *The health and welfare of Australia’s Aboriginal and Torres Strait Islander peoples 2015*, Cat. no. IHW 147, AIHW, Canberra.


Australian Population and Migration Research Centre 2015, *ARIA (Accessibility/Remoteness Index of Australia)*, The University of Adelaide, viewed October 2015,


Bame, SI, Petersen, N & Wray, NP. 1993, 'Variation in hemodialysis patient compliance according to demographic characteristics', *Social Science & Medicine*, vol. 37, no. 8, pp. 1035-43.


Burnette, LE & Kickett, M. 2009, 'Dislocation and Dialysis in Aboriginal Patients with Renal Failure', *Aboriginal and Islander Health Worker Journal*, vol. 33, no. 4, pp. 10-3.


Chondur, R & Guthridge, S. 2006, Population Data in the Northern Territory, Department of Health and Community Services, Darwin, viewed August 2013, <http://hdl.handle.net/10137/113%3E.


urban Indigenous people in the Darwin, Australia region: aims, methods and participation in the DRUID Study', *BMC Public Health*, vol. 6, p. 8.


Department of Health 2014, *Aboriginal Health Services and the Pharmaceutical Benefits Scheme (PBS)*, DoH, Canberra, viewed April
2015,


——. 1998c, "'They don't last long': Aboriginal patient experience of end-stage renal disease in Central Australia', *Nephrology (Carlton)*, vol. 4, Supplement, pp. s111-s7.


Disney, AP. 1995, 'Demography and survival of patients receiving treatment for chronic renal failure in Australia and New Zealand: report on dialysis and renal transplantation treatment from the
Australia and New Zealand Dialysis and Transplant Registry',


Elamin, S & Abu-Aisha, H. 2012, 'Reaching target hemoglobin level and having a functioning arteriovenous fistula significantly improve one
year survival in twice weekly hemodialysis', *Arab Journal of Nephrology and Transplantation*, vol. 5, no. 2, pp. 81-6.


Garg, AX, Mamdani, M, Juurlink, DN & van Walraven, C. 2005, 'Identifying individuals with a reduced GFR using ambulatory


Gray, NA, Dent, H & McDonald, SP. 2012, 'Renal replacement therapy in rural and urban Australia', *Nephrology Dialysis Transplantation*, vol. 27, no. 5, pp. 2069-76.


Haghhighi, AN, Broumand, B, D'Amico, M, Locatelli, F & Ritz, E. 2002, 'The epidemiology of end-stage renal disease in Iran in an
international perspective', *Nephrology Dialysis Transplantation*, vol. 17, no. 1, pp. 28-32.


Hansard – see Australia, House of Representatives


Hecking, E, Bragg-Gresham, JL, Rayner, HC, Pisoni, RL, Andreucci, VE, Combe, C, Greenwood, R, McCullough, K, Feldman, HI, Young, EW,
Held, PJ & Port, FK. 2004, 'Haemodialysis prescription, adherence and nutritional indicators in five European countries: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS)', *Nephrology Dialysis Transplantation*, vol. 19, no. 1, pp. 100-7.


Hoy, WE & Megill, DM. 1989, 'End-stage renal disease in southwestern Native Americans, with special focus on the Zuni and Navajo Indians', *Transplant Proceedings*, vol. 21, no. 6, pp. 3906-8.


birthweight, past poststreptococcal glomerulonephritis and current body mass index on levels of albuminuria in young adults: the multideterminant model of renal disease in a remote Australian Aboriginal population with high rates of renal disease and renal failure', *Nephrology Dialysis Transplantation*, DOI: 10.1093/ndt/gfu241.


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Khanal, N, Clayton, P, McDonald, S & Jose, M 2015, 'Differences in access to kidney transplantation for Indigenous Australians', paper presented to World Congress of Nephrology, Cape Town, South Africa.


Kimmel, PL, Peterson, RA, Weihs, KL, Simmens, SJ, Alleyne, S, Cruz, I & Veis, JH. 1998, 'Psychosocial factors, behavioral compliance and
survival in urban hemodialysis patients', *Kidney Int*, vol. 54, no. 1, pp. 245-54.


Kotwal, S, Webster, AC, Cass, A & Gallagher, M 2014, 'Validity of registry data: agreement between comorbidities recorded in ANZDATA
compared to NSW administrative data', paper presented to 50th Annual Scientific Meeting of the Australian and New Zealand Society of Nephrology, Melbourne, Nephrology (Carlton), vol. 19, no. S4, pp. 17-57


Levey, AS, Bosch, JP, Lewis, JB, Greene, T, Rogers, N & Roth, D. 1999, 'A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in
Renal Disease Study Group', *Annals of Internal Medicine*, vol. 130, no. 6, pp. 461-70.


Lim, WH, Boudville, N, McDonald, SP, Gorham, G, Johnson, DW & Jose, M. 2011, 'Remote indigenous peritoneal dialysis patients have higher risk of peritonitis, technique failure, all-cause and peritonitis-related
mortality', *Nephrology Dialysis Transplantation*, vol. 26, no. 10, pp. 3366-72.

Lim, WH, Chadban, S, Campbell, S, Cohney, S, Russ, G & McDonald, S. 2011, 'A review of utility-based allocation strategies to maximize graft years of deceased donor kidneys', *Nephrology (Carlton)*, vol. 16, no. 4, pp. 368-76.

Lim, WH, Johnson, DW & McDonald, SP. 2005, 'Higher rate and earlier peritonitis in Aboriginal patients compared to non-Aboriginal patients with end-stage renal failure maintained on peritoneal dialysis in Australia: analysis of ANZDATA', *Nephrology (Carlton)*, vol. 10, no. 2, pp. 192-7.


Lowe, M, Kerridge, IH & Mitchell, KR. 1995, "These sorts of people don't do very well": race and allocation of health care resources', *Journal of Medical Ethics*, vol. 21, no. 6, pp. 356-60.

Luyckx, VA, Bertram, JF, Brenner, BM, Fall, C, Hoy, WE, Ozanne, SE & Vikse, BE. 2013, 'Effect of fetal and child health on kidney
development and long-term risk of hypertension and kidney disease',


——. 2010, 'The clinical importance of nephron mass', *Journal of the American Society of Nephrology*, vol. 21, no. 6, pp. 898-910.


and Torres Strait Islander patients of remote Kimberley region origin', *Medical Journal of Australia*, vol. 193, no. 9, pp. 516-20.


McDonald, SP, Hoy, WE, Maguire, GP, Duarte, NL, Wilcken, DE & Wang, XL. 2002, 'The p53Pro72Arg polymorphism is associated with


Moss, AH & Davison, SN. 2015, 'How the ESRD quality incentive program could potentially improve quality of life for patients on dialysis', *Clinical Journal of the American Society of Nephrology*, vol. 10, no. 5, pp. 888-93.

Naik, N, Hess, R & Unruh, M. 2012, 'Measurement of health-related quality of life in the care of patients with ESRD: isn't this the metric that matters?', *Seminars in Dialysis*, vol. 25, no. 4, pp. 439-44.


NHMRC. 2003, *Values and Ethics: Guidelines for Ethical Conduct in Aboriginal and Torres Strait Islander Health Research*, E52, National Health & Medical Research Council, Canberra

—– 2014, *Guidelines Under Section 95 of the Privacy Act 1988*, PR1, National Health & Medical Research Council, Canberra,


Psaty, BM & Siscovick, DS. 2010, 'Minimizing bias due to confounding by indication in comparative effectiveness research: the importance of restriction', *JAMA*, vol. 304, no. 8, pp. 897-8.


Rivalland, P. 2006, *It's More Than Machines and Medicine: They should understand there’s a Yanangu way: Summary report, November 2006 (A short report by Paul Rivalland on the activities of Western Desert Nganampa Walytja Palyantjaku Tjutaku:’Making all our families*

Rix, EF, Barclay, L, Stirling, J, Tong, A & Wilson, S. 2014, 'Beats the alternative but it messes up your life': aboriginal people's experience of haemodialysis in rural Australia', *BMJ Open*, vol. 4, no. 9, p. e005945.


Rix, EF, Barclay, L, Wilson, S, Stirling, J & Tong, A. 2013, 'Service providers' perspectives, attitudes and beliefs on health services delivery for Aboriginal people receiving haemodialysis in rural Australia: a qualitative study', *BMJ Open*, vol. 3, no. 10, p. e003581.


Roderick, P, Byrne, C, Casula, A, Steenkamp, R, Ansell, D, Burden, R, Nitsch, D & Feest, T. 2009, 'Survival of patients from South Asian and Black populations starting renal replacement therapy in England and
Wales', *Nephrology Dialysis Transplantation*, vol. 24, no. 12, pp. 3774-82.


Shephard, MD, Allen, GG, Paizis, K, Barbara, JA, Batterham, M & Vanajek, A. 2006, 'Results of an Aboriginal community-based renal disease management program incorporating point of care testing for
urine albumin:creatinine ratio', *Rural & Remote Health*, vol. 6, no. 4, p. 591.


Weisbord, SD, Mor, MK, Sevick, MA, Shields, AM, Rollman, BL, Palevsky, PM, Arnold, RM, Green, JA & Fine, MJ. 2014, 'Associations of depressive symptoms and pain with dialysis adherence, health resource utilization, and mortality in patients receiving chronic
hemodialysis', *Clinical Journal of the American Society of Nephrology*, vol. 9, no. 9, pp. 1594-602.


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