ANTECEDENTS OF RENAL DISEASE IN ABORIGINAL CHILDREN (ARDAC STUDY)

LEIGH HAYSOM

A thesis submitted in fulfilment of the requirements

for the degree of

Doctor of Philosophy

Centre for Kidney Research, The Children's Hospital at Westmead

School of Public Health, University of Sydney

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DECLARATION

I hereby declare that this thesis is the result of original research, and to the best of my knowledge it contains no material previously published or written by another person, nor material which to a substantial extent has been accepted for the award of any other degree or diploma at the University of Sydney or any other educational institution.

Leigh Haysom Date

AUTHOR'S CONTRIBUTION

The work presented in this thesis has been carried out by the author under the supervision of Professor Jonathan Craig, School of Public Health, University of Sydney, and co-supervision of Associate Professor Andrew Rosenberg, School of Women's and Children's Health, University of New South Wales.

In this study, I prepared ethics submissions to The Children's Hospital at Westmead, University of Sydney, Department of Education and Training, New South Wales Area Health Services, Aboriginal Health and Medical Research Council and Aboriginal Medical Services. I prepared successful project grant applications to The National Health and Medical Research Council of Australia and The Financial Markets Foundation for Children. I analysed the data, interpreted results, revised study protocols, drafted and revised all manuscripts for submission to peer-reviewed journals, presented results back to the participating communities, and am fully responsible for this thesis. I assisted in the collection of ongoing ethics approvals from area health committees, community agreements, individual consents, data collection and data entry.

ETHICAL CLEARANCE

Approval for 'Antecedents of Renal Disease in Aboriginal Children (ARDAC)' was obtained from the Human Research Ethics Committees at The Children's Hospital at Westmead, the University of Sydney, the New South Wales Department of Education and Training, participating New South Wales Area Health Services, and participating Aboriginal communities.

Consent was obtained from the parents of all participating children. At follow-up, children older than 14 years gave their own consent.

ABSTRACT

Introduction

End-stage kidney disease is a more common and overwhelming disease for Indigenous people, and the reasons for this disparity are not well researched. Indigenous populations suffer more diabetes, hypertension and cardiovascular disease than their non-Indigenous countrymen, but these differences do not fully explain the two to forty-fold increased risk for end-stage kidney disease. Policies aimed at early prevention have been hampered by a complete absence of population-based prospective studies documenting the early causal chain to chronic kidney disease, and the physiological and environmental risk factors associated with the development of chronic kidney disease. Long-term prospective research in Indigenous communities needs to be culturally appropriate, sustainable, and be developed with the community and alongside a consultative body, such as an advisory board.

Aims

The primary aims of this thesis were to determine:

1. The prevalence of baseline and persistent early markers of chronic kidney disease in Australian Indigenous and non-Indigenous children.
2. The association of these markers with physiological and environmental health determinants, such as geographic remoteness and socio-economic disadvantage.
3. The accuracy of proteinuria dipsticks for detecting baseline and persistent albuminuria in Indigenous and non-Indigenous children.

Methods

A population-based prospective cohort study of Aboriginal and non-Aboriginal primary school-aged children was conducted in New South Wales, Australia. Markers of chronic kidney disease measured were haematuria, proteinuria, albuminuria, obesity, and systolic and diastolic hypertension. Risk factors known and thought to be associated with the development of these markers in Aboriginal and non-Aboriginal people were also recorded, including age, gender, growth parameters, birth weight and environmental health determinants: measures of geographic isolation and social disadvantage. Follow-up measurements were performed two and four years after baseline

testing at the primary or new high school on all available children, and the frequency of persistent chronic kidney disease markers (marker detected at both baseline and follow-up) was ascertained. The study aims and design were developed in consultation with the Senior Aboriginal Health Educator on the study, community elders, Aboriginal Education Assistants and Area Health Workers. An Aboriginal Health Research Advisory Board was created after it was known which communities would be participating in the study. The study results were presented to each community at the first and final follow-up visits, and a newsletter summarising the final study results was provided to all communities, families and schools.

Main Findings

From 2002 to 2004, 2266 children (55% Aboriginal, 51% male, mean age 8.9 years $\pm$ SD 3.0 years) were enrolled from 37 primary schools across urban, coastal, rural and remote regions of New South Wales.

From 2004 to 2006, there were 1432 children (63%) available for re-testing at two-year follow up (54.0% Aboriginal, 50.5% male, mean age 10.5 years $\pm$ SD 2.0 years).

At four-year follow-up from 2006 to 2008, there were 1506 children (67%) re-tested (55.1% Aboriginal, 51.0% male, mean age 13.3 years $\pm$ SD 3.2 years). There were no differences in the children at follow-up compared with those that were lost-to-follow-up with regards to ethnicity, gender, age, birth weight, body mass index and social disadvantage. There were proportionally more older children who were lost-to follow-up compared with those children at follow-up.

Baseline findings

The overall baseline prevalence of haematuria was 5.5%, proteinuria 7.3%, albuminuria 7.3%, obesity 7.1%, systolic hypertension 7.2% and diastolic hypertension 5.9%. Aboriginal children had almost twice the prevalence of haematuria at baseline when compared to non-Aboriginal children (7.1% versus 3.6%, p=0.001). Aboriginal children had no increased risk for any other marker of chronic kidney disease at baseline. Geographic isolation and socio-

economic disadvantage were not associated with any markers of chronic kidney disease in these children.

Two-year follow-up findings

Persistent obesity (5.3%) was frequent, but persistent markers of CKD were infrequent (systolic hypertension 1.1%, diastolic hypertension 0.2%, haematuria 1.1% and albuminuria 1.5%). While there were more Aboriginal than non-Aboriginal children with baseline haematuria (7.1% versus 3.6%, p=0.001), after adjustment for age, gender, birth weight and socio-demographic status, there was no increased risk for persistent haematuria, albuminuria, obesity or hypertension in Aboriginal children.

Four-year follow-up findings

Prevalence of baseline CKD markers was frequent, but most abnormalities found at baseline were transient. Besides persistent obesity (5.0%), persistence of CKD markers at final follow-up were infrequent; haematuria (1.9%), albuminuria (2.4%), systolic hypertension (1.5%) and diastolic hypertension (0.2%). There was no difference in prevalence of persistent markers of CKD between Aboriginal and non-Aboriginal children.

Proteinuria dipsticks had an overall sensitivity of 62% (95% CI 55-70%) and an overall specificity of 97% (95% CI 96-98%) at detecting albuminuria at baseline. In predicting persistent albuminuria, dipsticks had an overall sensitivity of 75% (95% CI 53-89%), and a specificity of 93% (95% CI 92-94%). Accuracy of proteinuria dipsticks for detection of albuminuria did not vary with ethnicity, gender or body mass index. Accuracy was less in younger children (4.0 to 7.9 years), and in children with haematuria.

Conclusions

The baseline prevalence of early markers of chronic kidney disease is high, however most of these abnormalities (besides obesity) are transient. At follow-up testing, the prevalence of persistent markers of chronic kidney disease is low. Persistent obesity is common and strongly predicts those children with persistent hypertension. Children who are initially found to be

obese are likely to remain obese, and therefore early intervention at initial diagnosis is important.

Overall only 20% of children found to have markers of early CKD have persistent abnormalities (diastolic and systolic hypertension, albuminuria, hematuria) 2 years later, equivalent to a population point prevalence of 1-2% in children with a mean age of 10 years. Aboriginal children have higher rates of baseline and transient haematuria, but no increased risk for persistent markers of CKD. These novel findings suggest that the increased risk for CKD in Indigenous adults is not manifest until young adulthood, and is likely to evolve through socio-demographic inequities, and adolescence and young adulthood is a critical time for preventative strategies.

The performance characteristics of proteinuria dipsticks make them a portable, low-cost and reliable test instrument for detection of albuminuria in Aboriginal and other higher risk groups of children. The reliability of the dipstick for detecting albuminuria may be less in younger children, and in children with haematuria.

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I would also like to thank Ms Rita Williams (Senior Aboriginal Health Educator at The Children's Hospital at Westmead) who conceived, designed, carried-out and nurtured the study to completion, and is busy doing the same for the next six-year phase of work. Many thanks to the Aboriginal communities and the Aboriginal and non-Aboriginal children and families who also made this work possible. Thanks also to the schools and Aboriginal Education Assistants for their tireless assistance during recruitment, consenting and data collection.

I would like to thank Dr Premala Sureshkumar, who helped me with many different things along the way, including data analysis and the writing of this thesis. Many thanks also to Dr Elisabeth Hodson, Ms Pamela Lopez-Vargas, Ms Sandra Puckeridge and Ms Tamara Borysko. Without these extremely capable people, the ARDAC Study would have long ago foundered.

Finally, thanks to my mum, Andrea Haysom (Lauren's Nana). What would we have done without you?

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PUBLICATIONS ARISING FROM THIS THESIS

Chapters 3, 4, 5, 6 and 7 have been published or accepted for publication in peer reviewed medical journals. Chapter 2 is being prepared for publication.

Chapter 3: Haysom L, Williams R, Hodson E, Roy LP, Lyle D, Craig JC. Early chronic kidney disease in Aboriginal and non-Aboriginal children: remoteness, socio-economic disadvantage or race? Kidney International 2007;71:787-794.

Chapter 4: Haysom L, Williams R, Hodson E, Lopez-Vargas P, Roy LP, Lyle D, Craig JC. Cardiovascular risk factors in Australian Indigenous and non-Indigenous children: a population-based study. Journal of Paediatrics and Child Health; accepted 3 June, 2008.

Chapter 5: Haysom L, Williams R, Hodson E, Lopez-Vargas P, Roy LP, Lyle D, Craig JC. Diagnostic accuracy of urine dipsticks for detecting albuminuria in Indigenous and non-Indigenous children in a community setting. Pediatric Nephrology; accepted 17 July, 2008.

Chapter 6: Haysom L, Williams R, Hodson E, Lopez-Vargas P, Roy LP, Lyle D, Craig JC. Risk for chronic kidney disease in Australian Indigenous and non-Indigenous children: a population-based follow-up study. American Journal of Kidney Diseases; accepted 4 August, 2008.

Chapter 7: Haysom L, Williams R, Hodson E, Lopez-Vargas P, Roy LP, Lyle D, Craig JC. Persistent markers for chronic kidney disease in Australian Indigenous and non-Indigenous children: a six-year follow-up study. Medical Journal of Australia; accepted as a short paper 7 August, 2008.

Abstracts from scientific meetings

Haysom L, Williams R, Hodson E, Lopez-Vargas P, Roy LP, Lyle D, Craig J. Risk for chronic disease in Australian Aboriginal and non-Aboriginal children: a population-based follow-up study; Chronic Disease Oral Session, Coalition of Researchers to Improve Aboriginal Health [CRIAH] Meeting. Sydney, Australia April 2008.

Haysom L, Williams R, Hodson E, Lopez-Vargas P, Roy LP, Lyle D, Craig J. Risk for chronic disease in Australian Aboriginal and non-Aboriginal children: a population-based follow-up study; Clinical Science Best Poster Award Session, Australian and New Zealand Society of Nephrology [ANZSN] Annual Scientific Meeting. Gold Coast, Queensland, Australia 10-12 September 2007

Haysom L, Williams R, Hodson E, Lopez-Vargas P, Roy LP, Lyle D, Craig J. Accuracy of urine dipsticks for diagnosing albuminuria in Indigenous and non-Indigenous children; Clinical Nephrology Award Session, Australian and New Zealand Society of Nephrology [ANZSN] Annual Scientific Meeting. Gold Coast, Queensland, Australia 10-12 September 2007

Haysom L, Williams R, Hodson E, Lopez-Vargas P, Roy LP, Lyle D, Craig J. Cardiovascular risk factors in Australian Indigenous and non-Indigenous children: a population-based study; Rue Wright Memorial Award session, Royal Australasian College of Physicians Congress [RACP]. Cairns, Queensland, Australia 7-11 May 2006

Haysom L, Williams R, Hodson E, Lopez-Vargas P, Roy LP, Lyle D, Craig J. Cardiovascular risk factors in Australian Indigenous and non-Indigenous children: a population-based study; Australian and New Zealand Society of Nephrology [ANZSN] Annual Scientific Meeting. Melbourne, Victoria, Australia 10-12 September 2006

Haysom L, Williams R, Hodson E, Roy LP, Lyle D, Craig JC. Early chronic kidney disease in Aboriginal and non-Aboriginal children: remoteness, socio-economic disadvantage or race? Australian and New Zealand Society of

Nephrology [ANZSN] Annual Scientific Meeting. Wellington, New Zealand, 10-12 September 2005

Haysom L, Williams R, Hodson E, Roy LP, Lyle D, Craig JC. Early chronic kidney disease in Aboriginal and non-Aboriginal children: remoteness, socio-economic disadvantage or race? Coalition of Researchers to Improve Aboriginal Health [CRIAH] Inaugural Meeting. Sydney, Australia, August 2005

CHAPTER 1: INTRODUCTION AND OVERVIEW OF THE THESIS

Aims of thesis

To determine:

1. The prevalence of baseline and persistent early markers of chronic kidney disease in Australian Indigenous and non-Indigenous children.
2. The association of these markers with physiological and environmental health determinants, such as geographic remoteness and socio-economic disadvantage.
3. The accuracy of proteinuria dipsticks for detecting baseline and persistent albuminuria in Indigenous and non-Indigenous children.

Background

This thesis was undertaken to determine the natural history of early chronic kidney disease in primary school aged Aboriginal and non-Aboriginal Australian children. End-stage kidney disease is over-represented among Indigenous people world wide, yet there are no epidemiological studies documenting the development of chronic and end-stage disease, and the contribution to risk of disease made by socio-demographic determinants.

The aim of the studies presented in this thesis were to establish and follow a cohort of Aboriginal and non-Aboriginal children to identify the frequency, risk factors and natural history of markers of chronic kidney disease (haematuria, albuminuria, proteinuria, obesity and systolic and diastolic hypertension) over a six year period. This knowledge will help us to understand the progression to chronic kidney disease in Indigenous people, and implement effective prevention strategies for those with persistent abnormalities.

In order to identify the magnitude of end-stage kidney disease and excess risk in Indigenous people, a detailed review of the literature was undertaken, listing the prevalence, incidence and risk for end-stage kidney disease as compared with non-Indigenous people by population studied (chapter two).

The third chapter describes the frequency of markers of chronic kidney disease (haematuria, proteinuria and albuminuria) in a population-based

sample of Aboriginal and non-Aboriginal children in New South Wales, and the association of these markers with environmental health determinants.

The fourth chapter describes the frequency of markers of cardiovascular disease (cardiovascular disease being strongly predictive for end-stage kidney disease); albuminuria, obesity, systolic and diastolic hypertension in this cohort of Aboriginal and non-Aboriginal children.

The fifth chapter assesses the accuracy of proteinuria dipsticks in detecting albuminuria at baseline and at two-year follow-up in Aboriginal and non-Aboriginal children, and in subsets of children at higher risk for chronic kidney disease, such as males, older children, children with haematuria, and overweight/obese children.

Chapter six describes the frequency of persistent markers of chronic kidney disease in Aboriginal and non-Aboriginal children at two-year follow-up, and whether Aboriginal children are at increased risk for chronic kidney disease after accounting for socio-demographic differences.

In chapter seven, the final results of the six-year prospective study are presented, with a comparison of risk for persistent markers of chronic kidney disease between Aboriginal and non-Aboriginal children.

Chapter eight provides a summary of the main findings of this thesis, with recommendations for future research.

CHAPTER 2: REVIEW OF THE LITERATURE – A SYSTEMATIC REVIEW OF THE PREVALENCE, INCIDENCE AND RISK FOR END-STAGE KIDNEY DISEASE IN INDIGENOUS PEOPLE

Introduction

In this chapter, I summarised the background data on the frequency and risk for end-stage kidney disease in Indigenous people worldwide compared with non-Indigenous people.

The published prevalence rates of end-stage kidney disease in Indigenous populations studies vary widely, both between and within different populations. The reasons for this are unclear, and few studies have attempted to address these differences, which are likely to result from a combination of physiological and environmental causes.

Risk factors for end-stage kidney disease in Indigenous populations are difficult to assess from cross-sectional studies. Causal relationships can only be defined from longitudinal studies, of which there are very few. The ARDAC study reported in this thesis, therefore, is important research into understanding the natural history and risk factors for persistent early chronic kidney disease markers in Aboriginal and non-Aboriginal children and youth.

2.1: Abstract

Background: The disparity in rates of end-stage kidney disease between Indigenous and non-Indigenous people varies widely and is poorly understood.

Methods: We performed a systematic review of population-based epidemiological studies that investigated prevalence, incidence and risk for end-stage kidney disease in Indigenous people compared with non-Indigenous people. MEDLINE, EMBASE, CINAHL, the Aboriginal and Torres Strait Islander (ATSI) Health bibliographic database, the Rural Health bibliographic database, reference lists and conference proceedings were searched to identify eligible studies. Results are expressed as odds ratio and relative risks (OR, RR). The effect of confounders was taken into account.

Results: There were 24 publications describing prevalence and/or incidence of all cause, non-diabetic and diabetic ESKD, and included the following Indigenous groups: American Indian/Alaskan Natives and their tribal groups, Canadian Native Indians and their tribal groups, Goajiro Indians, Indigenous Australians and their tribal groups, New Zealand Maori and Pacific Islanders. Fifteen studies documented prevalence and/or incidence of all-cause ESKD in Indigenous people, and 16 studies documented prevalence and/or incidence of diabetic ESKD in Indigenous people. All studies, besides 2 cross-sectional studies, were retrospective cohort study designs. Prevalence, incidence and risk for ESKD in Indigenous people compared with non-Indigenous people are universally greater for all-cause ESKD, and most of this excess risk is due to higher rates of diabetic ESKD. Zuni Indians, Indigenous Australians, Maori and Pacific Islander people have the highest risk for ESKD compared to other Indigenous groups, however it is difficult to compare between studies due to ascertainment bias, non-Indigenous comparators from different study bases and inconsistent adjustment for potential confounders. Only one study accounted for socio-demographic confounders. Of the three studies that looked at non-diabetic ESKD, the risk in Indigenous people is reduced, no different or only slightly greater. When compared to other disadvantaged groups, the excess risk for ESKD in Indigenous groups is modified.

Conclusions: There is a need for prospective epidemiological studies that evaluate the physiological and environmental risk factors for ESKD, particularly diabetic ESKD, in Indigenous people, and include a valid non-Indigenous comparator.

2.2: Background

The incidence of end-stage kidney disease (ESKD) is increasing world wide, but most noticeably among Indigenous populations. To coincide with this epidemic of kidney disease in Indigenous populations, there has been a marked increase in the relevant literature describing chronic and end-stage kidney disease.

Why Indigenous peoples have such an excess risk of ESKD is only partly understood. The three main causes of ESKD in Indigenous people are diabetic nephropathy, primary glomerulonephritis, and hypertension ([1]). A much larger proportion of ESKD in Indigenous people is attributed to diabetic nephropathy as compared to non-Indigenous people, however the ESKD excess is not explained solely by differences in diabetic prevalence or co-morbidities (1). The causal chain contributing to chronic kidney disease may start at or before birth, with maternal factors ([2]), low birth weight and reduced nephron mass ([3]) ([4]) possibly rendering the kidney more vulnerable to diabetes and hypertension. Marked regional differences in ESKD have been noted between Indigenous populations ([5]) and in ethnically homogeneous countries such as Japan, suggesting socio-demographic influences rather than genetic predispositions are responsible ([6]). Environmental factors such as isolated living and socioeconomic disadvantage, resulting in inadequate access to fresh food, comprehensive healthcare and other important health determining factors are likely to play an important role in the development of ESKD ([7]).

Previous systematic reviews of Indigenous health issues have highlighted a paucity of well-designed research, few studies of intervention, and a disproportionate number of publications from only a few communities or regions ([8])([9]). Only a few studies have collected adequate data on, or made adjustment for environmental determinants of ESKD such as remoteness of locality and socio-demographics ([10],[11],[12]).

Objectives

1. To determine the prevalence and incidence of end-stage kidney disease in Indigenous populations worldwide.
2. To determine the risk for end-stage kidney disease in Indigenous people compared with non-Indigenous people after accounting for other associated factors, such as diabetes, non-diabetic diseases, low birth weight, age, gender, socio-demographic status or geographical locality.

2.3: Methods

Inclusion criteria: We included studies of Indigenous people of any age group, gender or definition in their country of origin with a diagnosis of end-stage kidney disease. Definitions of ESKD from the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines include GFR < 15 ml/min/1.73 m^2, serum creatinine > 0.3 mmol/l or initiation of kidney replacement therapy (dialysis or transplant) for treatment of complications of decreased GFR ([13]). National renal failure registry and hospital ICD definitions of ESKD were also accepted. Observational studies (cross-sectional, cohort and case-control studies), systematic reviews and randomised controlled trials were included. Studies were included if they had a non-Indigenous comparator group, and if they provided enough data to perform or verify relative risk of ESKD in Indigenous people. Case reports and case series were excluded.

Search strategy: Studies were retrieved by electronic searches performed in MEDLINE (1966-December 2007), EMBASE (1988 – December 2007), CINAHL, ATSI and Rural Health databases (1988 – December 2007). The following medical subject heading terms and text words were used: the epidemiological terms risk, risk factors, cohort studies, case-control studies, cross-sectional studies, non-randomised and observational studies, aetiology, epidemiology, prevalence, incidence, and follow-up studies were combined with the diagnostic terms renal replacement therapy, end-stage kidney failure, kidney transplant, and the population group terms Oceanic ancestry group, American Native continental ancestry group, Alaskan Native, Canadian Native, Canadian Aboriginal, Aboriginal, Torres Strait Islander, Pacific Islander, Maori, Pima, Navajo, Inuit and Eskimo. Studies were considered without language restriction. Reference lists from all identified articles were searched and information about unpublished studies was sought from experts in the field. **Appendix 5** describes the search strategy in detail.

Data extraction and quality assessment: From all included studies, data were extracted on criteria used for diagnosis of end-stage kidney disease, characteristics of the study sample (using Indigenous terminologies as described by study authors),

setting, study design, selection criteria used for the population, age and gender of participants, participation rate, potential risk factors/confounders studied, methodological characteristics of the study and reported outcomes. The quality of the studies was assessed in accordance with the MOOSE guidelines ([14]). Quality criteria included scrutiny of study design, ascertainment and types of end-stage kidney disease, method of determination of Indigenous and non-Indigenous populations, sampling bias, intention-to-treat analysis and losses to follow-up, outcome blinding and adjustment for confounders. When data was missing or incomplete, the authors of the study were contacted for clarification.

Statistical analysis: Dichotomous data were analysed using odds ratios for prevalence studies, and relative risks for incidence studies, with 95% confidence intervals. Adjusted risks were calculated if data were available to do so using SAS statistical package ([15]). Results were expressed so that a relative risk or odds ratio more than 1 meant a greater risk ESKD in Indigenous groups when compared to non-Indigenous groups.

2.4: Results

Literature search: The search identified 525 articles, 350 from Medline and 175 from EMBASE, from which 377 abstracts were excluded because they were not about ESKD, and/or did not have a non-Indigenous comparator. Full text assessment of 148 papers identified 19 studies. In addition, 5 studies were identified from reference lists to articles (**figure 2.4.1**). Ineligible papers were excluded because they had no non-Indigenous comparator (47%), had insufficient data to verify a relative risk (28%) or had duplicated data (25%).

Included studies:

There were 24 studies describing prevalence and/or incidence of ESKD in Indigenous compared with non-Indigenous people, and these were conducted from 1971 to 2003. Studies grouped data within the categories of all-cause, diabetic and non-diabetic ESKD. There were 14 papers with data on all-cause ESKD (**table 2.4.1**), 3 papers with data on non-diabetic ESKD ([16],[17],[18]) (**table 2.4.1**) and 16 papers with data on diabetic ESKD (**table 2.4.2**). All tabulated data lists Indigenous and non-Indigenous groups by the descriptions used in included studies. Besides two cross-sectional studies ([19],[20]), all of the study designs were retrospective cohort studies describing data from hospital and health service records and renal failure database registries. **Figure 2.4.1** shows there were 6 studies including all American Indian/Alaskan Native people, 5 studies including Native American Indians (all Native Americans, Wisconsin Native Americans, Navajo Indians, Zuni Indians and Indigenous people of the Northern Mariana Islands), 4 studies including Canadian Native people (all Canadian Native people and Saskatchewan Indians), one study including all Goajiro Indians of Venezuela, 5 studies including Indigenous Australians (all Indigenous Australians, Northern Territory Aboriginals, Tiwi Islander Aboriginals and Western Australian Aboriginals) and 3 studies including all Maori and Pacific Islander people.

Prevalence and odds of all-cause, non-diabetic and diabetic end-stage kidney disease in Indigenous people compared with non-Indigenous people

In **table 2.4.1**, five studies documented prevalence of all-cause ESKD ([21],[22],[23],[24],17), and one of these included prevalence of non-diabetic ESKD (17). In **table 2.4.2**, three studies documented prevalence of diabetic ESKD (19,20,17).

Odds of all-cause ESKD

The odds of all-cause ESKD were significantly greater in all Indigenous groups. The odds varied from 1.5 to 3 times greater in all Native Americans and all Canadian Native Indians over the period 1983 to 2001, with the exception of Zuni Indians, who had odds of 11 times greater in 1983. In 1993, Western Australian and Northern Territory Aboriginals had 7 to 8 times the odds of ESKD.

Odds of non-diabetic ESKD

In 2001, Navajo Indians had 1.5 times greater odds of non-diabetic ESKD. There were no increased odds for all Native Americans and Native Indians in Arizona, New Mexico, Utah and Colorado (excluding the Navajo Nation).

Odds of diabetic ESKD

In 1991, all Maori and Pacific Islander people had 10 to 14 times greater odds of diabetic ESKD. In 1998, the odds were 1.5 times greater in all Native American veterans. In 2000, the odds were 5 times greater for all Indigenous People of the Mariana Islands. In 2001, odds were 2.5 times greater for all Native Indians, 4.5 times greater for Navajo Indians, and almost 7 times greater for Native Indians in Arizona, New Mexico, Utah and Colorado (excluding the Navajo Nation).

Incidence and relative risk of all-cause, non-diabetic and diabetic end-stage kidney disease in Indigenous people compared with non-Indigenous people

All studies in **table 2.4.1** describe incidence of all-cause ESKD, and three of these studies included data on non-diabetic ESKD (16,17,18). All but 2 studies in **table 2.4.2** (19,20) describe incidence of diabetic ESKD.

Relative risk of all-cause ESKD

The relative risk of all-cause ESKD was significantly greater in all Indigenous groups. From 1983 to 1986, the risk was 2 to 3 times greater in all American Indians/Alaskan Native people, and in 1985 it was 1.2 to 4 times greater in all Native Americans, 9 times greater in Zuni Indians and 18 times greater in Navajo Indians. From 1991 to 1998, the risk was 1.7 times greater in Goajiro Indians. From 1981 to 2002, the risk was 2.5 to 4.5 times greater in all Canadian Native people. From 1992 to 2001, the risk was 4.5 times greater for all Indigenous Australians, but was 16 times greater for the age group 45-54 years. In 1986, the risk was 2 times greater in Western Australian Indigenous Australians, and 14 times greater in 1994. From 1988 to 1993, the risk was 8 times greater in all Northern Territory Indigenous Australians, and four times greater in Northern Territory Tiwi islanders. From 1992 to 2001, risk was 3.5 times greater in Maori and Pacific Islander people, and from 1998 to 2002, the risk was 9 times greater.

Relative risk of non-diabetic ESKD

From 1981 to 1990, Saskatchewan females and males both had a 2.5 times increased risk of non-diabetic ESKD. From 1998 to 2002, all Canadian Native people had a significantly increased risk of 1.7 times. In 2001, all Native Americans and Navajo Indians had a significantly reduced risk of 0.6 to 0.8. Native Americans in Arizona, New Mexico, Utah and Colorado (excluding the Navajo Nation) had no difference in risk.

Relative risk of diabetic ESKD

From 1983 to 1987, the risk for all American Indians/Alaskan Native people was 2 to 7 times greater. From 1990 to 1994, it was 1.3 to 1.6 times greater. From 1994 to 2004, it was 4.5 to 3.6 times greater. The greatest risk was within the 45 to 54 years age group, where the risk was 16 times greater. From 1982 to 2003, Wisconsin Native Americans had a 4 to 5 times greater risk. In 1985, Navajo Indians had a 26 times greater risk. In 2001, Navajo Indians had a 3 times greater risk, and Native Americans in Arizona, New Mexico, Utah and Colorado (excluding the Navajo Nation) had a 4.6 times greater risk. From 1981 to 2002, all Canadian Native people had a 4 to 7 times greater risk, although

Saskatchewan Native people had a 7 to 9 times greater risk. From 1992 to 2002, within the age group 45 to 64 years, all Indigenous Australians had a 45 times greater risk; all Maori people 26 times greater risk; Pacific Islander people 43 times greater risk.

African Americans and Asian Americans were used as non-Indigenous comparators (in addition to the comparators used in the studies above of Caucasians or aggregate populations) for a number of diabetic studies (27,45,46). In 1994 and in 2004, American Indians/Alaskan Natives had no difference in risk for diabetic ESKD compared to African Americans. From 1983-1987 within the age group 45 to 54 years, the risk was 2 times greater than African Americans, six times greater than Asian Americans (and 16 times greater than Caucasian Americans). From 1997 to 2000 within the age group 45-54 years, the risk was 1.2 times greater than African Americans, 3 times greater than Asian Americans (and 5 times greater than Caucasian Americans).

Quality of included studies

Table 2.4.3 describes the study quality. Of the 24 included studies, 4 had non-Indigenous comparators from different study bases (17,[25],[26],19). Native American Indians of the Navajo Nation and in Arizona, New Mexico, Utah and Colorado were compared with the general US population (17). Navajo Indians of Ramah, Canoncito, and Alamo Reservations were compared with the US white population (25). Gaojiro Indians were compared with the total Venezuelan population (26). Indigenous people of the Northern Mariana Islands were compared with the total US population (19). Most studies determined Indigenous status by nomination at ESKD registration, on hospital and Registered Indian records, census data and Indian Health Service records. Two studies gave no method of determination for Indigenous status (23,26). Only one study included all ESKD (untreated ESKD patients and deaths from ESKD) (23). Three studies used tribal statistics and Indian Affairs departmental data in addition to national census and registered Indian records so as to ascertain total Indigenous population figures (25,24,[27]). Six studies had no information to allow adjustment or stratification by confounders in estimates on prevalence and incidence (21,22,26,19,[28],20). Seventeen studies adjusted for age and/or sex in their own risk estimates. One study adjusted for

other potential predictors in addition to age and sex, such as clinic visits, region, remoteness, hypertension and cardiovascular disease (12).

2.5: Discussion

This is the first study to summarise the risk for ESKD in Indigenous people compared to non-Indigenous people. Besides two cross-sectional reports, all studies described risk through retrospective review of registry, health service and hospital databases. Despite a large number of studies describing ESKD in Indigenous populations (**figure 2.4.1**), a disproportionate amount of the published literature originates from a handful of remote communities by a few research groups ([29],[30],[31]). These studies may not represent the interests of all Indigenous people in Australia, USA, Canada and New Zealand, where the majority reside in urban areas alongside non-Indigenous countrymen ([32],[33],[34],[35]). To date there have been no prospective population-based studies of risk for ESKD that include a non-Indigenous comparator group.

The prevalence, incidence and risk for all-cause and diabetic ESKD in Indigenous people is universally greater when compared to Caucasian populations, and the disparity appears to be widening over time. Most of the increased risk for all-cause ESKD is attributable to high rates of diabetic ESKD. For those studies that stratified for age, the age groups 45-54 years, and 45-64 years have the greatest disparity for Indigenous people when compared to non-Indigenous people for both all-cause and diabetic ESKD ([36],1,[37],18). Prevalence, incidence and risk for all-cause and diabetic ESKD were consistently higher over time among the Zuni Indians, Indigenous Australians, Maori and Pacific Islander people when compared to other Indigenous groups. A slightly increased prevalence and odds for non-diabetic ESKD was seen in Navajo Indians, although they had a significantly reduced relative risk of non-diabetic ESKD. Canadian Native people and tribal groups had a slightly increased risk of non-diabetic ESKD, but it was four times less than their risk for diabetic ESKD. In those studies comparing Indigenous groups to other minority or disadvantaged groups, the increased risk for ESKD was less, particularly in comparison with African Americans. This suggests socio-demographic factors common to all disadvantaged groups (rather than unique biological differences in Indigenous people) play a major part in the development of ESKD.

Some of the heterogeneity in risk between Indigenous groups can be accounted for by classification bias and use of inappropriate non-Indigenous comparators. Because most Indigenous populations are more youthful, have a higher proportion of females, and have higher rates of diabetic ESKD in women, adjustment of analyses for age and sex increases the risk in Indigenous people almost universally (36,[38],[39],17). Inconsistent adjustment of estimates between studies for age and sex increases the heterogeneity of these results, and makes meta-analysis or summary estimates of risk across Indigenous groups difficult.

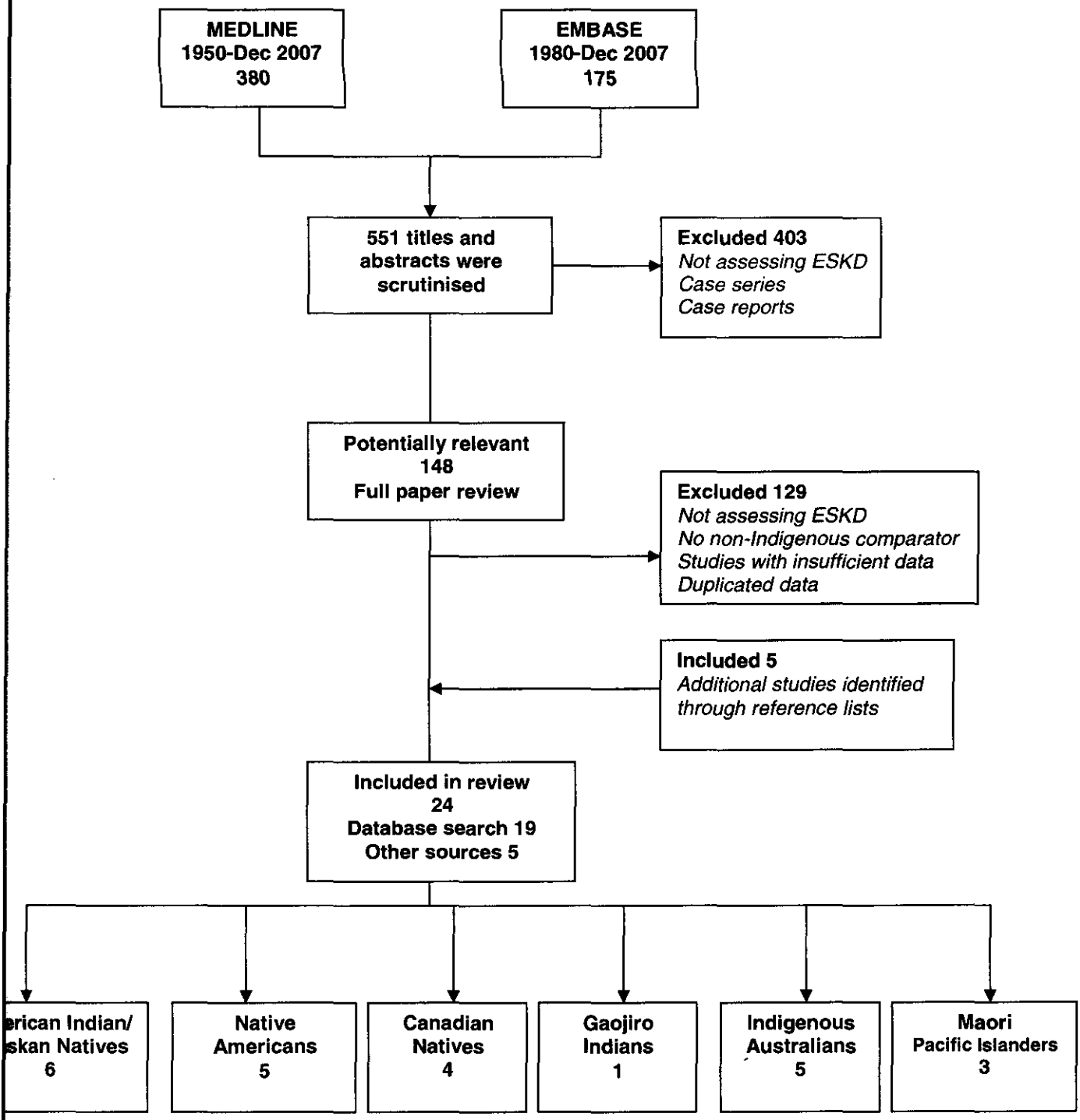
Most studies had some degree of ESKD ascertainment bias through accounting only for treated cases of ESKD. All ESKD registries in included studies assessed the prevalence and incidence by the number of patients either on treatment or beginning treatment, but not accounting for those who refuse treatment, have no insurance to pay for it, have limited access to it, or die before gaining access to treatment. These disadvantages are likely to affect many more Indigenous than non-Indigenous people. Despite the fact that Goajiro Indians have a twice higher risk of ESKD than the general population and they make up 3% of the population, they represent only 3% of the dialysis population (26). Because the absolute numbers of Indigenous cases of ESKD are small, accounting for even one or two extra cases can make a large difference to risk estimates. Only one study checked health service records and death certificates to account for untreated renal failure patients, and found a 7% under-ascertainment of Indigenous ESKD cases when using registry data only (23).

Only two papers lacked a description of how Indigenous status was determined (23,26). Despite this, racial and ethnic misclassification on databases still accounts for a significant underreporting of ESKD cases, and a reduction in real risk estimates. Nomination of Indigenous status on hospital and registry data is usually performed by medical or clerical staff, and is vulnerable to error ([40],[41]). Underreporting of ethnicity on population census counts or national registers will in contrast increase risk estimates, however this increase is likely to be smaller than the decrease resulting from Indigenous

status and ESKD ascertainment bias (36).Odds for all-cause ESKD in all Canadian Native people increased from 1.5 times to 2.5 times greater when only registered Native Canadians were accounted for, and relative risk increased from 2.5 times to 4 times greater.

Most of the excess risk in Indigenous people for ESKD is due to increased rates of diabetic ESKD. Why diabetes behaves differently in Indigenous populations may in part be explained by socio-demographic inequities that delay the diagnosis and adequate treatment of diabetes and diabetic kidney disease. Only one paper adjusted for these risk factors that affect Indigenous and other disadvantaged groups, such as remote living, lack of access to health care and inadequate social capital (12). Measurement and adjustment for potential socio-demographic confounders is essential in teasing out the complex relationship between race, disadvantage and risk for ESKD. Without appropriate adjustment, race becomes the proxy for the increased risk for ESKD. Well-defined socio-demographic risk factors are amenable to generational change, and are largely preventable (as opposed to biological variants, which are not). Future research into ESKD needs to consider the early causal chain to these disease outcomes, and include acceptable (local) non-Indigenous comparator groups as part of prospective population-based research.

Figure 2.4.1: Flow chart showing the identification of studies



Abbreviations: AI/AN, American Indian/Alaskan Native; CN, Canadian Native, ESKD, end-stage kidney disease; IA, Indigenous Australian; IPNMA, Indigenous People of the Northern Mariana Islands; NA, Native American; NT IA, Northern Territory Indigenous Australian; PI, Pacific Islander; WA IA, Western Australian Indigenous Australian.

Table 2.4.1: Characteristics of prevalence and incidence studies evaluating the effect of Indigenous status on end-stage kidney disease*

Author Date of publication	Setting & study period	Design	Age range (years)	ESKD type	Indigenous[∞] (P)revalence (I)ncidence	Non-Indigenous[∞] (P)revalence (I)ncidence	OR/RR ESKD in Indigenous vs Non-Indigenous (95% CI)
Megill D (25) 1988	Shiprock IHS records ESRD Network VI Albuquerque Navajo tribal statistics University New Mexico databank 1985	Retrospective cohort study	NS	Treated	Navajo Indians Ramah, Canoncito,Alamo reservations (I) 259/170,000	US Whites (I) 24624/296670000	RR 18.32 (16.22-20.71)
Pasinski R (21) 1987	Zuni IHS records Albuquerque Gallup Dialysis Centre ESKD Network VI Albuquerque 1973-1983 US census 1970 & 1980	Retrospective cohort study	14-81	Treated	a) Zuni Indians (P) 1983 20/6892 Average (I) 3.8/5263 b) Native Indians Area VI (P) 1983 808 pmp	a) Whites Area VI (P) 1983 266 pmp a) All races Area VI Average (I) 83 pmp b) Whites Area VI (P) 1983 266 pmp	a) OR 1983 10.91 (6.92-17.20) a) RR 8.70 (3.11-24.33) b) OR 1983 3.04 (2.64-3.49)
Young T (24) 1989	Canadian National Renal Failure Register DINA Canadian census 1981-1986	Retrospective cohort study	0-65+	Treated	Canadian Native Peoples Average (I) a) All registered Indians 305/1316017 b) All Native people 305/2193362 (P) 31 Dec 1986 c) All registered Indians	All Canadians Average (I) 8432/148975265 (P) 31 Dec 1986	RR a) 4.09 (3.65-4.59) b) 2.46 (2.19-2.75) OR 1986

					702/1316017 d) All Native people 702/2193362	33221/148975265	c) 2.39 (3.22-2.58) d) 1.44 (1.33-1.55)
Dyck R (16) 1998	Canadian Organ Replacement Register 1981-1990	Retrospective cohort study	0-60+	Treated non-diabetic	Saskatchewan First Nation people Average (I) 17/20988 females 22/16667 males	Saskatchewan non-Aboriginals Average (I) 158/493750 females 263/496226 males	RR Females 2.53 (1.53-4.18) Males 2.49 (1.61-3.85)
Stolzmann K ([42]) 2005	US Upper Midwest Renal Network 11 CDC-WONDER 1982 & 2003	Retrospective cohort study	0-75+	Treated	Wisconsin Native American (I) 1982 6/21352 (I) 2003 27/27054	Wisconsin Whites (I) 1982 352/4455696 (I) 2003 1276/5316667	RR 1982 3.56 (1.59-7.97) 2003 4.16 (2.84-6.09)
Hoy W ([43]) 1989	US HCFA data 1983-1986	Retrospective cohort study	0-75+	Treated	Native Americans/ Alaskan Natives Average (I) 189 pmp 303 pmp adjusted (I) 1985 Arizona Indians 382 pmp New Mexico Indians 399 pmp Zuni Indians 912 pmp Navajo Indians 176 pmp	US Whites Average (I) 100 pmp	RR Native American/Alaskan Natives 1.89 (1.48-2.41) 3.03 (2.14-4.21) adjusted Arizona Indians 3.82 (3.07-4.76) New Mexico Indians 3.99 (3.20-4.97) Zuni Indians 9.12 (7.42-11.21) Navajo Indians 1.76 (1.38-2.25)
Newman J (39) 1990	US HCFA data 1983-1986	Retrospective cohort study	0-75+	Treated	Alaskan Natives/ American Indians	US Whites	RR

	IHS records 1985 US census 1980				Average (I) 108/642857	Average (I) 7529/79004197	1.76 (1.46-2.13)
Brameld K (23) 1999	Western Australian Health Services Research Linked Data Health Department Western Australia 1986-1994	Retrospective cohort study	NS	All	Aboriginals in Western Australia (I) (yr) pt yrs (1986) 6.8/100,000 (1994) 79/100,0000 (P) Dec 31 1993 140/100,000 pt years	Non- Aboriginals Western Australia (I) (yr) pt yrs (1986) 3.6/100,000 (1994) 5.1/100,000 (P) Dec 31 1993 15.6/100,000 pt yrs	RR 1986 2.84 (1.19-28.14) 1994 14.31 (6.26-57.49) OR 1993 8.0 (4.60-41.58)
Hoy W (22) 1995	Northern Territory Australia Hospital and dialysis files 1988-1993 ABS 1991	Retrospective cohort study	0-60+	Treated	Aboriginals Northern Territory Average (I) a) All Aboriginals 83/25387 b) Tiwi Islander Aboriginals 1636 pmp c) Non-Tiwi Aboriginals 358 pmp (P) 1993 All Aboriginals Northern Territory 40/25387	Non-Aboriginals Northern Territory Average (I) 44/105405 (P) 1993 Non-Aboriginals Northern Territory 28/105405	RR All Aboriginals 7.83 (5.43-11.29) Tiwi Islander Aboriginals 3.91 (2.90-5.29) Non-Tiwi Aboriginals 3.42 (1.13-5.17) OR 1993 7.83 (5.43-11.29)
Herrera J (26) 2003	Nth Western Venezuela University Hospital records Annual records public health system 1991-1998	Retrospective cohort study	NS	Treated	Goajiro Indians Average (I) 7.3/184000	Whole population Venezuela Average (I) 132 pmp	RR 1.67 (1.34-2.07)

Stewart J (36) 2004	ANZDATA ABS 1992-2001	Retrospective cohort study	0-65+	Treated	Indigenous Australians Average (l) (yrs) (45-54) 387/260256 (55-64) 289/137750	Non-Indigenous Australians Average (l) (yrs) (45-54) 2106/23066813 (55-64) 2900/15760870	RR 16.29 (14.61-18.15) 8.74 (7.76-9.84)
Stewart J (1) 2004	ANZDATA ABS Stats NZ 1992-2001	Retrospective cohort study	0-65+	Treated	a) Indigenous Australians Average (l) (yrs) pmp (0-14) 7.9 (15-44) 282 (45-64) 1732 (65+) 1161 Total 1262/372737 b) Maori Average (l) (yrs) pmp (0-14) 4.3 (15-44) 85.3 (45-64) 1028 (65+) 920 Total 1037/554517 c) Pacific Islander Average (l) (yrs) pmp (0-14) 10.1 (15-44) 141 (45-64) 1087 (65+) 932 Total 421/204076	a) Non-Indigenous Australians Average (l) (yrs) pmp (0-14) 6.4 (15-44) 34.5 (45-64) 131 (65+) 250 Total 13574/18040714 b) Non-Indigenous New Zealander Average (l) (yrs) pmp (0-14) 8.5 (15-44) 33.5 (45-64) 106 (65+) 148 Total 1787/2949905 c) as b) above	RR All Indigenous Australians 4.50 (4.25-4.77) All Maori 3.09 (2.86-3.33) All Pacific Islanders 3.40 (3.06-3.79)
Stewart J (18) 2006	Multiple ESKD and census databases from different countries 1998-2002	Retrospective cohort study	45-74	Treated	All ESKD Average (l) a) New Zealand Maori/Pacific Islander 161/123851 b) Canadian Aboriginal	All ESKD Average (l) a) New Zealand non-Polynesian 282/1880981 b) Canadian non-	RR New Zealand Maori/Pacific Islander 8.67 (7.14-10.52) Canadian Aboriginal

					162/160756	Aboriginal 5056/17678042	3.52 (3.01-4.12)
					All other non-diabetic ESKD Average (I) a) New Zealand Maori/Pacific Islander 32/123851 b) Canadian Aboriginal 35/160756	All other non-diabetic ESKD Average (I) a) New Zealand non-Polynesian 166/1880981 b) Canadian non-Aboriginal 2280/17678042	Non-diabetic New Zealand Maori/Pacific Islander 2.93 (2.01-4.27) Canadian Aboriginal 1.69 (1.21-2.36)
Hochman M (17) 2007	USRDS 2001 US census 2000	Retrospective cohort study	≥ 18	Treated	All ESKD a) Native Americans Navajo Nation (P) 636/130907 (I) 109/130907 b) All Native Americans (P) 5556/2023000 (I) 1108/2023000 c) Native Americans in AZ, NM, UT CO (excludes Navajo Nation) (P) 1481/250820 (I) 283/250820	All ESKD a) General US population (P) 400605/212673000 (I) 93886/212673000	All Native Americans Navajo Nation OR 2.58 (2.39-2.79) RR 1.89 (1.56-2.28) All Native Americans OR 1.46 (1.42-1.50) RR 1.24 (1.17-1.32) Native Americans in AZ, NM, UT, CO (excludes Navajo Nation) OR 3.13 (2.98-3.30) RR 2.56 (2.27-2.87)
					Non-diabetic ESKD a) Native Americans Navajo Nation (P) 223/130907 (I) 24/130907	Non-diabetic ESKD a) General US population (P) 255208/212673000 (I) 51042/212673000	Non-diabetic Native Americans Navajo Nation OR 1.42 (1.24-1.62) RR

					b) All Native Americans (P) 2023/2023000 (I) 283/2023000 c) Native Americans in AZ, NM, UT CO (excludes Navajo Nation) (P) 326/250820 (I) 53/250820		0.83 (0.80-0.87) Native Americans OR 0.53 (0.51-0.55) RR 0.59 (0.52-0.66) Native Americans in AZ, NM, UT, CO (excludes Navajo Nation) OR 1.08 (0.97-1.21) RR 0.88 (0.67-1.15)
Tareen N (38) 2005	USRDS 2001 US census 2000	Retrospective cohort study	≥ 18	Treated	Native Americans (I) 1408/2023000	US Whites (I) 254 pmp	RR 2.74 (2.40-3.13)

* Studies are arranged chronologically based on the initiation of study enrolment

[e]Indigenous and non-Indigenous group descriptions are as given in the included studies

Abbreviations: ABS, Australian Bureau Statistics; ANZDATA, Australia and New Zealand Dialysis and Transplant Registry; AZ, Arizona; CDC-WONDER, Centers for Disease Control and Prevention, Wide-Ranging OnLine Data for Epidemiological Research; CO, Colorado; DINA, Department of Indian and Northern Affairs; ESKD, end-stage kidney disease; HCFA, The Health Care Financing Administration; ID, identification number; IHS, Indian Health Service; NM, New Mexico; OR, odds ratio; pmp, per million population; RR, relative risk; Stats NZ, Statistics New Zealand; US, United States; USRDS, United States Renal Data System; UT, Utah.

Table 2.4.2: Characteristics of prevalence and incidence studies evaluating the effect of Indigenous status on diabetic end-stage kidney disease*

Author Date of publication	Setting & study period	Design	Age range (years)	Diabetic ESKD type	Indigenous[ω] (P)revalence (I)ncidence	Non-Indigenous[ω] (P)revalence (I)ncidence	OR/RR ESKD in Indigenous vs Non-Indigenous (95% CI)
Megill D (25) 1988	Shiprock IHS records ESRD Network VI Albuquerque Navajo tribal statistics University New Mexico databank 1985	Retrospective cohort study	NS	Treated	Navajo Indians Ramah, Canoncito,Alamo reservations (I) 102/170000	US Whites (I) 6785/295000000	RR 26.09 (21.45-31.72)
Young T (24) 1989	Canadian National Renal Failure Register DINA Canadian census 1981-1986	Retrospective cohort study	0-65+	Treated	Canadian Native Peoples Average (I) a) All registered Indians 78/337662 b) All Native people 78/562770	All Canadians Average (I) 1492/26175439	RR All registered Indians 4.05 (3.23-5.09) All Native people 2.43 (1.94-3.05)
Dyck R (28) 1994	Canadian Organ Replacement Register Registered Native Peoples Sasketchewan 1981-1990	Retrospective cohort study	≥ 20	Treated	Saskatchewan Natives Average (I) a) 50/2107 diabetics b) 50/28318 total population	Non-Natives Saskatchewans Average (I) a) 135/41646 diabetics b) 135/668259 total population	RR a) 7.32 (5.28-10.16) b) 8.74 (6.32-12.09)

Stolzmann K (42) 2005	Renal Network Upper Midwest Network 11 CDC-WONDER 1982 & 2003	Retrospective cohort study	0-75+	Treated	Wisconsin Native American (I) 1982 3/35294 (I) 2003 23/49676	Wisconsin Whites (I) 1982 99/4500000 (I) 2003 483/4979381	RR 1982 3.86 (1.23-12.19) 2003 4.77 (3.14-7.25)
Teutsch S (37) 1989	US Medicare database 1983-1985	Retrospective cohort study	All	Treated	American Indians Average (I) (yrs) pmp (45-54) 310 (55-64) 600	US Whites Average (I) (yrs) pmp (45-54) 20 (55-64) 50 US Blacks Average (I) (yrs) pmp (45-54) 150 (55-64) 220 US Asians Average (I) (yrs) pmp (45-54) 50 (55-64) 130	RR 15.50 (9.68-24.36) 12.00 (8.99-16.01) 2.07 (1.70-2.51) 2.73 (2.34-3.18) 6.20 (4.60-8.36) 4.61 (3.82-5.58)
Newman J (39) 1990	US Medicare US IHS databases US census 1983-1986	Retrospective cohort study	0-75+	Treated	Alaskan Natives American Indians Average (I) 597/3553571	US Whites Average (I) 20253/212518363	RR 1.76 (1.63-1.91)
Muneta B (27) 1993	US Medicare database IHS data 1983-1987 US census 1980	Retrospective cohort study	All	Treated	American Indian Alaskan Native (I) 196 pmp	a) US Whites (I) 29 pmp b) US Blacks (I) 109 pmp	RR 6.76 (4.58-9.98) 1.80 (1.42-2.27)
Simmons D (20) 1994	Sth Auckland Middlemore	Cross-sectional	18-79	Treated	Maori a) (P) diabetics	Europeans (P) diabetics	OR Maori

	Hospital records GP referrals 1991	study			4/84 Pacific Islanders b) (P) diabetics 4/123	1/297	14.14 (1.56-128) Pacific Islanders 9.66 (1.07-87.3)
CDC report ([44]) 1999	US Medicare database US census 1990 & 1996	Retrospective cohort study	All	Treated	American Indian/ Alaskan Native Average (I) diabetics a) (1990) 394/83475 b) (1996) 719/123116	Total US population Average (I) diabetics 378/100000	RR 1990 1.25 (1.08-1.44) 1996 1.55 (1.36-1.75)
Stewart J (1) 2004	ANZDATA ABS Stats NZ 1992-2001	Retrospective cohort study	0-65+	Treated	a) Indigenous Australians Average (I) (45-64yrs) 409/389524 b) Maori Average (I) (45-64yrs) 475/1000000 c) Pacific Islander Average (I) (45-64yrs) 169/211514	a) Non-Indigenous Australians Average (I) (45-64yrs) 879/37887931 b) c) Other New Zealander Average (I) (45-64yrs) 122/6594595	RR Indigenous Australians 45.26 (40.25-50.89) Maori 25.68 (21.04-31.32) Pacific Islander 43.19 (34.22-54.52)
Gilbertson D ([45]) 2007	USRDS 1994-2004 US census 2000	Retrospective cohort study	NS	Treated	American Indian/ Alaska Native (I) (yr) pmp (1994) 360 (2004) 360	a) US White b) US Black (I) (yr) pmp (1994) a) 80 b) 300 (2004) a) 100 b) 380	RR 1994 a) 4.50 (3.35-5.73) b) 1.20 (1.03-1.40) 2004 a) 3.60 (2.88-4.49) b) 0.95 (0.82-1.09)
Young B (12) 2003	US Dept Veterans Affairs health database 1998	Retrospective cohort study	Mean 64.1 ± 11.4	Treated	Native American Veterans (P) 105/222 diabetics 105/1747 veterans	a) US Caucasian Veterans (P) 9489/26212 diabetics 9489/241548 veterans	OR a)Diabetics 1.31 (1.03-1.65) Veterans

							1.53 (1.26-1.87)
Lopes A ([46]) 2004	USRDS 1997-2000	Retrospective cohort study	NS	Treated	Native American Indians Average (I) per 10mp 5233	Average (I) per 10mp a) US whites 1024 b) US Asians 1836 c) US Blacks 4208	RR a) 5.11 (4.78-5.46) b) 2.85 (2.70-3.00) c) 1.24 (1.19-1.30)
Stewart J (18) 2006	Multiple ESKD and census databases from different countries 1998-2002	Retrospective cohort study	45-74	Treated	New Zealand Maori/Pacific Islander Average (I) 117/123851 Canadian Aboriginal Average (I) 119/160756	New Zealand non-Polynesian Average (I) 71/1880981 Canadian non-Aboriginal Average (I) 1891/17678042	RR New Zealand Maori/Pacific Islander 25.03 (18.64-33.01) Canadian Aboriginal 6.92 (5.75-8.33)
Abidi S (19) 2005	US Medicare database Dec 31 2000 US census 2000	Cross-sectional study	All	Treated	Indigenous people Northern Mariana Islands (P) 57/23908	Total US population (P) 46/100000	OR 5.18 (3.51-7.65)
Hochman M (17) 2007	USRDS 2001 US census 2000	Retrospective cohort study	≥ 18	Treated	a) Native Indians Navajo Reservation (P) 406/130907 (I) 86/130907 b) All Native Americans (P) 3439/2023000	a) General US population (P) 146744/212673000 (I) 42535/212673000	Native Indians Navajo Reservation OR 4.50 (4.08-4.96) RR 3.28 (2.66-4.06) All Native Americans

	(I) 829/2023000	OR 2.46 (2.38-2.55) RR 2.05 (1.91-2.19)
	c) Native Americans in AZ, NM, UT CO (excludes Navajo Nation) (P) 1154/250820 (I) 231/250820	All Native Americans in AZ, NM, UT, CO OR 6.67 (6.29-7.07) RR 4.60 (4.05-5.24)

* Studies are arranged chronologically based on the initiation of study enrolment

[ω] Indigenous and non-Indigenous group descriptions are as given in the included studies

Abbreviations: ABS, Australian Bureau Statistics; ANZDATA, Australia and New Zealand Dialysis and Transplant Registry; CDC, Centers for Disease Control and Prevention; CDC-WONDER, Centers for Disease Control and Prevention, Wide-Ranging OnLine Data for Epidemiological research; DINA, Department of Indian and Northern Affairs; ESKD, end-stage kidney disease; GP, general practitioner; IHS, Indian Health Service; pmp, per million population; Stats NZ, Statistics New Zealand; US, United States; USRDS, United States Renal Data System.

Table 2.4.3: Quality of included studies evaluating risk of Indigenous status on end-stage kidney disease (n=24)

Characteristic	Yes	No	Comment
Non-Indigenous comparator from same study base	20	4*	*Indigenous group vs non-Indigenous comparator: • Navajo Indians vs US whites or total population • Goajiro Indians vs total Venezuelan population • Indigenous people of Northern Mariana Islands vs total US population
Indigenous status adequately determined	22*	2#	*Indigenous status determined by: • ESKD database • Hospital record racial nomination • IHS nomination • Registered Indian records • Census data collection #No description of determination given
Sampling biases			
Numerator (ESKD sample)	23*	1#	*Treated ESKD only #Treated and untreated ESKD
Denominator (Indigenous population)	21*	3#	*Determined by: • National census • Registered Indian records #Determined by: • Indigenous census • Tribal statistician • Adjustment for registered Indian bias • Indian health service records
Adjustment/stratification for confounders			
Age and/or sex only	17	7	*Age, sex, clinic visits, region, non-service connection, hypertension, cardiovascular disease
Other	1*	23	
None	4	20	

Abbreviations: ESKD, End-stage kidney disease; ICD, International Classification Diseases; IHS, Indian Health Service.

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CHAPTER 3: EARLY CHRONIC KIDNEY DISEASE IN ABORIGINAL AND NON-ABORIGINAL CHILDREN: REMOTENESS, SOCIO-ECONOMIC DISADVANTAGE OR RACE?

3.1: Abstract

Indigenous minorities have substantially higher rates of ESKD, especially Australian Aboriginals. Previous work suggests a causal pathway beginning early in life. No studies have shown the prevalence of early markers of chronic kidney disease in both Indigenous and non-Indigenous children or the association of these markers with environmental health determinants, such as geographic remoteness and socioeconomic disadvantage.

Height, weight, blood pressure and urinary abnormalities were measured in age and gender-matched Aboriginal and non-Aboriginal children from primary schools across geographically diverse areas of New South Wales, Australia. Haematuria was defined as $\geq$25 RBC/uL ($\geq$1+), proteinuria $\geq$0.30g/L ($\geq$1+), and albuminuria (ACR) $\geq$3.4mg/mmoL. Remoteness of locality and socioeconomic status were assigned using the Accessibility and Remoteness Index of Australia (ARIA++) and Socio-Economic Indexes For Areas (SEIFA).

From 2002 to 2004, 2266 children (55% Aboriginal, mean age 8.9 years) were enrolled from 37 primary schools. Overall prevalence of haematuria was 5.5%, proteinuria 7.3%, and albuminuria 7.3%. Only haematuria was more common in Aboriginal children (7.1 versus 3.6%; $p = 0.002$). Socioeconomic disadvantage and geographical isolation were neither significant nor consistent risk factors for any marker of CKD.

Aboriginal children have double the prevalence of hematuria compared with non-Aboriginal children but no increase in albuminuria or proteinuria, which are more important risk factors for CKD. Geographical isolation and socioeconomic disadvantage are not risk factors for markers of CKD in children. This suggests the causal pathways for ESKD in Aboriginal people are not established by childhood and are therefore preventable.

3.2: Introduction

Indigenous minorities have almost universally poorer health outcomes than non-Indigenous majority populations worldwide and this is particularly true for kidney disease ([1])([2])([3]). Australian Aboriginal and Torres Strait Islander people (hereafter referred to as Aboriginal) are eight-times more likely to develop end-stage kidney disease (ESKD) than non-Aboriginal people, are 10 years younger on average, are only half as likely to be listed for transplantation, and have almost 30% lower graft and 8% lower patient survival 5-years post-transplantation (1). This pattern of excessive burden due to increased prevalence and poorer outcomes once ESKD occurs is also found in the Inuit and Native Canadians in Canada (2), Native Americans in the USA (3), and in the Maori people of New Zealand (1).

Why Indigenous peoples have such an excess risk of ESKD is largely unknown. The three main causes of ESKD in Aboriginal people are diabetic nephropathy, primary glomerulonephritis, and hypertension ([4]). A much larger proportion of ESKD in Aboriginal Australians is attributed to diabetic nephropathy (47%) as compared to non-Aboriginal Australians (17%), however the ESKD excess is not explained solely by differences in diabetic prevalence or co-morbidities (1). The causal chain contributing to chronic kidney disease (CKD) may start at or before birth, with maternal factors ([5]), low birth weight and reduced nephron mass ([6]) ([7]) rendering the kidney more vulnerable to diabetes and hypertension. However marked regional differences in ESKD have been noted between Aboriginal populations ([8]) and in ethnically homogeneous countries such as Japan, suggesting sociodemographic influences rather than genetic predisposition are responsible ([9]). Environmental factors such as isolated living and socioeconomic disadvantage may play the more important role in the development of CKD (8).

Current knowledge about the risk factors for CKD in Aboriginal people in Australia is mainly limited to adult-based research that comes from areas of high remoteness and socioeconomic disadvantage in Northern Australia, and lacks non-Aboriginal control groups or adjustment for variability in locality and sociodemographics ([10]). The aims of our study were to determine whether the increased risk of CKD in Aboriginal adults is

evident in childhood, and to determine whether environmental health determinants could explain any difference in observed risk.

3.3: Methods

Selection of participants: Government-run primary schools were approached for testing from urban, coastal, rural and remote locations across the state of New South Wales (**Appendix 6**). This state has the highest Aboriginal population in Australia. Non-government schools (private and denominational) have very few Aboriginal enrolments, and were not considered for recruitment. To maximise power, sampling was done to obtain equal numbers of Aboriginal and non-Aboriginal children, and in similar proportions from urban, coastal, rural and remote areas. All primary schools in remote communities were approached and other areas were sampled if greater than twenty Aboriginal children in the relevant age range attended.

Aboriginal status was determined using the Australian Bureau of Statistics best practice recommendations, asking the Standard Indigenous Question on the consent form "Is your child of Aboriginal or Torres Strait Islander origin?" ([11]). All Aboriginal children in the participating primary schools were offered testing for height, weight, blood pressure and urinary dipstick abnormalities. Non-aboriginal children were matched for gender and age (nearest birthday) using class lists. We aimed to recruit equal numbers of boys and girls, Aboriginal and non-Aboriginal children, and approximately equal numbers of children from each 12 month age group.

Aboriginal community engagement: Consultation with local Aboriginal Medical Services and consent from community leaders was undertaken prior to commencement of the study. Approval was obtained from the Ethics Committees of the Children's Hospital at Westmead, the University of Sydney, New South Wales Area Health Services and the New South Wales Department of Education and Training. Informed consent was obtained for each child and, in accordance with NHMRC Guidelines for Ethical Conduct in Aboriginal and Torres Strait Islander Research ([12]), data was collected onto a standardised form and de-identified for storage and analysis before being returned to each community after the study visit. Permission to publish data was also obtained from each community.

Measurement of markers of chronic kidney disease and associated risk factors: Markers of chronic kidney disease measured were haematuria, proteinuria and albuminuria. Risk factors known and thought to be associated with the development of CKD in Aboriginal people were also recorded, including age, gender, growth parameters, birth weight, blood pressure and environmental health determinants: categories of isolation, disadvantage and region.

A morning clean catch specimen was collected from each child, with dipstick analysis for haematuria, proteinuria and albuminuria performed at the survey site on fresh specimens using a Bayer Clinitek 50 machine ([13]). Leukocytes and nitrites were also recorded for later adjustment for abnormalities of presumed urinary tract infection. Girls older than eight years who were found to have haematuria were questioned about menses, and if appropriate, collection was performed at another time.

Haematuria was defined as greater than or equal to 25 RBC per microlitre (1+), proteinuria as greater than or equal to 0.30 g/L (1+) and albuminuria as albumin:creatinine (ACR) greater than or equal to 3.4 mg/mmol.

Standardisation of urban, coastal, rural and remote locality was made using the Accessibility and Remoteness Index of Australia (ARIA++), with each subject given an Index score according to their postcode of residence ([14]). Using geographical information system (GIS) capabilities, distances, services and population density for each locality are converted to a continuous variable with values ranging from zero for high accessibility, to 18 for extreme remoteness ([15]). ARIA++ values for this NSW study ranged from 0 to 14, and for categorical analysis the scores were grouped into quartiles. Isolation categories (and ARIA++ score range) used were: Least isolation (0-1.1), low-mid isolation (1.2-2.4), high-mid isolation (2.5-4.9) and highest isolation (5.0-14.0). Locality was also classified by region (in order of increasing remoteness by ARIA score); Urban, south coast, north coast, rural and remote.

To determine the level of social and economic well being of areas studied, the Socio-Economic Indexes for Areas 2001 ([16]) Index of Disadvantage was applied to subjects at the level of collection district of residence. This is the smallest geographic area for which the Index is available. The Index of Disadvantage is a continuous score, and is based upon characteristics such as low income, lower level of education, high unemployment, and unskilled jobs. It has been standardised to a mean of 1000, and a standard deviation of 100 across all collection districts in Australia, ie, 95% of scores are between 800 and 1200. Higher scores indicate higher socio-economic status (SES) and least disadvantage. For categorical analysis, the scores were grouped into quartiles: Highest disadvantage (680-835), high-mid disadvantage (836-960), low-mid disadvantage (961-988) and least disadvantage (989-1103).

Birth weight was provided by the parent/carer by recall or from the child's health record. Height was measured in stocking feet to the nearest 0.1cm with a SECA 220 telescopic portable stadiometer ([17]) that was calibrated between screening visits. Weight was measured in stocking feet and in school uniform on digital scales to the nearest 0.01 kg. Body surface area (BSA), body mass index (BMI), height and weight standard deviation z-scores were calculated using an age and sex-adjusted program ([18]). Blood pressure was measured on the right arm with the child sitting, using an aneroid sphygmomanometer and the largest cuff to encircle the arm and cover at least three-quarters of the length of the upper arm ([19]). In children less than 13 years, diastolic pressure was measured at the point of muffling (Korotkov 4). For older children the point of disappearance was used (Korotkov 5) ([20]). For children with diastolic and/or systolic blood pressure greater than the 90th centile for age and sex, two further blood pressures were recorded after resting the child, and the lowest blood pressure according to the systolic reading was recorded in mmHg ([21]).

Data analysis: Proportions of CKD markers (haematuria, proteinuria and albuminuria) and associated risk factors (age, gender, birth weight, systolic and diastolic blood pressure, height standard deviation (SD), weight SD, body mass index SD, and category of isolation, disadvantage and region) were compared between Aboriginal and

non-Aboriginal groups using the chi-squared or Fisher's exact test. The Mantel extension test was used to determine linear trends across categories and quartiles. Odds ratios for markers of chronic kidney disease by isolation category, disadvantage category and region were determined using logistic regression, with 95% confidence intervals. Analyses were adjusted for age, gender, diastolic and systolic blood pressure, height SD, weight SD, body mass index SD and categories of isolation, disadvantage and region. Where appropriate, analyses were then further adjusted for Aboriginal race. Adjustment was made in all analyses for the effect of cluster sampling by school.

The Hosmer and Lemeshow test for goodness of fit was applied in the multivariate models. Tests for interactions between race, gender, age, categories of isolation, disadvantage and region and other significant variables in the final model were performed. Significance was set at a p-value of <0.05 for main effects and for interactions. Statistical analysis was completed using SAS ([22]) and SPSS software ([23]).

We planned to collect data from 1000 Aboriginal and 1000 non-Aboriginal children which was sufficient to detect differences in prevalence of markers of CKD between the two groups of 2.9 versus 1.1%, 4.0 versus 1.8%, 5.5 versus 2.9% at 80% power for haematuria, proteinuria and albuminuria respectively.

3.4: Results

*Baseline characteristics (**table 3.4.1**)* From February 2001 to June 2004, 2266 children were enrolled from 37 primary schools across New South Wales. There were 1248 (55.1%) Aboriginal and 1018 (44.9%) non-Aboriginal children, 51% were male, and the mean age was 8.9 years. There were proportionally more Aboriginal children in the youngest age group (4-6 years), in the lowest weight SD quartile (both p<0.0001) and in the lowest systolic (p<0.0001) and diastolic blood pressure quartiles (p=0.02). Aboriginal children were more likely to live within the categories of highest isolation and disadvantage, and in the most remote region (p<0.0001). There were no differences between the groups for sex, birth weight, height SD and body mass index SD quartiles.

Design effect estimates for the impact of cluster sampling by school were small for all markers of CKD: 1.10 for haematuria, 1.20 for proteinuria and 1.28 for albuminuria.

*Prevalence of baseline markers of CKD: (**table 3.4.2**)* The overall prevalence of haematuria was 5.5%, proteinuria 7.3% and albuminuria 7.3%.

Risk factors for baseline markers of CKD:

*Aboriginality (**table 3.4.2**)* Aboriginal children were more likely to have haematuria than non-Aboriginal children, and this association was more significant after adjustment for environmental health determinants and other covariates (adjusted OR 2.25, 95% CI 1.37-3.69, p=0.001). Even after adjustment, there were no differences in the frequency of proteinuria (adjusted OR 0.93, 95% CI 0.68-1.27, p=0.65) or albuminuria (adjusted OR 1.37, 95% CI 0.93-2.01, p=0.11) between the Aboriginal and non-Aboriginal children.

*Geographical isolation (**table 3.4.3**)* Children from low-mid isolation areas had a relatively low prevalence of haematuria (unadjusted OR 0.36, 95% CI 0.18-0.71, p=0.002) compared with the least isolated-referent category, which did not change appreciably with adjustment, but there was no evidence of a linear trend in the association between isolation and frequency of haematuria (trend p=0.05, non-trend p

<0.05). There was no association between prevalence of proteinuria and isolation category. There appeared to be an inconsistent relationship between isolation category and frequency of albuminuria detected, with the most isolated children having the lowest prevalence of albuminuria, especially after adjustment for race and other environmental health determinants (race adjusted OR 0.49, 95% CI 0.26-0.90, p=0.01). There was, however, no evidence of a linear trend between isolation and frequency of albuminuria (trend p=0.19).

*Region (**table 3.4.4**)* No association between regional categories and markers of CKD was found. There was an increasing trend in risk for proteinuria from urban to remote regions (p=0.04), however deviation from trend was also significant (p<0.05).

*Social disadvantage (**table 3.4.5**)* No association between social disadvantage categories and markers of CKD was found. There was a decreasing trend in risk for proteinuria from least to highest disadvantage categories (p=0.004).

There were no interactions found between environmental health determinants and race, age, gender or other covariates in any model.

3.5: Discussion

Aboriginal children are no more likely to have early urinary markers of CKD than non-Aboriginal children, except for haematuria, and we were unable to show any consistent clear association between proposed environmental determinants of health – social disadvantage and isolation – and risk of early CKD. Race is often used incorrectly as a proxy for many risk factors in health that are indicators of disadvantage, including geographical remoteness and socioeconomic status ([24]). We measured all these potential risk factors in our study and have shown that neither racial nor environmental risk factors appear predictive of early chronic kidney disease. This is the first study designed to differentiate the relative contributions of race and environmental health determinants on early markers of CKD.

Our results are surprising, as we expected to find an increased prevalence of CKD, especially albuminuria, in Aboriginal children and particularly in remote communities. This hypothesis is largely based on studies of adult Aboriginal people. In remote Aboriginal communities in the Northern Territory of Australia, where the incidence of ESKD is the highest in Australia and the world (1000-2500 cases per million population annually), microalbuminuria and overt albuminuria in Aboriginal adults are highly prevalent (23% and 30% respectively). Over 1-8 years follow-up, albuminuria was strongly predictive of chronic kidney disease, although this association was not followed from childhood (10). The current prevalence of albuminuria (ACR > 3.4 mg/mmol) in those aged 5-19 years from this community is 7.6%, similar to the rate seen in our Aboriginal (8.1%) and non-Aboriginal participants (6.5%) ([25]). However the lack of non-Aboriginal control groups and the socioeconomic similarities in these remote settings forces a presumption of race as the major contributor. This study has found no significant differences in albuminuria or proteinuria between Aboriginal and non-Aboriginal children across New South Wales, even when controlling for levels of isolation, disadvantage and region. From a sociodemographic perspective, when compared with lower risk determinants, areas of remoteness, high isolation and high disadvantage carried no increased risk for CKD in this cohort.

The higher prevalence of haematuria in the Aboriginal children, which was even more significantly associated with race after adjustment for environmental confounders, has been noted in other Indigenous populations. An excess of haematuria has been found in Aboriginal children from remote communities with high rates of post-infectious glomerulonephritis ([26]). In a population of Aboriginal children aged 5-19 years screened from remote Northern Territory communities, the rate of asymptomatic haematuria (7.7%) was similar to that in our Aboriginal cohort (7.1%) (25). In non-diabetic Indigenous adults a higher prevalence of haematuria has been associated with familial factors ([27]) ([28]), mesangioproliferative glomerulonephritis ([29]) and IgA nephropathy ([30]). In Aboriginal children with haematuria, ESKD outcomes have not yet been demonstrated ([31]) and prospective studies are needed. A two-fold increased risk of haematuria in our Aboriginal cohort does not explain the almost nine-fold greater risk for ESKD in Aboriginal Australians when compared to non-Aboriginal Australians.

What are the possible reasons in this study for the lack of differentiation in risk for CKD between Aboriginal and non-Aboriginal children from sociodemographically diverse environments? The study had an adequate sample size; even with larger numbers any increase in risk would be small. The precision in risk for albuminuria is already narrowly defined, with the upper limit of any 95% confidence interval being 2.3. Cluster sampling bias appeared minimal and adjustment for this bias made little difference to the summary estimates.

Measurement of the main predictors of risk (Aboriginal status and categories of isolation, disadvantage and region) was performed using standardised systems (11) (14) (16). There is no easy solution to the misclassification bias introduced when spatially-aggregated measures are applied to individual data, and there is no method available to identify and measure ecological bias. These standards, however, have been used reliably in geographically and ethnically-similar population-based samples (8) ([32]). High levels of disadvantage in some areas of lowest isolation demonstrate the disparities between environmental determinants of health ([33]), emphasising the

importance of using more than one measure, across urban to very remote regions as we have done.

It is unlikely there was error in recording the outcome, as measurement of proteinuria was performed using both standard machine dipstick analysis, but confirmed with a more precise albumin:creatinine (ACR). Early morning protein:creatinine correlates well with 24 hour urinary protein in children with normal renal function ([34]). Spot ACR has been shown to have very good receiver operator characteristic curves for detecting pathological albuminuria at the cut-off used in this study ([35]). Unfortunately, the test performance for proteinuria screening tests in low prevalence populations has not been validated. Semi-quantitative, one-off estimations of urinary protein in children vary according to posture, exercise, illness and time of day (34), and repeat testing to demonstrate persistent markers is likely to be of more importance. We look forward to reporting the results of prospective testing over six years in this cohort.

Have we misclassified or omitted outcome measures for early CKD? Proteinuria was found to be the strongest risk factor for ESKD in the largest community-based study of mass screening, with an adjusted relative risk of 14.9 ([36]). With regards to recording other possible outcomes, measuring creatinine or glomerular filtration rate in a healthy paediatric sample is unlikely to be helpful in determining risk for CKD. Renal ultrasound added little to the evaluation of high risk Aboriginal children and adults with asymptomatic proteinuria or haematuria (25).

This study indicates that within NSW, there is no increased risk of early CKD in healthy primary school-aged Aboriginal children when compared to non-Aboriginal children. In addition, environmental determinants of health are not associated risk factors for CKD in these children. Our findings suggest whilst the causal pathways for end-stage kidney disease in Aboriginal people may exist in childhood or earlier, an increased risk for CKD is not yet apparent. Therefore, preventative measures addressing and lifestyle factors such as smoking, obesity, diet and alcohol abuse in Aboriginal children and young adults are likely to make a significant impact on CKD development ([37]).

Longitudinal data are currently being collected on this cohort, and will provide unique and valuable information on the natural history of chronic kidney disease in Aboriginal and non-Aboriginal children across different levels of sociodemographic risk.

Table 3.4.1: Baseline sociodemographic and clinical characteristics

Variable	All subjects n = 2266	%	Aboriginal n=1248	%	Non-Aboriginal n=1018	%	p
Gender							
Male	1155	51.0	634	50.8	521	51.2	0.86
Female	1111	49.0	614	49.2	497	48.8	
Age groups (years)							
4-5.9	211	9.3	142	11.3	69	6.8	<0.0001
6-6.9	281	12.4	170	13.6	111	10.9	
7-7.9	329	14.5	189	15.2	140	13.7	
8-8.9	337	14.9	185	14.8	152	14.9	
9-9.9	351	15.5	168	13.5	183	18.0	
10-10.9	361	15.9	172	13.8	189	18.6	
11-14.8	396	17.5	222	17.8	174	17.1	
Birth weight quartiles (g)*							
412-2920	217	25.7	119	29.6	98	22.1	0.08
2921-3316	210	24.9	92	23.1	118	26.4	
3317-3685	210	24.9	98	24.4	112	25.3	
3686-5272	208	24.6	92	22.9	116	26.2	
Height SD quartiles*							
-4.8 to -0.7	563	25.1	334	26.9	229	22.8	0.12
-0.8 to 0.1	564	25.1	306	24.6	258	25.7	
0.2 to 1.0	558	24.8	305	24.7	253	25.0	
1.1 to 4.8	562	25.0	295	23.8	267	26.6	
Weight SD quartiles*							
-6.6 to -0.5	560	24.9	351	28.3	209	20.8	<0.0001
-0.4 to 0.3	560	24.9	301	24.3	259	25.7	
0.4 to 1.2	567	25.2	269	21.7	298	29.7	
1.3 to 13.3	559	24.9	319	25.7	240	23.9	
BMI SD quartiles*							
-4.8 to -0.8	560	24.9	333	26.9	227	22.5	0.08
-0.7 to 0.1	562	25.0	298	24.0	264	26.3	
0.2 to 0.7	566	25.2	298	24.0	268	26.7	
0.8 to 6.9	558	24.8	311	25.1	247	24.6	
Isolation category (ARIA score)							
Least isolation (0-1.1)	610	26.9	323	25.9	287	28.2	<0.0001
Low-mid isolation (1.2-2.4)	639	28.2	340	27.2	299	29.4	
High-mid isolation (2.5-4.9)	521	23.0	242	19.4	279	27.4	
Highest isolation (5.0-14.0)	496	21.9	343	27.5	153	15.0	
Disadvantage category (SEIFA score)							
Least disadvantage (989-1103)	548	24.2	273	21.9	275	27.0	<0.0001
Low-mid disadvantage (960-988)	585	25.8	287	23.0	298	29.3	
High-mid disadvantage (836-960)	576	25.4	334	26.8	242	23.8	
Highest disadvantage (680-835)	557	24.6	354	28.4	203	19.9	
Region							
Urban	370	16.3	201	16.1	169	16.6	<0.0001
South coast	364	16.1	192	15.4	172	16.9	
North coast	497	21.9	260	20.8	237	23.3	
Rural	599	26.4	304	24.4	295	29.0	
Remote	436	19.2	291	23.3	145	14.2	

Abbreviations : ARIA++, Accessibility and Remoteness Index of Australia; BMI, body mass index; BP, blood pressure; SD, standard deviation; SEIFA, Socio-Economic Indexes For Areas.
*Indicates where data does not total 2266.

Table 3.4.1 cont: Baseline sociodemographic and clinical characteristics

Variable	All subjects n = 2266	%	Aboriginal n=1248	%	Non-Aboriginal n=1018	%	p
Systolic BP quartiles (mmHg)*							
62-92	562	25.1	347	28.2	215	21.4	<0.0001
93-100	608	27.2	328	26.6	280	27.9	
101-108	542	24.2	266	21.6	276	27.5	
109-170	525	23.5	291	23.6	234	23.3	
Diastolic BP quartiles (mmHg)*							
28-53	522	23.2	316	25.6	206	20.5	0.02
54-58	618	27.6	344	27.9	274	27.3	
59-64	585	26.2	303	24.6	282	28.1	
65-98	512	22.9	269	21.8	243	24.2	

Abbreviations : ARIA++, Accessibility and Remoteness Index of Australia; BMI, body mass index; BP, blood pressure; SD, standard deviation; SEIFA, Socio-Economic Indexes For Areas.
*Indicates where data does not total 2266.

Table 3.4.2: Prevalence of baseline chronic kidney disease markers in Aboriginal and non-Aboriginal children

	Overall	Non-Aboriginal (referent category)	Aboriginal	p
Hematuria				
Events (%)	122 (5.5)	36 (3.6)	86 (7.1)	
Unadjusted OR		1.00	2.02 (1.30-3.13)	0.002
Adjusted OR [Ψ]		1.00	2.25 (1.37-3.69)	0.001
Proteinuria				
Events (%)	161 (7.3)	75 (7.6)	86 (7.0)	
Unadjusted OR		1.00	0.93 (0.65-1.32)	0.67
Adjusted OR[Ψ]		1.00	0.93 (0.68-1.27)	0.65
Albuminuria (ACR mg/mmol)				
Events (%)	157 (7.3)	63 (6.5)	94 (8.1)	
Unadjusted OR		1.00	1.27 (0.87-1.84)	0.22
Adjusted OR[Ψ]		1.00	1.37 (0.93-2.01)	0.11

[Ψ]Adjusted for age, gender, birth weight, height SD, weight SD, BMI SD, systolic BP, diastolic BP, isolation category, disadvantage category and region.
Definitions: Hematuria $\geq$ 25 RBC per HPF (1+); proteinuria $\geq$ 0.30 g/L (1+); albuminuria, albumin:creatinine (ACR) $\geq$ 3.4 mg/mmol.
Abbreviations: ACR, albumin:creatinine; BMI, body mass index; BP, blood pressure; SD, standard deviation.

Table 3.4.3: Association between baseline chronic kidney disease markers and geographical isolation

	Lowest isolation (referent category)	Low-mid isolation	High-mid isolation	Highest isolation	Trend p
Hematuria					
Events (%)	34 (5.7)	15 (2.4)	40 (7.9)	33 (6.8)	
Unadjusted OR	1.00	0.36 (0.18-0.71)	1.26 (0.75-2.10)	1.07 (0.49-2.37)	0.05*
Adjusted OR [Ψ]	1.00	0.31 (0.14-0.66)	1.26 (0.73-2.16)	0.99 (0.46-2.16)	
Race adjusted OR [Δ]	1.00	0.29 (0.13-0.63)	1.31 (0.77-2.23)	0.84 (0.38-1.85)	
Proteinuria					
Events (%)	41 (6.9)	58 (9.3)	28 (5.5)	34 (7.0)	
Unadjusted OR	1.00	1.78 (0.89-3.59)	0.96 (0.46-2.00)	1.24 (0.58-2.62)	0.48*
Adjusted OR [Ψ]	1.00	1.62 (0.78-3.39)	0.99 (0.46-2.14)	1.16 (0.53-2.55)	
Race adjusted OR [Δ]	1.00	1.63 (0.78-3.42)	0.99 (0.46-2.13)	1.17 (0.54-2.57)	
Albuminuria					
Events (%)	45 (7.9)	47 (7.5)	42 (8.3)	23 (5.2)	
Unadjusted OR	1.00	0.82 (0.48-1.40)	0.96 (0.62-1.50)	0.59 (0.27-1.27)	0.19
Adjusted OR [Ψ]	1.00	0.63 (0.35-1.13)	0.87 (0.58-1.31)	0.52 (0.28-0.97)	
Race adjusted OR [Δ]	1.00	0.62 (0.35-1.11)	0.88 (0.59-1.32)	0.49 (0.26-0.90)	

*Non-trend $p<0.05$
[Ψ]Adjusted for age, gender, height SD, weight SD, BMI SD, systolic BP, diastolic BP, disadvantage category and region.
[Δ]Adjusted for race, age, gender, height SD, weight SD, BMI SD, systolic BP, diastolic BP, disadvantage category and region.
Definitions: Hematuria $\geq$ 25 RBC per HPF (1+); proteinuria $\geq$ 0.30 g/L (1+); albuminuria, albumin:creatinine (ACR) $\geq$ 3.4 mg/mmol.
Abbreviations: ACR, albumin:creatinine; BMI, body mass index; BP, blood pressure; SD, standard deviation.

Table 3.4.4. Association between baseline chronic kidney disease markers and region

	Urban (referent category)	Coastal	Rural	Remote	Trend p
Hematuria					
Events (%)	26 (7.3)	41 (4.8)	29 (4.9)	26 (6.2)	
Unadjusted OR	1.00	0.64 (0.34-1.22)	0.66 (0.29-1.49)	0.83 (0.35-1.95)	0.68
Adjusted OR $^{\Psi}$	1.00	0.67 (0.32-1.42)	0.56 (0.24-1.30)	1.02 (0.41-2.58)	
Race adjusted OR $^{\Delta}$	1.00	0.66 (0.31-1.40)	0.55 (0.22-1.37)	0.89 (0.36-2.24)	
Proteinuria					
Events (%)	14 (3.9)	61 (7.2)	55 (9.4)	31 (7.4)	
Unadjusted OR	1.00	1.89 (0.81-4.42)	2.53 (1.06-6.05)	1.94 (0.81-4.65)	0.04*
Adjusted OR $^{\Psi}$	1.00	2.26 (0.68-7.53)	2.03 (0.78-5.32)	2.30 (0.71-7.41)	
Race adjusted OR$^{\Delta}$	1.00	2.27 (0.68-7.57)	2.04 (0.78-5.33)	2.32 (0.72-7.51)	
Albuminuria					
Events (%)	20 (6.1)	71 (8.4)	44 (7.5)	22 (5.9)	
Unadjusted OR	1.00	1.41 (0.85-2.35)	1.25 (0.75-2.10)	0.96 (0.41-2.28)	0.60
Adjusted OR $^{\Psi}$	1.00	1.33 (0.66-2.68)	1.01 (0.60-1.72)	0.95 (0.39-2.30)	
Race adjusted OR $^{\Delta}$	1.00	1.32 (0.65-2.70)	1.01 (0.59-1.73)	0.91 (0.37-2.27)	

*Non-trend $p<0.05$

$^{\Psi}$Adjusted for age, gender, height SD, weight SD, BMI SD, systolic BP, diastolic BP, isolation category and Disadvantage category.

$^{\Delta}$Adjusted for race, age, gender, height SD, weight SD, BMI SD, systolic BP, diastolic BP, isolation category and Disadvantage category.

Definitions: Hematuria $\geq$ 25 RBC per HPF (1+); proteinuria $\geq$ 0.30 g/L (1+); albuminuria, albumin:creatinine (ACR) $\geq$ 3.4 mg/mmol.

Abbreviations: ACR, albumin:creatinine; BMI, body mass index; BP, blood pressure; SD, standard deviation.

Table 3.4.5: Association between baseline chronic kidney disease markers and social disadvantage

	Least disadvantage (referent category)	Low-mid disadvantage	High-mid disadvantage	Highest disadvantage	Trend p
Hematuria					
Events (%)	32 (6.0)	25 (4.4)	32 (5.7)	33 (6.0)	
Unadjusted OR	1.00	0.73 (0.28-1.91)	0.95 (0.40-2.24)	0.99 (0.47-2.12)	0.78
Adjusted OR [Ψ]	1.00	0.55 (0.21-1.41)	0.82 (0.35-1.93)	0.76 (0.34-1.72)	
Race adjusted OR [Δ]	1.00	0.59 (0.22-1.57)	0.79 (0.33-1.91)	0.72 (0.30-1.73)	
Proteinuria					
Events (%)	53 (9.9)	43 (7.6)	34 (6.0)	31 (5.6)	
Unadjusted OR	1.00	0.75 (0.41-1.39)	0.58 (0.32-1.05)	0.54 (0.27-1.06)	0.004
Adjusted OR [Ψ]	1.00	0.57 (0.21-1.58)	0.53 (0.22-1.28)	0.57 (0.27-1.24)	
Race adjusted OR [Δ]	1.00	0.57 (0.21-1.58)	0.53 (0.22-1.28)	0.58 (0.27-1.23)	
Albuminuria					
Events (%)	43 (8.1)	42 (7.5)	41 (8.2)	31 (5.6)	
Unadjusted OR	1.00	0.93 (0.53-1.63)	1.02 (0.67-1.57)	0.68 (0.40-1.16)	0.18
Adjusted OR [Ψ]	1.00	0.80 (0.39-1.68)	0.87 (0.46-1.65)	0.68 (0.42-1.11)	
Race adjusted OR [Δ]	1.00	0.82 (0.38-1.74)	0.86 (0.45-1.66)	0.66 (0.40-1.10)	

[Ψ]Adjusted for age, gender, height SD, weight SD, BMI SD, systolic BP, diastolic BP, isolation category and region.
[Δ]Adjusted for race, age, gender, height SD, weight SD, BMI SD, systolic BP, diastolic BP, isolation category and region.
Definitions: Hematuria $\geq$ 25 RBC per HPF (1+); proteinuria $\geq$ 0.30 g/L (1+); albuminuria, albumin:creatinine (ACR) $\geq$ 3.4 mg/mmol.
Abbreviations: ACR, albumin:creatinine; BMI, body mass index; BP, blood pressure; SD, standard deviation.

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CHAPTER 4: CARDIOVASCULAR RISK FACTORS IN AUSTRALIAN INDIGENOUS AND NON-INDIGENOUS CHILDREN: A POPULATION-BASED STUDY

4.1: Abstract

Objective Indigenous people have a two to tenfold increased risk of premature death from cardiovascular disease. We aimed to determine whether some key risk factors for cardiovascular disease occur more commonly in Aboriginal than non-Aboriginal Australian children.

Participants and Setting Children were enrolled from primary schools throughout New South Wales, the state with the highest number of Aboriginal people.

Exposures and Outcome Measures Associations between ethnicity, gender, birth weight, socio-demographic status and hypertension, obesity, baseline and persistent albuminuria were determined.

Results 2266 children (55% Aboriginal) were enrolled. Mean age was 8.9 years ($\pm$ 3.8 years). Obesity (body mass index $\geq$ 2 standard deviations) was detected in 7.1%, systolic hypertension (blood pressure >90th percentile) in 7.2%, diastolic hypertension in 5.9%, baseline albuminuria (albumin:creatinine $\geq$ 3.4 mg/mmol) in 7.3%, and persistent albuminuria in 1.5% with no differences between Aboriginal and non-Aboriginal children. Hypertension was less common with increasing social disadvantage (trend $p<0.02$). Increasing BMI SD was strongly associated with systolic and diastolic hypertension (both $p<0.0001$).

Conclusions Many risk factors for cardiovascular disease are already common in young children, but not more prevalent in Aboriginal than non-Aboriginal children. In all children, overweight and obesity have the strongest association with hypertension but social disadvantage appears protective for hypertension. Our findings suggest that risk for cardiovascular health disparities seen in Indigenous adults manifests beyond childhood, and that a window of opportunity exists to prevent some of these outcomes.

4.2: Introduction

Cardiovascular disease is the leading cause of premature death in Indigenous people world-wide, and there is an increasing disparity in rates of cardiovascular deaths between Indigenous and white populations that is pronounced by middle age. Recent data for American Indian and Alaskan Natives shows the cardiovascular death rate in 45-55 year olds is twice that of US whites with a 4.1% annual increase, compared with a 1.7% annual decrease in whites ([1]). By age 40, Aboriginal Australians are 10 times more likely to die of ischaemic heart disease compared with non-Aboriginal Australians ([2]).

The causal pathways to these health disparities are poorly researched, and are likely to be multi-determinant, due to differences in physiological and socio-economic risk factors. Overall rates of obesity and hypertension in American Indian and Alaskan Native adults are higher than US whites, and the disparity widens with age ([3]). Australian Aboriginals more than 15 years of age are 1.5 times more likely to be overweight or hypertensive ([4]). Diabetes prevalence is twice the national rate in American Indians and Alaskan Natives, and more than four times the national rate in remote Aboriginal Australians (3) ([5]). Albuminuria presents early as part of the metabolic syndrome complex in Aboriginal Australians and Native Americans ([6]) ([7]), and it robustly predicts cardiovascular morbidity and death (6). This increased burden of risk factors found in Indigenous adults contributes to the widening gap in cardiovascular health outcomes between Indigenous and non-Indigenous people, and a tendency for disease at a much younger age (7) (7). The social and environmental inequalities that Indigenous people are born and raised with, such as the lack of access to healthcare, inadequate healthcare delivery and social disadvantage, are also likely to contribute to these outcomes ([8]).

There are no population-based studies in ethnically and socio-economically diverse children evaluating the early prevalence of risk factors for cardiovascular disease. This study aims to determine whether established risk factors for cardiovascular disease (obesity, hypertension and albuminuria) are more prevalent in Aboriginal than non-Aboriginal Australian children, and whether these risk factors are associated with physiological determinants of ethnicity, gender and birth weight, and

environmental health determinants of geographical isolation and social disadvantage.

4.3: Methods

Selection of participants Government-run primary schools were selected from urban, coastal, rural and remote locations known for their high Aboriginal population across the state of New South Wales. This state has the highest proportion of Aboriginal people. To maximise power, sampling was done to obtain equal numbers of Aboriginal and non-Aboriginal children, and in similar proportions from urban, coastal, rural and remote areas. All primary schools in remote communities were approached, and other areas were sampled if greater than twenty Aboriginal children in the relevant age range attended.

Aboriginal status was determined using the Australian Bureau of Statistics best practice recommendations, asking the Standard Indigenous Question on the consent form "Is your child of Aboriginal or Torres Strait Islander origin?" ([9]). All Aboriginal children in the participating primary schools were offered measurement of height, weight, blood pressure and urinary dipstick abnormalities. We aimed to recruit equal numbers of boys and girls, Aboriginal and non-Aboriginal children, and approximately equal numbers of children from each 12 month age group.

Aboriginal community engagement Consultation with local Aboriginal Medical Services and consent from community leaders was undertaken prior to commencement of the study. Approval was obtained from the Ethics Committees of the Children's Hospital at Westmead, the University of Sydney, New South Wales Area Health Services and the New South Wales Department of Education and Training. Informed consent was obtained for each child in accordance with NHMRC Guidelines for Ethical Conduct in Aboriginal and Torres Strait Islander Research ([10]). Data was collected onto a standardised form and de-identified for storage and analysis before being returned to each community after the study visit. Permission to publish data was also obtained from each community.

Measurement of birth weight, growth parameters and blood pressure Birth weight was provided by the parent/carer by recall or from the child's health record. Height was measured in stocking feet to the nearest 0.1cm with a SECA 220 telescopic portable stadiometer ([11]) that was calibrated between screening visits. Weight was measured in stocking feet and in school uniform on digital scales to the nearest 0.01

kg. Body mass index (BMI), height and weight standard deviation z-scores (SD) were calculated using an age and gender adjusted program based upon international normative data ([12]). Blood pressure was measured on the right arm with the child sitting, using an aneroid sphygmomanometer and the largest cuff to encircle the arm and cover at least three-quarters of the length of the upper arm ([13]). In children less than 13 years, diastolic pressure was measured at the point of muffling (Korotkoff 4). For older children the point of disappearance was used (Korotkoff 5) ([14]). For children with diastolic and/or systolic blood pressure greater than the 90th percentile for age and gender (using normative data from Australian children, including Aboriginal children), two further blood pressures were recorded after resting the child, and the lowest blood pressure according to the systolic reading was recorded in mmHg ([15]).

Measurement of albuminuria A morning clean catch specimen of urine was collected from each child, with dipstick analysis for albuminuria performed at the survey site on fresh specimens using a Bayer Clinitek 50 machine and Albustix dipsticks ([16]). Leukocytes and nitrites were also recorded for later adjustment for abnormalities of presumed urinary tract infection. Girls older than eight years who were found to have haematuria were questioned about menses, and if appropriate, collection was performed at another time. Because albuminuria is often transient, follow-up urinalysis was performed two years after baseline testing on all available children and the frequency of persistent albuminuria (albuminuria detected at baseline and follow-up) and non-persistent or transient albuminuria (albuminuria detected at either baseline or follow-up) was also ascertained.

Measurement of environmental health determinants Standardisation of urban, coastal, rural and remote locality was made using the Accessibility and Remoteness Index of Australia (ARIA++), with each subject given an index score according to their postcode of residence ([17]). Using geographical information system (GIS) capabilities, distances, services and population density for each locality are converted to a continuous variable with values ranging from zero for high accessibility, to 18 for extreme remoteness ([18]). ARIA++ values for this NSW study ranged from 0 to 14, and for categorical analysis the scores were grouped into quartiles. Isolation categories (and ARIA++ score range) used were: Least isolation

(0-1.1), low-mid isolation (1.2-2.4), high-mid isolation (2.5-4.9) and highest isolation (5.0-14.0).

To determine the level of social and economic well being of areas studied, the Socio-Economic Indexes for Areas 2001 ([19]) Index of Disadvantage was applied to subjects at the level of collection district of residence. This is the smallest geographic area for which the Index is available, and includes approximately 200 households. The Index of Disadvantage is a continuous score, and is based upon characteristics such as low income, lower level of education, high unemployment, and unskilled jobs. It has been standardised to a mean of 1000 and a standard deviation of 100 across all collection districts in Australia, ie, 95% of scores are between 800 and 1200. Higher scores indicate higher socio-economic status (SES) and least disadvantage. For categorical analysis the scores were grouped into quartiles: Highest disadvantage (680-835), high-mid disadvantage (836-960), low-mid disadvantage (961-988) and least disadvantage (989-1103).

Data analysis Cardiovascular risk factors considered were systolic and diastolic hypertension (blood pressure greater than the 90th percentile for age and gender), obesity (BMI SD greater than or equal to 2), albuminuria at baseline (albumin:creatinine, ACR, greater than or equal to 3.4 mg/mmol) and persistent albuminuria (albuminuria at both baseline and at 2 year follow-up). Potential predictors of cardiovascular risk factors were Aboriginal status, female gender, low birth weight (less than or equal to 2500g), higher isolation categories (ARIA score 1.2-14.0) and higher disadvantage categories (SEIFA score 680 to 988). Categories of gender, age group, systolic and diastolic blood pressure percentiles, isolation and disadvantage, quartiles of birth weight, height SD, weight SD, body mass index SD and cardiovascular risk factors were compared between Aboriginal and non-Aboriginal groups using the chi-squared test. The association between predictors and cardiovascular risk factors was determined using odds ratios and 95% confidence intervals with the presumed lowest risk category of predictor as the referent group. Logistic regression was used to adjust for differences in ethnicity, age, gender, diastolic and systolic blood pressure, body mass index SD and categories of isolation and disadvantage. The Mantel extension test was used to determine linear trends across categories and quartiles. Adjustment was made in all

analyses for the effect of cluster sampling by school. Tests for interactions between ethnicity, gender, age, categories of isolation and disadvantage and other significant variables in the final model were performed. Significance was set at a p-value of <0.05. Statistical analysis was completed using SAS ([20]) and SPSS software ([21]).

With data collection planned from1000 Aboriginal and 1000 non-Aboriginal children, the study was adequately powered to detect differences in prevalence of albuminuria, hypertension and obesity between the two groups of 5.5 versus 2.9%, 12.0 versus 10.0% and 9.0 versus 7.0% given a two-tailed significance of less than 0.05.

4.4: Results

*Baseline characteristics (**table 4.4.1**)* From February 2002 to June 2004, 2266 children were enrolled from 37 primary schools across New South Wales. There were 1248 (55.1%) Aboriginal and 1018 (44.9%) non-Aboriginal children, 51% were male, and the mean age was 8.9 years (± 3.8 years). There were proportionally more Aboriginal children in the youngest age group (4 to 6 years), in the lowest weight SD quartile, in the most isolated area and in the most disadvantaged category (all $p<0.0001$). There were no differences between the groups for gender, birth weight, height SD, body mass index SD quartiles, and blood pressure percentile categories. At two year follow-up there were 1334 children available for urinalyses. Twenty children (1.5%) had persistent albuminuria, and 157 children (11.8%) had transient albuminuria (albuminuria at either baseline or at follow-up).

Prevalence of cardiovascular risk factors The observed frequencies of outcomes of interest were systolic hypertension (7.2%), diastolic hypertension (5.9%), obesity (7.1%), baseline albuminuria (7.3%) and persistent albuminuria (1.5%).

*Physiological predictors of cardiovascular risk factors (**table 4.4.2**)* Aboriginal children were no more likely to have cardiovascular risk factors than non-Aboriginal children. At baseline testing, female children were at higher risk of albuminuria compared with male children (adjusted OR 1.81, 95 % CI 1.46-2.15, p=0.001). There were no differences in rates of persistent and transient albuminuria between males and females (χ^2 2.12, p=0.15), nor between Aboriginal and non-Aboriginal children (χ^2 0.15, p=0.70). When compared with higher birth weight, low birth weight was not associated with any cardiovascular risk factor. None of these physiological determinants were associated with obesity or hypertension.

*Environmental predictors of cardiovascular risk factors (**table 4.4.2**)* There was a trend for higher risk of systolic and diastolic hypertension in less disadvantaged children (trend p=0.01 and 0.02 respectively). There were no significant trends across isolation categories for any cardiovascular risk factor. None of these environmental determinants were associated with albuminuria or obesity.

*Association between cardiovascular risk factors (**table 4.4.3**)* Increasing systolic blood pressure centiles were associated with diastolic hypertension, and increasing diastolic blood pressure centiles were associated with systolic hypertension (both trend p< 0.0001).There was a strong association between increasing BMI SD and risk of systolic and diastolic hypertension (both trend p<0.0001). Compared with children in the lowest BMI SD quartile, the adjusted risk of systolic and diastolic hypertension for children in the highest BMI SD quartile was 12.37 (6.17-24.78) and 5.05 (2.74-9.32) respectively, both p<0.0001. Conversely, higher systolic and diastolic blood pressure centiles were strongly associated with obesity (both trend p < 0.0001). There was a trend for lower risk of albuminuria in children with higher BMI SD (trend p=0.005). Compared with children in the lowest BMI SD quartile, the adjusted risk of albuminuria for children in the highest BMI SD quartile was 0.51 (0.32-0.82), p=0.001.

There were no interactions found between ethnicity, age, gender, isolation and disadvantage categories, or other covariates in any model.

4.5: Discussion

Aboriginal children in New South Wales have no increased prevalence of traditional cardiovascular risk factors (hypertension, albuminuria and obesity) when compared with non-Aboriginal children. Ethnicity is prone to misuse as a proxy of disadvantage ([22])([23]), though it is likely the socio-demographic factors associated with being Aboriginal contribute cumulatively to the poor cardiovascular health of Aboriginal adults. Such factors include lower income and education levels, geographic isolation, limited access to health care and diseconomies of scale due to sparsely distributed populations ([24]). This is one of the few studies that differentiate the contributions of ethnicity and environmental health determinants towards risk of cardiovascular disease in children. We have found that ethnicity is not associated with increased cardiovascular risk, even after adjustment for differences in socio-demographic status.

The lack of non-Indigenous control groups and the socio-economic similarities in studies of Indigenous adults from non-population-based, remote community settings forces the presumption that Indigenous status is the major contributor of disease ([25]). However, in Aboriginal communities with the highest rates of cardiovascular death in Australia ([26]), a similar prevalence of albuminuria to our study findings has been found on cross-sectional testing of the children. The frequency of albuminuria (ACR>3.4 mg/mmol) in those aged 5-19 years from such communities was 7.6%, which is not different to the baseline rate seen in our Aboriginal (8.1%) and non-Aboriginal (6.5%) children. Accepting that much of this albuminuria is likely to be only transient ([27]), at two-year follow-up we found no significant differences in transient or persistent albuminuria between Aboriginal and non-Aboriginal children.

Study design issues are unlikely to explain the reasons for a lack of differentiation in risk for cardiovascular disease between Aboriginal and non-Aboriginal children from socio-demographically diverse environments. The study was adequately powered in terms of sample size for the cardiovascular risk factors. Adjustment for cluster sampling bias made little difference to the summary estimates. Measurement of the ethnic and environmental predictors of risk was performed using standardised

systems (9)(17)(19). We accept that unmeasured confounding from individual-level socio-economic factors remains as a study bias. With further data collection, multi-level analyses could be used to identify, measure and correct for ecological bias when spatially-aggregated measures are applied to individual data ([28]). The standards used in this study, however, have been applied reliably in geographically and ethnically similar samples ([29]) ([30]). Parentally recalled birth weight has been shown as a reliable proxy for recorded birth weight in population-based research ([31]) ([32]).

It is unlikely there was error in recording the outcomes. Blood pressure was measured using appropriate cuff sizes, particularly for obese and older children, and repeat measures were performed in hypertensive children. Spot ACR has been shown to have good receiver operator characteristic curves for detecting pathological albuminuria at the cut-off used in this study ([33]). Obesity was determined using BMI standard deviations, which has been validated for use in this age group of children ([34]). Overall prevalence of obesity of 7.1% in our cohort is comparable to 6% for Australian children ([35]). Waist circumference has been shown to be more predictive of cardiovascular risk in Indigenous adults ([36]), and measurement of outcomes such as central obesity, blood lipid, glucose, HbA1C and insulin levels would have been desirable for evidence of metabolic syndrome ([37]). Measuring all possible cardiovascular risk factors was beyond the practicalities of such a large school-based screening study, and painful or embarrassing procedures would have been counter-productive to the current success of our follow-up recruitment rates.

Overweight and obesity were most significantly associated with hypertension. Without early intervention, these obese and hypertensive pre-pubertal children are at high risk for diabetes and cardiovascular disease in adulthood, and they are likely to have shorter life expectancies than their parents ([38]) ([39]). The increasing risk for hypertension in socially advantaged children seems contradictory to other studies ([40]) ([41]). Our study sampled children where Aboriginal populations reside, in areas of the lowest socio-economic status ([42]). The highest SES quartile in our cohort (indicating lesser disadvantage) correlates with mid-range SES categories in other comparative studies ([43]) ([44]). Our findings are consistent with these studies that show the prevalence of disease risk factors follow a bell shaped curve across different

socio-economic environments. Lowest risk occurs at either extreme of socio-economic status and highest risk in mid-range SES categories (43)(44).

Female children were found to be at increased risk of albuminuria at baseline, even after adjustment for presumed urinary tract infection, and testing menstruating females at another time. Transient proteinuria is a common cause of albuminuria in this age group (27), and most of the albuminuria found in these children was transient. At two year follow-up there was no difference in rates of persistent and transient albuminuria between males and females.

Low birth weight was not associated with any cardiovascular disease risk factor. Low birth weight has been associated with higher risk of hypertension in children from observational studies with well and poorly defined study bases ([45]) ([46]). A systematic review of 55 studies showed that birth weight had little association to blood pressure levels in later life. Being currently overweight had a much more relevant and significant association with hypertension (46), as we have shown in our study.

Microalbuminuria is an established marker with obesity as part of the metabolic syndrome in adults (37), however our finding that children in higher BMI SD quartiles have no increased risk for albuminuria is not novel, and has been found even in children with insulin resistance ([47]). Measurement error may also contribute to a spurious increase in risk for albuminuria in underweight children. An overestimation of microalbuminuria by ACR may result in these children with low muscle mass due to a combination of normal excretion of urinary albumin with a low urinary creatinine excretion ([48]). Whether albuminuria is predictive of cardiovascular disease in youth, as it is in adults, remains to be proven.

This study indicates that within New South Wales, there is no increase in prevalence of these risk factors for cardiovascular disease in primary school aged Aboriginal children when compared to non-Aboriginal children. Children who are obese and children from areas of mid-range socio-economic status are at higher risk of developing cardiovascular disease. This suggests that some of the difference in cardiovascular risk for Indigenous people manifests beyond childhood, and may therefore result from broader social inequalities. It also suggests that a window of

opportunity exists to develop strategies for all children that deal with obesity and underlying social disparities, which in turn may prevent some of the cardiovascular disease inequality in Aboriginal adults.

Table 4.4.1: Baseline characteristics

Variable	All subjects n = 2266	%	Aboriginal n=1248	%	Non-Aboriginal n=1018	%	p
Gender							
Male	1155	51.0	634	50.8	521	51.2	0.86
Female	1111	49.0	614	49.2	497	48.8	
Age groups (years)							
4-5.9	211	9.3	142	11.3	69	6.8	<0.0001
6-6.9	281	12.4	170	13.6	111	10.9	
7-7.9	329	14.5	189	15.2	140	13.7	
8-8.9	337	14.9	185	14.8	152	14.9	
9-9.9	351	15.5	168	13.5	183	18.0	
10-10.9	361	15.9	172	13.8	189	18.6	
11-14.8	396	17.5	222	17.8	174	17.1	
Birth weight quartiles (g)*							
412-2920	217	25.7	119	29.6	98	22.1	0.08
2921-3316	210	24.9	92	23.1	118	26.4	
3317-3685	210	24.9	98	24.4	112	25.3	
3686-5272	208	24.6	92	22.9	116	26.2	
Height SD quartiles*							
-4.8 to -0.7	563	25.1	334	26.9	229	22.8	0.12
-0.8 to 0.1	564	25.1	306	24.6	258	25.7	
0.2 to 1.0	558	24.8	305	24.7	253	25.0	
1.1 to 4.8	562	25.0	295	23.8	267	26.6	
Weight SD quartiles*							
-6.6 to -0.5	560	24.9	351	28.3	209	20.8	<0.0001
-0.4 to 0.3	560	24.9	301	24.3	259	25.7	
0.4 to 1.2	567	25.2	269	21.7	298	29.7	
1.3 to 13.3	559	24.9	319	25.7	240	23.9	
BMI SD quartiles*							
-4.8 to -0.8	560	24.9	333	26.9	227	22.5	0.08
-0.7 to 0.1	562	25.0	298	24.0	264	26.3	
0.2 to 0.7	566	25.2	298	24.0	268	26.7	
0.8 to 6.9	558	24.8	311	25.1	247	24.6	
Isolation category (ARIA score)							
Least isolation (0-1.1)	610	26.9	323	25.9	287	28.2	<0.0001
Low-mid isolation (1.2-2.4)	639	28.2	340	27.2	299	29.4	
High-mid isolation (2.5-4.9)	521	23.0	242	19.4	279	27.4	
Highest isolation (5.0-14.0)	496	21.9	343	27.5	153	15.0	
Disadvantage category (SEIFA score)							
Least disadvantage (989-1103)	548	24.2	273	21.9	275	27.0	<0.0001
Low-mid disadvantage (960-988)	585	25.8	287	23.0	298	29.3	
High-mid disadvantage (836-959)	576	25.4	334	26.8	242	23.8	
Highest disadvantage (680-835)	557	24.6	354	28.4	203	19.9	
Systolic BP percentiles*							
<50th	1258	56.2	711	57.7	547	54.4	0.09
50th to 90th	817	36.5	426	34.6	391	38.9	
>90th	162	7.2	95	7.7	67	6.7	
Diastolic BP percentiles*							
<50th	1410	63.0	793	64.4	617	61.4	0.34
50th to 90th	696	31.2	370	30.0	326	32.4	
>90th	131	5.9	69	5.6	62	6.2	

Abbreviations: ARIA, Accessibility and Remoteness Index of Australia; BMI, body mass index; BP, blood pressure; SD, standard deviation; SEIFA, Socio-Economic Index For Areas.
*Indicates where data does not total 2266

Table 4.4.2: Physiological and environmental predictors of cardiovascular risk factors

Predictor	Systolic Hypertension N (%)	Systolic Hypertension AOR‡ (95% CI)	Diastolic Hypertension N (%)	Diastolic Hypertension AOR‡ (95% CI)	Albuminuria N (%)	Albuminuria AOR‡ (95% CI)	Obesity N (%)	Obesity AOR‡ (95% CI)
Aboriginality								
Non-Aboriginal*	67 (6.7)	1.00	62 (6.2)	1.00	63 (6.5)	1.00	63 (6.7)	1.00
Aboriginal	95 (7.7)	1.22 (0.87-1.57)	69 (5.6)	0.94 (0.57-1.31)	94 (8.1)	1.37 (0.93-2.01)	82 (7.4)	1.10 (0.76-1.44)
Gender								
Male*	76 (6.7)	1.00	70 (6.1)	1.00	59 (5.4)	1.00	72 (7.0)	1.00
Female	86 (7.8)	1.34 (0.99-1.69)	61 (5.6)	0.88 (0.50-1.25)	98 (9.4)	1.81(1.46-2.15) †	73 (7.2)	1.03 (0.69-1.37)
Birth weight								
> 2500 *	100 (7.8)	1.00	80 (6.3)	1.00	94 (7.7)	1.00	86 (7.3)	1.00
≤ 2500g	11 (8.7)	1.10 (0.43-1.76)	5 (4.0)	0.63 (0.33-1.63)	6 (5.0)	0.58 (0.25-1.53)	7 (6.0)	0.77 (0.32-1.81)
Isolation								
Least isolation*	34 (5.6)	1.00	19 (3.1)	1.00	45 (7.9)	1.00	44 (7.8)	1.00
Low-mid isolation	71 (11.3)	2.20 (1.38-3.51)	62 (9.9)	3.75 (2.14-6.55)	47 (7.5)	0.91 (0.58-1.42)	45 (7.9)	1.01 (0.66-1.56)
High-mid isolation	25 (4.9)	0.89 (0.50-1.49)	34 (6.7)	2.24 (1.23-4.01)	42 (8.3)	1.04 (0.67-1.64)	27 (5.7)	0.70 (0.41-1.17)
Highest isolation	32 (6.5)	1.20 (0.72-1.95)	16 (3.2)	1.04 (0.52-2.06)	23 (5.2)	0.61 (0.36-1.09)	29 (6.5)	0.83 (0.50-1.36)
Social disadvantage								
Least disadvantage*	55 (10.2)	1.00	33 (6.1)	1.00	43 (8.1)	1.00	34 (6.9)	1.00
Low-mid disadvantage	43 (7.4)	0.70 (0.46-1.10)	47 (8.1)	1.37 (0.84-2.23)	42 (7.5)	0.87 (0.66-1.37)	27 (5.0)	0.89 (0.57-1.39)
High-mid disadvantage	30 (5.3)	0.51 (0.30-0.83)	31 (5.5)	0.96 (0.59-1.54)	41 (8.2)	1.00 (0.70-1.62)	44 (8.5)	1.22 (0.76-2.00)
Highest disadvantage	34 (6.2)	0.59 (0.35-0.95) †	20 (3.6)	0.62 (0.36-1.05) †	31 (5.6)	0.70 (0.46-1.11)	40 (8.1)	1.20 (0.72-1.89)

*Referent category

† Trend $p < 0.05$

‡Adjusted for ethnicity, age, gender, body mass index, birth weight, blood pressure and categories of isolation and disadvantage.

Abbreviations: ACR, albumin:creatinine; AOR, adjusted odds ratio; ARIA, Accessibility and Remoteness Index of Australia; BMI, body mass index; SD, standard deviation; SEIFA, Socio-Economic Indexes For Areas.

Definitions: Systolic hypertension, systolic blood pressure > 90th percentile; diastolic hypertension, diastolic blood pressure > 90th percentile; albuminuria, albumin:creatinine (ACR) ≥ 3.4 mg/mmol; obesity, BMI ≥ 2 SD; least isolation, ARIA score 0-1.1; low-mid isolation, ARIA score 1.2-2.4; high-mid isolation,

ARIA score 2.5-4.9; highest isolation, ARIA score 5.0-14.0; least disadvantage, SEIFA score 989-1103; low-mid disadvantage, SEIFA score 960-988; high-mid disadvantage, SEIFA score 836-959; highest disadvantage, SEIFA score 680-835.

Table 4.4.3: Association between cardiovascular risk factors

Cardiovascular risk factors	Systolic hypertension AOR (95% CI)‡	Diastolic hypertension AOR (95% CI)‡	Albuminuria AOR (95% CI)‡	Obesity AOR (95% CI)‡Ψ
Systolic BP centiles				
≤50th*	-	1.00	1.00	1.00
51st-90th	-	5.36 (3.18-9.02)	0.98 (0.70-1.38)	3.65 (2.36-5.66)
>90th	-	29.11 16.59-51.09)†	0.55 (0.25-1.22)	15.41(9.32-25.49)†
Diastolic BP centiles				
≤50th*	1.00	-	1.00	1.00
51st-90th	3.95 (2.65-5.87)	-	0.65 (0.44-0.95)	3.01 (2.05-4.43)
>90th	54.80 (34.0-88.0)†	-	0.73(0.35-1.53)†	8.75 (5.31-14.44)†
Albuminuria (ACR mg/mmol)				
<3.4	1.00	1.00	-	1.00
≥3.4	0.61 (0.27-1.35)	1.06 (0.52-2.16)	-	0.45 (0.18-1.11)
BMI SD quartiles				
-4.8 to -0.8	1.00	1.00	1.00	-
-0.7 to 0.1	2.50 (1.14-5.49)	1.88 (0.95-3.74)	0.67 (0.44-1.04)	-
0.2 to 0.7	4.26 (2.04-8.91)	2.67 (1.40-5.12)	0.65 (0.42-1.02)	-
0.8 to 6.9	12.37(6.17-24.78)†	5.05 (2.74-9.32)†	0.51(0.32-0.82)†	-

* Referent category
† Trend $p < 0.05$
‡ Adjusted for ethnicity, age, gender, body mass index, birth weight, blood pressure and categories of isolation, disadvantage and region.
Abbreviations: ACR, albumin:creatinine; AOR, adjusted odds ratio; BMI, body mass index; BP, blood pressure; SD, standard deviation.
Definitions: Systolic hypertension, systolic blood pressure > 90th percentile; diastolic hypertension, diastolic blood pressure > 90th percentile; albuminuria, albumin:creatinine (ACR) ≥ 3.4 mg/mmol; obesity, BMI ≥ 2 SD.

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CHAPTER 5: DIAGNOSTIC ACCURACY OF URINE DIPSTICKS FOR DETECTING ALBUMINURIA IN INDIGENOUS AND NON-INDIGENOUS CHILDREN IN A COMMUNITY SETTING

5.1: Abstract

Background Albuminuria predicts cardiovascular and end-stage kidney disease in Indigenous populations. Early detection in Indigenous children may identify those who could benefit from early treatment. Community-based detection of albuminuria needs to be performed using a reliable, inexpensive and widely available test, such as a proteinuria dipstick. Dipstick accuracy for detecting albuminuria in a community setting has not been evaluated.

Aims We assessed the accuracy of Multistix 10 SG dipsticks to detect baseline albuminuria and predict for persistent albuminuria at two-year follow up in a population-based cohort of Australian Aboriginal and non-Aboriginal elementary school-aged children. Variability in the accuracy of dipsticks in subgroups of higher risk children was analysed using the relative diagnostic odds ratio (RDOR).

Using Multistix 10 SG dipsticks, index test positive cases were defined as greater than or equal to 0.30g/L (1+) proteinuria, and index test negative cases as less than 0.30g/L (negative or trace) proteinuria. Referent test positive cases were defined as spot albumin:creatinine (ACR) greater than or equal to 3.4 mg/mmoL, and referent test negative cases as ACR less than 3.4 mg/mmoL.

Results 2266 children (55.1% Aboriginal, 51.0% male, mean age 8.9 years) were enrolled. At two-year follow-up, 1432 (63.0%) children were retested (54.0% Aboriginal, 50.5% male, mean age 10.5 years). Prevalence of baseline albuminuria was 7.3%, and persistent albuminuria was 1.5%. Dipsticks had a sensitivity of 62%, specificity of 97% at baseline. In predicting persistent albuminuria, sensitivity was 75%, specificity 93%. Accuracy did not vary with ethnicity, gender or body mass index. Accuracy was less in younger children (4.0-7.9 years), and in those with haematuria.

Conclusions The performance characteristics of Multistix dipsticks make them suitable for albuminuria detection in Aboriginal and other higher risk groups of children. More than two-thirds of children detected at a single test will have transient rather than persistent albuminuria. Multistix dipsticks are particularly useful for detecting children who will have persistent albuminuria.

5.2: Introduction

Morbidity and premature mortality from chronic disease are a much greater burden for Indigenous than for non-Indigenous populations. Cardiovascular disease is the leading cause of premature death in Indigenous people from 45 years of age, which is 20 years earlier than in non-Indigenous populations. Death rates from cardiovascular disease in Indigenous people are two to tenfold higher than in non-Indigenous people ([1]). In 2005, there were record numbers of new cases of kidney failure patients entering dialysis or transplant programs across the world ([2]) ([3]), and Indigenous people were vastly over represented in this group ([4]) (2). Indigenous Australians are, on average, eight times more likely than non-Indigenous Australians of the same age and sex to develop end-stage kidney disease ([5]). End-stage kidney disease occurs almost 10 years earlier in Indigenous people, at a median age of 51 versus 60 years in non-Indigenous people ([6]). With treatments now available to reduce the rate of progression of these chronic diseases, health interest groups have called for governments to commence national programs for the early identification of those at greatest risk (2) (3) ([7]) ([8]).

Albuminuria presents early in Indigenous populations with high background rates of cardiovascular and kidney disease ([9]) ([10]). Even after adjustment for other traditional risk factors, albuminuria strongly predicts all-cause mortality, cardiovascular morbidity, cardiovascular mortality and end-stage kidney disease (8). In Australian Aboriginal communities, an albuminuria secondary prevention program has demonstrated significant reduction in mortality and morbidity from cardiovascular and chronic kidney disease ([11]). A program aimed at early detection and monitoring of albuminuria in Aboriginal children should provide an inexpensive, portable, point-of-care diagnostic service given the remoteness of many Indigenous communities ([12]). Urine dipsticks for spot albumin:creatinine have been shown to be accurate in diagnosing albuminuria ([13]), however their cost prohibits them as a screening instrument ([14]). Inexpensive urine dipsticks for proteinuria could serve this purpose, but there are currently no data on their accuracy to detect albuminuria in children in community-based settings.

The aims of our study were to evaluate the accuracy of Multistix proteinuria dipsticks for detecting albuminuria in Aboriginal children, to determine whether accuracy varies with subject characteristics, and to determine the predictive ability of dipsticks to identify those children with persistent albuminuria over two years of follow-up, who are at greatest risk of chronic disease.

5.3: Methods

The Standards for Reporting of Diagnostic Accuracy (STARD) checklist was adopted for the reporting of these data ([15]).

Selection of participants: Government-run elementary schools were approached for testing from urban, coastal, rural and remote locations across the state of New South Wales. This state has the highest Aboriginal population in Australia ([16]). Non-government schools (private and denominational) have very few Aboriginal enrolments, and were not considered for recruitment. To maximise power and generalisability, consecutive sampling was done to obtain equal numbers of Aboriginal and non-Aboriginal children, males and females, and in similar proportions from urban, coastal, rural and remote areas. All elementary schools in remote communities were approached and other areas were sampled if greater than twenty Aboriginal children in the relevant age range attended.

Aboriginal status was determined using the Australian Bureau of Statistics best practice recommendations, asking the Standard Indigenous Question on the consent form "Is your child of Aboriginal or Torres Strait Islander origin?" (16). All Aboriginal children in the participating elementary schools were offered testing. Non-Aboriginal children were matched for gender and age from the same class. We aimed to recruit equal numbers of boys and girls, Aboriginal and non-Aboriginal children, and equal numbers of children from each 12 month age group.

Approval was obtained from the Ethics Committees of the Children's Hospital at Westmead, the University of Sydney, New South Wales Area Health Services and the New South Wales Department of Education and Training. Informed consent was obtained for each child and, in accordance with NHMRC Guidelines for Ethical Conduct in Aboriginal and Torres Strait Islander Research ([17]), data was collected onto a standardised form and de-identified for storage and analysis before being returned to each community after the study visit. Permission to publish data was also obtained from each community.

Multistix proteinuria dipstick (index test): The Multistix-10 SG reagent dipstick costs approximately $ US 0.80 per stick, and detects urinary protein by the protein-error-of-indicators principle ([18]). At a constant pH, the development of any green colour is due to the presence of protein. The colour is then read spectrophotometrically by the Bayer Clinitek 50 urinalysis machine within four proteinuria categories: negative/trace (protein <0.30 g/L), 1+ (protein 0.30 g/L), 2+ (protein 1g/L), 3+ (protein 3 g/L) and 4+ (≥ 20 g/L) ([19]).

Spot urine albumin:creatinine dipstick (referent test): The Clinitek dipstick detects urine albumin and creatinine concentrations, at an approximate cost of $ US 3.80 per stick (14). Urine albumin is measured by dye-binding of albumin with sulphonephthalein dye resulting in a colour shift at a constant pH. This is referred to as the protein error of pH indicators. Urine creatinine complexes with copper and the copper-creatinine complex reacts with hydroperoxide and a dye to produce a colour change. Colour changes are then read spectrophotometrically by the Bayer Clinitek 50 urinalysis machine as a ratio of albumin:creatinine concentration within three categories: normal/no pathological albuminuria (ACR < 3.4 mg/mmoL), microalbuminuria (ACR 3.4-33.9 mg/mmoL) and macroalbuminuria (ACR > 33.9 mg/mmoL). This method has been validated as a referent standard test for verifying albuminuria in children ([20]).

Sample collection and handling: All children were given verbal instructions by the study nurse about the method of urine collection. Parent/carer assistance was provided in the younger age group. A morning clean catch urine specimen was collected from each child into a sterile container and analysed immediately with the index and referent tests by the nurse at the survey site. Girls older than eight years who were found to have haematuria were questioned about menses, and if this was present, collection was performed at another time.

Definition of positivity: All samples were tested according to the manufacturer's instructions by the index and referent tests at the same time point by the study nurse

([21]). A computer print-out of results at the following cut-offs was produced by the urinalysis machine at the end of each test. Kidney Disease Outcomes Quality Initiative (KDOQI) recommendations for cut-off values were used to define proteinuria, albuminuria and haematuria (20). Test positive cases were defined as greater than or equal to 0.30g/L proteinuria (Multistix dipstick 1+), and test negative cases were defined as less than 0.30g/L proteinuria (Multistix dipstick negative or trace). Referent test positive cases were defined as albumin:creatinine (ACR) greater than or equal to 3.4 mg/mmoL at initial testing (baseline albuminuria present), and referent test negative cases as ACR less than 3.4 mg/mmoL at initial testing (no baseline albuminuria).

Because albuminuria can be a benign transient phenomenon in the paediatric age group ([22]), we also assessed test performance of Multistix dipsticks in predicting persistent albuminuria, with referent test positive cases classified as those children with spot urine ACR greater than or equal to 3.4 mg/mmoL at both initial testing and two-year follow-up. Referent test negative cases were then defined as ACR less than 3.4 mg/mmoL at both initial testing and two year follow-up, or a combination of positive and negative tests at baseline and follow-up (none or transient albuminuria). Haematuria was defined as greater than or equal to 25 RBC/uL (Multistix dipstick 1+) at baseline testing, and no haematuria as less than 25 RBC/uL (Multistix dipstick negative or trace) at baseline testing. Albuminuria in association with suspected urinary tract infection (leucocytes and/or nitrites on Multistix dipstick testing), and macroalbuminuria (ACR greater than or equal to 34 mg/mmoL) were found in less than 1% of children. These children were included in the analyses.

Precision of the referent and index tests was assessed by the study nurse using quality control calibration materials at each screening centre prior to testing any samples. All positive and negative control calibrations fell within the acceptable cut-offs designated by the manufacturer ([23]), based upon national and international precision goals derived from biological variation and international concensus data on performance criteria ([24]) ([25]).

Statistical Methods:

For albuminuria at baseline and for persistent albuminuria, comparisons between the index and referent tests for the entire cohort and sub-groups were represented in two-by-two contingency tables. Indicators of test performance derived from these tables were sensitivity, specificity and relative diagnostic odds ratios with 95% confidence intervals. The diagnostic odds ratio is the ratio of the odds of albuminuria in proteinuria dipstick positives relative to the odds of albuminuria in proteinuria dipstick negatives. The value of the diagnostic odds ratio ranges from zero to infinity, with higher values indicating better discriminatory test performance ([26]). The relative diagnostic odds ratio compares this ratio of test performance in at risk sub-groups (Aboriginal children, males, older children, children with haematuria and normal weight and overweight/ obese children) against the presumed lower risk referent group (non-Aboriginal children, females, younger children, children without haematuria and underweight children) with 95% confidence intervals for proportions calculated using exact binomial methods. Age was divided into tertiles, with younger children defined as 4.0 to 7.7 years at baseline, and 6.0 to 9.4 years at two year follow-up. Older children were defined as 7.8 to 14.8 years at baseline, and 9.5 to 15.4 at two year follow-up. Underweight was defined as body mass index (BMI) standard deviation (SD) less than 1, overweight and obese as BMI SD greater than 1, and normal weight as BMI SD –1 to +1 ([27]). Statistical analyses were completed using SAS ([28]) and SPSS ([29]).

5.4: Results

Participants: From February 2002 to September 2004, 2266 healthy children were enrolled from 37 elementary schools across New South Wales, and included 1248 (55.1%) Aboriginal children. Overall, 51.0% were male, and the mean age was 8.9 years (± 2.0 years). There were proportionally more Aboriginal children in the youngest age tertile (37.4% versus 28.5%, X^2 20.01, 2df, $p < 0.0001$), with no significant differences between Aboriginal and non-Aboriginal children for gender and BMI categories. There were significantly more Aboriginal children with haematuria at baseline testing compared with non-Aboriginal children (7.1% versus 3.6%, X^2 12.31, 1df, p=0.002). A more detailed description of subject characteristics at baseline is available elsewhere ([30]).At two-year follow-up from March 2004 to December 2006, there were 1432 (63.0%) children available for re-testing; 773 (54.0%) were Aboriginal, 50.4% were male, and the mean age was 10.5 years (± 2.0 years). When comparing the overall group at follow-up to those children lost-to-follow-up, there were significantly more children from the oldest age group who were lost-to-follow-up compared with younger age groups ($p<0.0001$). There were no differences in ethnicity, gender or BMI SD between children at follow-up and those children lost-to-follow-up.

Figures 5.4.1 and **5.4.2** show the process of patient recruitment, order of tests and the crude test results. Of the 2266 children enrolled at baseline, 53 (2.3%) children would not provide a urine sample on the test day and 78 children (3.4%) did not receive an ACR due to equipment failure at the study site. Of the 1432 (63%) children available for two-year follow-up testing, 74 (5.2%) did not have both an initial Multistix dipstick test and initial ACR, and 17 (1.2%) did not receive a follow-up ACR.

The prevalence of baseline albuminuria was 7.3%, and persistent albuminuria (at two year follow-up) was 1.5%. There was no significant difference in the prevalence of baseline or persistent albuminuria between Aboriginal and non-Aboriginal children (8.1% versus 6.5%, X^2 1.97, 1df, p=0.16 and 1.4% versus 1.5%, X^2 0.03, 1 df, p=0.86). Baseline and follow-up data for the cohort have been described in more detail elsewhere (30).

Accuracy for baseline albuminuria: **Table 5.4.1** shows the accuracy of the Multistix dipstick for the diagnosis of albuminuria at baseline. Overall sensitivity was 62% (55-70%) and overall specificity was 97% (96-98%). There were no significant differences in the accuracy of Multistix dipsticks in detecting baseline albuminuria in Aboriginal compared with non-Aboriginal children (RDOR 0.97, 95% CI 0.42-2.25, p=0.62), females compared with males (RDOR 0.53, 95% CI 0.23-1.23, p=0.56), and overweight/obese and normal weight children compared with underweight children (RDOR<0.5), although there was a trend towards lower accuracy with increasing BMI (trend p=0.01). Multistix dipsticks were more accurate in diagnosing baseline albuminuria in older children (8.0-15.0 years) compared with the youngest age tertile (4.0-7.9 years), RDOR>4, trend p=0.01, and in children with haematuria compared to children without haematuria (RDOR 7.51, 95% CI 2.27-24.82, p=0.01).

Accuracy for persistent albuminuria: **Table 5.4.2** shows the results of Multistix dipsticks in predicting persistent albuminuria. Overall sensitivity was 75% (53-89%), and overall specificity was 93% (92-94%). There were no significant differences in the accuracy of Multistix dipsticks in predicting persistent albuminuria in Aboriginal compared with non-Aboriginal children (RDOR 0.81, 95% CI 0.10-6.60, p=0.82), females compared with males (RDOR 1.05, 95% CI 0.13-8.55, p=0.36), older children (8.0-15.0 years) compared with the youngest age tertile (4.0-7.9 years), RDOR<0.9, trend p=0.31, and overweight/obese and normal weight children compared with underweight children, although there was a trend towards better accuracy with increasing BMI (RDOR>1.6, trend p=0.01). Multistix dipsticks were substantially less accurate in predicting persistent albuminuria in children with haematuria compared to children without haematuria (RDOR 0.03, 95% CI 0.001-0.93, p=0.02).

Absolute accuracy: **Table 5.4.3** shows the absolute accuracy per 1000 children tested using ACR and Multistix dipsticks. Out of a hypothetical cohort of 1000 children, with 73 having baseline albuminuria (a prevalence of 7.3%), Multistix dipsticks would correctly identify 45 children with albuminuria at the expense of 20 false positives and 28 false

negatives. At two-year follow-up, 15 children will have persistent albuminuria. Multistix dipsticks would identify 11, at the expense of 60 false positives (including those with transient albuminuria) and 4 false negatives.

5.5: Discussion

In this first large-scale community-based cohort study of the test performance of urine dipsticks in detection of albuminuria in Indigenous children, we have shown that Multistix dipsticks are accurate for cross-sectional detection, and more accurate for detecting children with persistent albuminuria. We have also shown that accuracy does not vary with ethnicity. Multistix dipsticks are a cheap, convenient and portable diagnostic method for albuminuria detection.

Many of the design features of this study suggest the results are valid and generalisable. This was a prospective evaluation of dipstick urinalysis testing for albuminuria in a consecutive series of children from a clinically relevant and generalisable population. The children tested at follow-up were similar in demographic characteristics to the original population-based cohort at baseline. Many previous studies have used diseased cases with controls for dipstick evaluation, which leads to an over estimate of the true test performance (spectrum bias) ([31]) ([32]) ([33]). There was no verification bias because all children received both the dipstick and referent tests. The study nurse was not blinded to the results of either test; however interpretation of each was quantitative. The nurse had no information on the previous referent test result at the follow-up testing, and therefore, no significant effect from unblinding is expected ([34]) ([35]). A single referent test was used, and there was no time interval or treatment between the dipstick and baseline referent tests. We accept that because some of the samples were collected at a time other than first-morning, some of the proteinuria detected will be orthostatic, particularly for the adolescents. Persistence of proteinuria in these children at first-morning follow-up testing would make orthostatic proteinuria less likely.

Twenty four-hour proteinuria is conventionally considered the gold standard for diagnosing albuminuria, but this method is unreliable due to collection errors and inconvenience ([36]) ([37]). These problems are compounded in the paediatric population and in highly mobile, remote populations with limited access to health services, as seen in Aboriginal communities (12). For these reasons we used spot urine ACR as our

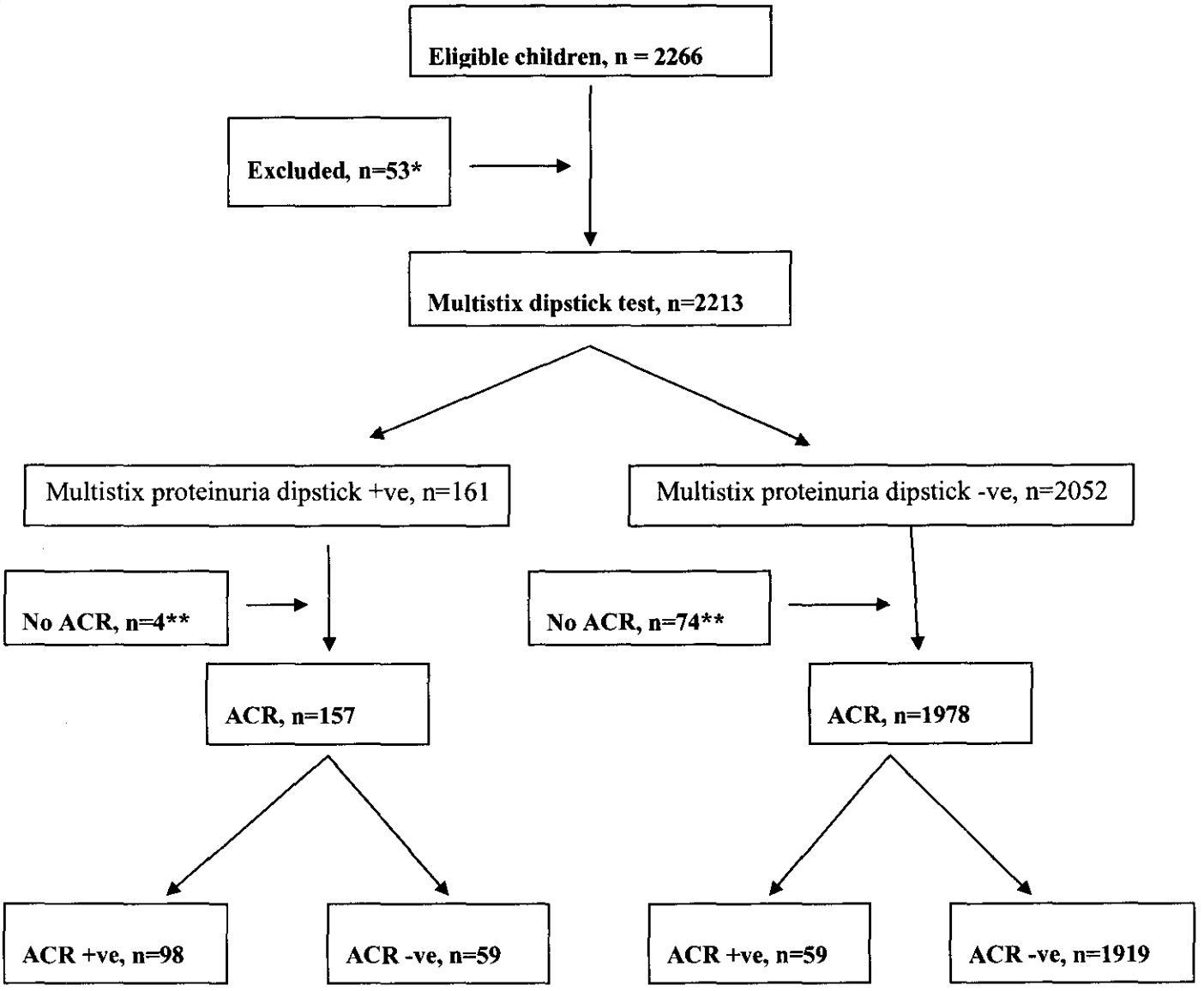
surrogate referent test in this study. Replacement of 24-hour urine protein by spot urine ACR for follow-up diagnostic purposes has been justified by substantial agreement between the two methods for all age groups with a wide spectrum of renal function, and over the entire proteinuria range ([38]) ([39]) ([40]) (13). There was no specific treatment for any child with albuminuria found at baseline before the follow-up referent test was performed, and we used predefined, standard cut-off values for index and referent test positives and negatives (20).

We found that test performance varied with a number of subject characteristics. Multistix dipsticks were more accurate in detecting albuminuria in older children at baseline, due to a low sensitivity, but this finding was not confirmed for the more important outcome of persistent albuminuria. However, this result may have been influenced by the disproportionate losses at follow-up between the oldest age group and the younger age groups. Dipsticks were less accurate for detecting albuminuria in children with higher BMI at baseline, but more accurate in predicting persistent albuminuria in children with higher BMI at follow-up (again due to differences in sensitivity). Dipsticks were better at detection of albuminuria in the presence of haematuria, although haematuria worsened the prediction of persistent albuminuria at follow-up. These inconsistent findings in children with haematuria need to be interpreted cautiously. There are no comparable data from other studies, and these results are largely influenced by the continuity correction of 0.5, resulting in unstable estimates.

Long-term prospective studies are needed to determine the risk of ESKD in Aboriginal children and young adults with albuminuria, and how the risks change in association with other co-morbidities such as hypertension and diabetes. Compared with the cost of relocation, dialysis and other treatments for sustaining an Aboriginal Australian on dialysis for an average survival period of 20 years ([41]), it may eventuate that health dollars and much psychological suffering could be saved through a primary prevention program, as has been proposed for other high risk populations ([42]) ([43]). Point-of-care testing for community risk assessment is culturally appropriate and widely accepted within Aboriginal communities (12) (11). Our results support the use of Multistix

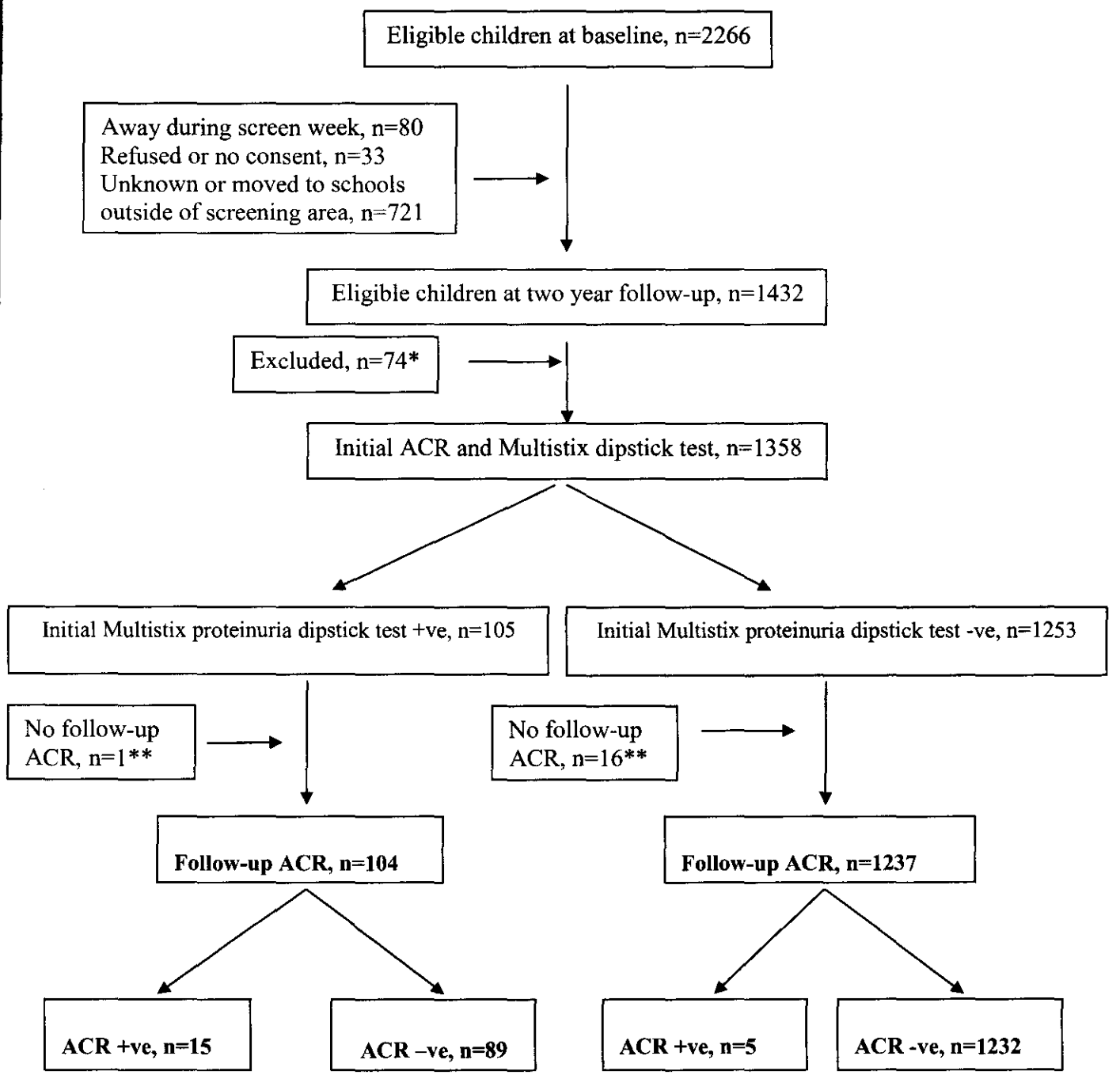
dipsticks as a reliable, low-cost diagnostic instrument for albuminuria in Aboriginal and other children.

Figure 5.4.1: Flow diagram of recruitment and testing of children at baseline



*Child refused to void
**Equipment failure

Figure 5.4.2: Flow diagram of recruitment and testing of children at two-year follow-up.



*No initial Multistix dipstick test, and/or no initial ACR
** Equipment failure

Table 5.4.1: Accuracy of Multistix dipsticks in detecting albuminuria at baseline (prevalence 7.3%)

cteristics	**Prevalence albuminuria %**	**TP**	**TN**	**FP**	**FN**	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**	**Relative Diagnostic Odds Ratio (95% CI)**
e cohort	7.3	98	1919	59	59	62 (55-70)	97 (96-98)	NA
icity								
e-Aboriginal*	6.5	42	877	31	21	67 (54-77)	97 (95-98)	1.00
riginal	8.1	56	1042	28	38	60 (49-69)	97 (96-98)	0.97 (0.42-2.25)
der								
le*	5.4	38	1014	24	21	64 (52-75)	98 (97-98)	1.00
male	9.4	60	905	35	38	61 (51-70)	96 (95-97)	0.53 (0.23-1.23)
rtiles (years)								
-7.9*	6.0	12	633	14	29	29 (19-40)	98 (97-99)	**1.00**
9-9.9	7.2	37	658	20	16	70 (59-79)	97 (96-98)	**4.07 (1.31-12.68)**
0-15.0	8.8	49	628	25	14	78 (68-85)	98 (97-99)	**4.70 (1.54-14.36)**
r sediment								
maturia absent*	6.8	83	1823	58	55	60 (52-68)	97 (96-98)	**1.00**
maturia present	16.5	15	95	1	4	79 (57-91)	99 (94-100)	**7.51 (2.27-24.82)**
SD								
derweight*	11.1	31	299	13	8	80 (68-88)	96 (94-97)	1.00
mal weight	7.2	57	1237	36	42	58 (50-65)	97 (96-98)	0.52 (0.18-1.53)
erweight/obese	4.8	10	364	10	9	53 (34-69)	97 (96-98)	0.45 (0.11-1.92)

*Referent group
Abbreviations: BMI, body mass index; FN, false negative; FP, false positive; SD, standard deviation; TN, true negative; TP, true positive.
Definitions: Albuminuria, ACR $\geq$ 3.4 mg/mmol; haematuria $\geq$ 25 RBC per HPF (1+); underweight, BMI SD < -1; normal weight, BMI SD -1 to +1; overweight and obese, BMI SD > +1.

Table 5.4.2: Accuracy of Multistix dipsticks in detecting persistent albuminuria (prevalence 1.5%)

Characteristics	Prevalence albuminuria %	TP	TN	FP	FN	Sensitivity % (95% CI)	Specificity % (95% CI)	Relative Diagnostic Odds Ratio (95% CI)
Whole cohort	1.5	15	1232	89	5	75 (53-89)	93 (92-94)	NA
Ethnicity								
Non-Aboriginal*	1.4	7	576	43	2	78 (45-94)	93 (91-95)	1.00
Aboriginal	1.5	8	656	46	3	73 (43-90)	93 (91-95)	0.81 (0.10-6.60)
Gender								
Male*	1.5	7	640	35	3	70 (40-89)	95 (93-96)	1.00
Female	1.5	8	592	54	2	80 (49-94)	92 (89-94)	1.05 (0.13-8.55)
Age tertiles (years)								
6.0-9.4*	0.9	3	412	20	1	75 (31-95)	95 (94-96)	1.00
9.5-11.4	1.1	4	415	31	1	80 (38-96)	93 (92-94)	0.87 (0.04-21.23)
11.5-15.4	2.4	8	405	38	3	73 (44-90)	91 (90-92)	0.46 (0.03-6.74)
Other sediment[†Ψ]								
Haematuria absent*	1.5	15	1190	77	4	78 (56-90)	94 (93-95)	**1.00**
Haematuria present	1.9	0	41	12	1	25 (21-27)	77 (76-79)	**0.03 (0.001-0.93)**
BMI SD								
Underweight*	1.8	3	204	21	1	70 (31-93)	91 (90-92)	1.00
Normal weight	1.9	11	740	53	4	72 (48-88)	93 (93-94)	1.59 (0.17-15.15)
Overweight/obese	0.3	1	281	15	0	75 (20-97)	95 (94-96)	2.46 (0.10-108.09)

*Referent group
[†]0.5 was added to all cells to obtain an estimate that deals with the zero cell.
[Ψ] Haematuria absent or present at baseline
Abbreviations: BMI, body mass index; FN, false negative; FP, false positive; TN, true negative; TP, true positive; SD, standard deviation.
Definitions: Albuminuria, ACR $\geq$ 3.4 mg/mmol; haematuria $\geq$ 25 RBC per HPF (1+); underweight, BMI SD < -1;normal weight, BMI SD -1 to +1;overweight and obese, BMI SD>+1.

Table 5.4.3: Absolute accuracy per 1000 children screened by Multistix dipsticks (assuming a point prevalence of 7.3% for albuminuria at baseline and 1.5% for persistent albuminuria)

Target condition	Number detected with ACR	Number detected with dipstick	Difference	Number excluded with ACR	Number excluded with dipstick	Difference
Baseline albuminuria	73	45	28	927	899	28
Persistent albuminuria	15	11	4	985	916	69

Abbreviations: ACR, albumin:creatinine

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CHAPTER 6: RISK FOR CHRONIC KIDNEY DISEASE IN AUSTRALIAN INDIGENOUS AND NON-INDIGENOUS CHILDREN: A POPULATION-BASED FOLLOW-UP STUDY

6.1: Abstract

Background Aboriginal Australians have a nine-fold increased risk for end-stage renal disease. There is no information on the natural history and risk for chronic kidney disease (CKD) in Aboriginal and non-Aboriginal children.

Study Design Using a prospective study design, we aimed to determine the prevalence of persistent markers and risk factors for CKD in Australian Aboriginal and non-Aboriginal children, and whether Aboriginal children are at increased risk for persistent markers of CKD after accounting for socio-demographic differences.

Setting and Participants Children were enrolled from elementary schools throughout New South Wales.

Predictors, Outcomes, Measurements Urine analysis, height, weight, blood pressure, birth weight and socio-demographic status were measured at baseline and two-year follow up. Albuminuria was defined as ACR $\geq$ 3.4 mg/mmol, haematuria as $\geq$25 RBC/uL ($\geq$1+), obesity as BMI $\geq$ 2 standard deviations, and systolic and diastolic hypertension as blood pressure >90th percentile.

Results 2266 children (55.1% Aboriginal, 51.0% male, mean age 8.9 years $\pm$ SD 2.0 years) were enrolled at baseline. Early markers and predictors of CKD at baseline were frequent: haematuria (5.5%), albuminuria (7.3%), obesity (7.1%), systolic hypertension (7.2%) and diastolic hypertension (5.8%). There were 1432 children (63%) available for re-testing at two-year follow up (54.0% Aboriginal, 50.5% male, mean age 10.5 years $\pm$ SD 2.0 years). Persistent obesity (5.3%) was frequent, but persistent markers of CKD were infrequent (systolic hypertension 1.1%, diastolic hypertension 0.2%, haematuria 1.1% and albuminuria 1.5%). While there were more Aboriginal than non-Aboriginal children with baseline haematuria (7.1% versus 3.6%, p=0.001), after adjustment for age, gender, birth weight and socio-demographic status, there was no increased risk for persistent haematuria, albuminuria, obesity or hypertension in Aboriginal children.

Limitations Persistent markers of CKD were much less frequent than anticipated, which may have affected study power. The group lost at follow-up were older children which may have biased the results.

Conclusions Overall only 20% of children found to have markers of early CKD have persistent abnormalities (diastolic and systolic hypertension, albuminuria, hematuria) 2 years later, equivalent to a population point prevalence of 1-2% in children with a mean age of 10 years. Aboriginal children have higher rates of baseline and transient haematuria, but no increased risk

for persistent markers of CKD, suggesting that adolescence and young adulthood is a critical time for preventative strategies.

6.2: Introduction

Morbidity and premature mortality from chronic kidney disease are a much greater burden for Indigenous than for non-Indigenous populations. Native American Indians have a twice higher incidence of end-stage kidney disease compared with non-Indigenous Americans, although the disparity is almost four times higher for South Western Native Americans ([1]). Canadian Indians have two-and-a-half times higher incidence of end-stage kidney disease compared with the total Canadian population ([2]). Aboriginal and Torres Strait Islander Australians (hereafter referred to as Aboriginal) are nine times more likely than non-Aboriginal Australians to develop end-stage kidney disease ([3]). End-stage kidney disease occurs almost 10 years earlier in Australian Aboriginal people, at a median age of 51 versus 60 years in non-Aboriginal Australians ([4]).

A much larger proportion of end-stage kidney disease in Aboriginal Australians is attributed to diabetic nephropathy (47%) as compared to non-Aboriginal Australians (17%), but little is known about the early causal pathways leading to these health disparities (4). Most research to date has documented disease end-points in high-risk communities (1,2,4), with few studies measuring or adjusting for environmental risk factors that will also affect non-Indigenous people, such as lack of access to health care, remote and lower standards of living ([5]). There are several studies from high risk Indigenous communities describing the prevalence of early chronic kidney disease markers ([6]) ([7]) ([8]), but there are no population-based studies that document the persistence of early chronic kidney disease markers in Indigenous children compared with non-Indigenous children.

Our aim was to determine the prevalence of persistent markers and risk factors for chronic kidney disease (CKD) in Australian Aboriginal and non-Aboriginal children, and whether Aboriginal children are at increased risk for chronic kidney disease after accounting for socio-demographic differences.

6.3: Methods

Selection of participants: Government-run elementary schools were approached for testing from urban, coastal, rural and remote locations across the state of New South Wales. This state has the highest Aboriginal population in Australia, and Aboriginal people within New South Wales have three times the risk of ESKD than non-Aboriginals (3). To maximise power, sampling was done to obtain equal numbers of Aboriginal and non-Aboriginal children, and in similar proportions from urban, coastal, rural and remote areas. All elementary schools in remote communities were approached and other areas were sampled if greater than twenty Aboriginal children in the relevant age range attended. We attempted to enrol all Aboriginal students from participating schools, and to age and gender match them with a random sample of non-Aboriginal students.

Aboriginal status was determined using the Australian Bureau of Statistics best practice recommendations, asking the Standard Indigenous Question on the consent form "Is your child of Aboriginal or Torres Strait Islander origin?" ([9]) . All Aboriginal children in the participating elementary schools were offered testing for height, weight, blood pressure and urinary dipstick abnormalities. We aimed to recruit equal numbers of boys and girls, Aboriginal and non-Aboriginal children, and approximately equal numbers of children from each 12 month age group.

Aboriginal community engagement: Consultation with local Aboriginal Medical Services and consent from community leaders was undertaken prior to commencement of the study. Approval was obtained from the Ethics Committees of the Children's Hospital at Westmead, the University of Sydney, New South Wales Area Health Services and the New South Wales Department of Education and Training. Informed consent was obtained for each child and, in accordance with NHMRC Guidelines for Ethical Conduct in Aboriginal and Torres Strait Islander Research ([10]), data were collected onto a standardised form and de-identified for storage and analysis before being returned to each community after the study visit. Permission to publish data was also obtained from each community.

Measurement of markers of chronic kidney disease: Markers and predictors of CKD measured were haematuria, albuminuria, systolic and diastolic hypertension, and obesity. Risk factors known and thought to be associated with the development of these markers in Aboriginal and

non-Aboriginal people were also recorded, including age, gender, growth parameters, birth weight and environmental health determinants: measures of geographic isolation and social disadvantage.

A morning clean catch specimen was collected from each child, with dipstick analysis for haematuria, and albuminuria performed at the survey site on fresh specimens using a Bayer Clinitek 50 machine ([11]). Leukocytes and nitrites were also recorded for later adjustment for abnormalities of presumed urinary tract infection. Girls older than eight years who were found to have haematuria were questioned about menses, and if appropriate, collection was performed at another time. According to Kidney Disease Outcomes Quality Initiative (K/DOQI) definitions, haematuria was defined as greater than or equal to dipstick 1+ (equivalent to 25 RBC per microlitre 1+), and albuminuria as albumin:creatinine (ACR) greater than or equal to 3.4 mg/mmol ([12]).

Birth weight was provided by the parent/carer by recall or from the child's health record. Height was measured in stocking feet to the nearest 0.1cm with a SECA 220 telescopic portable stadiometer ([13]) that was calibrated between screening visits. Weight was measured in stocking feet and in school uniform on digital scales to the nearest 0.01 kg. Body mass index (BMI) standard deviation z-scores (SD) were calculated using an age and sex-adjusted program ([14]). Blood pressure was measured on the right arm with the child sitting, using an aneroid sphygmomanometer and the largest cuff to encircle the arm and cover at least three-quarters of the length of the upper arm ([15]). In children less than 13 years, diastolic pressure was measured at the point of muffling (Korotkov 4). For older children the point of disappearance was used (Korotkov 5) ([16]). Systolic and diastolic hypertensions were defined as blood pressure greater than the 90th percentile for age and gender.

Follow-up measurements were performed two years after baseline testing at the elementary or new high school on all available children, and the frequency of persistent chronic kidney disease markers (markers detected at baseline and follow-up) was ascertained.

Standardisation of urban, coastal, rural and remote locality was made using the Accessibility and Remoteness Index of Australia (ARIA++), with each subject given an Index score according to their postcode of residence ([17]). Using geographical information system capabilities,

distances, services and population density for each locality are converted to a continuous variable with values ranging from zero for high accessibility, to 18 for extreme remoteness. ARIA++ values for this NSW study ranged from 0 to 14, and for categorical analysis the scores were grouped into quartiles. Isolation categories (and ARIA++ score range) used were: Least isolation (0-1.1), low-mid isolation (1.2-2.4), high-mid isolation (2.5-4.9) and highest isolation (5.0-14.0).

To determine the level of social and economic well being of areas studied, the Socio-Economic Indexes for Areas 2001 ([18]) Index of Disadvantage was applied to subjects at the level of collection district of residence. This is the smallest geographic area for which the Index is available, and includes approximately 200 households. The Index of Disadvantage is a continuous score, and is based upon characteristics such as low income, lower level of education, high unemployment, and unskilled jobs. It has been standardised to a mean of 1000, and a standard deviation of 100 across all collection districts in Australia, ie, 95% of scores are between 800 and 1200. Higher scores indicate higher socio-economic status (SES) and least disadvantage. For categorical analysis, the scores were grouped into quartiles: Highest disadvantage (680-835), high-mid disadvantage (836-960), low-mid disadvantage (961-988) and least disadvantage (989-1103).

Data analysis: Comparisons between children followed-up and those with only baseline data were made by ethnicity, gender, age groups, birth weight quartiles, body mass index SD quartiles, and categories of isolation and disadvantage using the chi-squared test. Odds ratios and relative risks for baseline and persistent markers of CKD in Aboriginal compared with non-Aboriginal children (referent group) were determined using logistic regression with 95% confidence intervals. The relative risk between other potential predictors (gender, age, birth weight, body mass index, geographic isolation and social disadvantage) and persistent markers of CKD was determined using logistic regression with 95% confidence intervals. The presumed lowest risk category of each predictor was used as the referent group. The mantel extension test was used to determine linear trends across categories. Analyses were adjusted for age, gender, body mass index SD, birth weight, categories of isolation and disadvantage and school using a random effects model.

Tests for interactions between ethnicity, gender, age, categories of isolation, disadvantage and other significant variables in the final model were performed. Significance was set at a p-value of <0.05 for main effects and interactions. Statistical analysis was completed using SAS ([19]) and SPSS software ([20]).

We planned to collect data at baseline from 1000 Aboriginal and 1000 non-Aboriginal children which were sufficient to detect differences in prevalence of markers of CKD between the two groups of 2.9 versus 1.1%, 5.5 versus 2.9%, 8.2 versus 6.0%, and 9.4 versus 7.2% at 80% power for haematuria, albuminuria, obesity and systolic hypertension respectively. We anticipated a 60-70% follow-up rate which would allow detection of differences in persistent markers between Aboriginal and non-Aboriginal children of 3.8 versus 1.5%, 3.2 versus 1.0%, 7.6 versus 5.3% and 7.3 versus 5.0% at 80% power for haematuria, albuminuria, obesity and systolic hypertension respectively.

6.4: Results

From February 2001 to June 2004, 2266 children were enrolled from 37 primary schools across New South Wales. Participation rates for both Aboriginal and non-Aboriginal students were 85-100%. There were 1248 (55.1%) Aboriginal children, 51% were male, and the mean age was 8.9 years (± SD 2.0 years). A more detailed description of baseline characteristics has been reported elsewhere ([21]).

*Characteristics at two-year follow-up (**table 6.4.1**)* At two-year follow-up from March 2004 to December 2006, there were 1432 (63.0%) children available for re-testing; 773 (54.0%) were Aboriginal, 50.4% were male, and the mean age was 10.5 years (± SD 2.0 years). When comparing the overall group at follow-up to those children with only baseline data, there were significantly more children from the older age groups and from urban areas who had no follow-up data (p<0.0001). There were no differences in ethnicity, gender, birth weight, BMI SD and social disadvantage category between children at follow-up and those children with only baseline data.

*Prevalence of baseline markers of chronic kidney disease in Aboriginal and non-Aboriginal children (**table 6.4.2**)* Obesity (7.1%) and early markers of CKD at baseline were common: haematuria (5.5%), albuminuria (7.3%), systolic hypertension (7.2%) and diastolic hypertension (5.8%). There was no increased risk for these early markers of chronic kidney disease in Aboriginal compared with non-Aboriginal children, with the exception of haematuria, 7.1% versus 3.6% (adjusted odds ratio 2.25, 95% CI 1.37-3.69, p=0.001).

*Prevalence of persistent markers of chronic kidney disease in Aboriginal and non-Aboriginal children (**table 6.4.2**)* At two-year follow-up, the overall prevalence of persistent markers of CKD was much less frequent. Haematuria (1.1%), albuminuria (1.5%), systolic hypertension (1.0%) and diastolic hypertension (0.1%). Obesity remained relatively frequent at 5.3%. There was no increased risk for any persistent marker in Aboriginal when compared to non-Aboriginal children.

*Physiological and socio-demographic predictors for persistent markers of chronic kidney disease (**table 6.4.3**)* There was no increased risk of any persistent marker of CKD for females compared with males, nor for lower birth weight compared with higher birth weight. Risk of

persistent haematuria increased with increasing age (trend p=0.004). Increasing age was not a risk factor for any other persistent marker of CKD. Risk of persistent systolic hypertension increased with increasing BMI SD (trend p= 0.001), and the highest BMI SD quartile was significantly associated with risk for persistent systolic hypertension (adjusted RR 5.78, 95% CI 1.24-26.73, p=0.03). There was a decreasing risk for persistent systolic hypertension and persistent albuminuria with increasing social disadvantage (both trend p<0.02). The quartile with the highest social disadvantage had a significantly lower risk of persistent albuminuria (adjusted RR 0.17, 95% CI 0.05-0.57, p=0.004). There were no physiological or socio-geographic predictors of persistent obesity found.

There were no interactions found between environmental health determinants of geographic isolation and social disadvantage and ethnicity, age, gender or other covariates in any model.

6.5: Discussion

This is the first population-based cohort study describing the natural history of early CKD in Indigenous children that includes a non-Indigenous comparator group, and measures and adjusts for social disadvantage and geographic isolation. Non-Indigenous comparators are essential in deciding the level of increased risk for Indigenous children against the background population rates, and measurement of socio-demographic factors is important in adjusting for the potentially confounded relationship between health, isolated living and social disadvantage. In our prospective study of 2266 children, 50% of whom are Aboriginal, over two years of follow-up we have shown that persistent markers of CKD are infrequent, and there is no increased risk for persistent markers in Aboriginal children when compared to non-Aboriginal children, even after adjustment for social disadvantage and geographic isolation.

The follow up data showed that while baseline markers are frequent in Aboriginal and non-Aboriginal elementary school-aged children, most of these abnormalities are transient. At a single test, Aboriginal children have twice the risk of haematuria as non-Aboriginal children, but no increased risk for persistent haematuria. Other Australian Indigenous studies have a similarly high cross-sectional prevalence of haematuria and albuminuria in children ([22],6). These studies are from extremely disadvantaged communities with the highest rates of end-stage kidney and cardiovascular disease in the world. Without follow-up testing, or comparative data from a non-Indigenous group, the assumption is that these frequent one-off markers lead to the high states of disease seen in adulthood, and that ethnically-based biological effects are causative ([23]). Our baseline results show that almost 80% of baseline urinary abnormalities are transient. Semi-quantitative single estimations of urinary blood and protein in children vary according to posture, illness, exercise and time of day ([24]). A twice higher rate of transient haematuria may reflect the higher incidence of transient disease seen in Indigenous children, such as post-infectious glomerulonephritis (8). The persistence of these markers are infrequent in our cohort, and do not occur more frequently in Aboriginal children.

Obesity is a frequent predictor of CKD in these children, although no more so in Aboriginal children. Rates of persistent obesity of 5.3% found in our study are similar to national rates of obesity in Australian elementary school-aged children of 6% ([25]). Increasing BMI was predictive of persistent systolic hypertension, and these children are at risk for early onset diabetes,

cardiovascular disease ([26], [27]) and most likely chronic kidney disease. They will be closely followed-up over the final two-years of the study.

There was a decreasing risk for persistent systolic hypertension and persistent albuminuria in the most disadvantaged children. These associations seem contradictory to other studies ([5],[28],[29]). Our study sampled children in areas where Aboriginal children reside, in areas of greatest disadvantage for the state of New South Wales ([30]). Therefore, the highest socio-economic quartile in our cohort (indicating lesser disadvantage) correlates with mid-range socio-economic categories in other comparative studies ([31],[32]). Our findings are consistent with these studies showing risk factors for chronic disease following a bell-shaped curve across different socio-economic environments – lowest risk occurs at either extreme of socio-economic status, with highest risk occurring in mid-range socio-economic categories.

A potential limitation of our study was the 37% lost-to-follow-up, but we have shown that this group is not significantly different to the children followed-up, apart from their age and geographic location. There were proportionally more children followed-up in the remote areas, when compared to urban areas. This reflects the close relationships originally established between Area Health Workers in remote communities, and shows a higher degree of disengagement among urban children. The higher proportion of older children lost-to-follow-up results from older children absent or no longer at school, and we accept that they are likely to be the children most at risk of chronic disease. We are attempting to address these differences at our final four year follow-up. Even though these issues are a concern in terms of sampling bias, the regression analyses for risk of CKD markers in Aboriginal children were adjusted for age and location in an attempt to account for these imbalances.

The study was adequately powered to find relatively small differences in risk for persistent markers of CKD if they existed between Aboriginal and non-Aboriginal children. However, persistent markers were much less frequent than anticipated which may have affected the study power. Measurement of the main predictor of risk, Aboriginal status, was performed using best practise recommendations (9). Measurement of social disadvantage and geographic isolation was made using standardised systems that have been applied reliably in geographically and ethnically similar population-based samples ([33],3). We accept that unmeasured confounding from individual-level socio-economic factors remains as a study bias ([34]). With further data

collection, multi-level analyses could be used to identify, measure and correct for ecological bias when spatially-aggregated measures are applied to individual data, an approach we will use for future follow-up ([35]). Parentally recalled birth weight has been shown as a reliable proxy for recorded birth weight in population-based research ([36]).

Albuminuria is the strongest predictor of death, cardiovascular disease and end-stage renal disease in Aboriginal adults which is why it was used in our study ([37],[38]). Spot ACR, at the cut-off used in this study, has good receiver operator curve characteristics for detecting pathological albuminuria ([39]). Blood pressure was measured using appropriate cuff sizes, with repeat measures performed in hypertensive children. A 90th percentile cut-off was used to classify hypertension because we anticipated insufficient outcomes to perform analyses at a 95th percentile cut-off. Obesity was determined using BMI standard deviations, which has been validated for use in this age group of children ([40]), and our prevalence of obesity is comparable to national surveys (25). Measurement of outcomes such as central obesity, blood lipid, glucose and insulin levels would have been desirable for evidence of pre-diabetes and the metabolic syndrome ([41]), however measuring all possible risk factors was beyond the practicalities of such a large school-based screening study. Painful and embarrassing procedures would have been counter-productive to the current success of our follow-up recruitment rates.

Within New South Wales, there is no increased risk for persistent markers of CKD in Aboriginal children compared with non-Aboriginal children, and the three-fold increased risk for CKD experienced by Aboriginal adults in New South Wales and nine-fold increased risk for all Indigenous Australians is not yet established in this age group. This suggests that adolescence and young adulthood are likely to be critical times for preventative strategies. These results also show that a single measurement of markers of CKD in children is misleading as almost 80% of all abnormalities are transient. Increasing BMI is the strongest risk factor for persistent hypertension and persistent haematuria in these children, and obesity remains the most concerning and persistent predictor of CKD in this age group. This suggests overweight and obesity in children should be addressed from an elementary school age. These results provide useful information for primary health care practitioners, paediatricians, nephrologists, policy-makers and families.

We look forward to reporting the four-year follow-up of these children and adolescents. This study highlights a need for long-term prospective observational studies of risk for CKD in Aboriginal and non-Aboriginal young adults over a range of socio-geographic areas. We plan to follow this cohort of children for a further eight years into young adulthood ([42]).

Table 6.4.1: Characteristics of children at baseline stratified by follow-up status

Variable	Follow-up data available (n = 1432)	%	Baseline data only available (n=834)	%	p
Ethnicity					
Aboriginal	773	54.0	475	57.0	0.18
Non-Aboriginal	659	46.0	359	43.0	
Gender					
Male	723	50.5	432	51.8	0.54
Female	709	49.5	402	48.2	
Age groups (years)					
4-5.9	144	10.1	67	8.0	<0.0001
6-6.9	192	13.4	89	10.7	
7-7.9	237	16.6	93	11.2	
8-8.9	221	15.4	112	13.4	
9-9.9	231	16.1	120	14.4	
10-10.9	196	13.7	165	19.8	
11-14.8	211	14.7	188	22.5	
Birth weight quartiles (g)*					
412-2920	259	25.6	86	21.1	0.31
2921-3316	255	25.2	107	26.2	
3317-3685	246	24.4	111	27.2	
3686-5272	250	24.8	104	29.4	
BMI SD quartiles*					
-4.8 to -0.8	355	25.0	205	24.9	0.96
-0.7 to 0.1	352	24.8	210	25.5	
0.2 to 0.7	363	25.5	203	24.6	
0.8 to 6.9	352	24.8	206	25.0	
Geographic Isolation (ARIA score)					
Least isolation (0-1.1)	358	25.0	252	30.2	<0.0001
Low-mid isolation (1.2-2.4)	453	31.6	186	22.3	
High-mid isolation (2.5-4.9)	261	18.2	260	31.2	
Highest isolation (5.0-14.0)	360	25.2	136	16.3	
Social Disadvantage (SEIFA score)					
Least disadvantage (989-1103)	342	23.9	206	24.7	0.34
Low-mid disadvantage (960-988)	385	26.9	200	24.0	
High-mid disadvantage (836-960)	370	25.8	206	24.7	
Highest disadvantage (680-835)	335	23.4	222	26.6	

Abbreviations: ARIA, Accessibility and Remoteness Index of Australia; BMI, body mass index; SD, standard deviation; SEIFA, Socio-Economic Indexes For Areas.
*Indicates where data does not equal column totals.

Table 6.4.2: Prevalence of baseline and persistent markers of chronic kidney disease in Aboriginal and non-Aboriginal children at two year follow-up

	Baseline Markers				Persistent Markers			
Marker of chronic kidney disease	**Overall**	**Non-Aboriginal (referent category)**	**Aboriginal**	**p**	**Overall**	**Non-Aboriginal (referent category)**	**Aboriginal**	**p**
Hematuria (dipstick ≥ 25 RBC per HPF)								
Events (%)	122 (5.5)	36 (3.6)	86 (7.1)		15 (1.1)	6 (0.9)	9 (1.2)	
Adjusted OR [Ψ]		1.00	2.25 (1.37-3.69)	0.001		1.00	1.36 (0.29-6.36)	0.88
Albuminuria (ACR ≥ 3.4 mg/mmol)								
Events (%)	157 (7.3)	63 (6.5)	94 (8.1)		20 (1.5)	9 (1.4)	11 (1.5)	
Adjusted OR[Ψ]		1.00	1.37 (0.93-2.01)	0.11		1.00	1.80 (0.70-4.65)	0.60
Obesity (BMI ≥ 2 SD)								
Events (%)	145 (7.1)	63 (6.7)	82 (7.4)		74 (5.3)	33 (5.1)	41 (5.4)	
Adjusted OR[Ψ]		1.00	1.10 (0.76-1.44)	0.52		1.00	1.09 (0.67-1.78)	0.20
Systolic hypertension (SBP > 90th centile)								
Events (%)	162 (7.2)	67 (6.7)	95 (7.7)		14 (1.0)	6 (0.9)	8 (1.1)	
Adjusted OR[Ψ]		1.00	1.22 (0.87-1.57)	0.34		1.00	1.25 (0.45-3.47)	0.66
Diastolic hypertension (DBP > 90th centile)								
Events (%)	131 (5.8)	62 (6.2)	69 (5.6)		2 (0.1)	1 (0.2)	1 (0.1)	
Adjusted OR[Ψ]		1.00	0.94 (0.57-1.31)	0.57		1.00	-	-

[Ψ]Adjusted where appropriate for age, gender, birth weight, BMI SD, systolic BP, diastolic BP, isolation category and disadvantage category.
Abbreviations: ACR, albumin:creatinine; BMI, body mass index; DBP, diastolic blood pressure; HPF, high power field; OR, odds ratio; RBC, red blood cell; SBP, systolic blood pressure; SD, standard deviation.

Definitions: Persistent marker = marker found at both baseline and follow-up.

Table 6.4.3: Physiological and environmental predictors of persistent markers of chronic kidney disease

	Haematuria (dipstick ≥ 25 RBC per HPF)		Albuminuria (ACR ≥ 3.4 mg/mmol)		Obesity (BMI ≥ 2 SD)		Systolic Hypertension (SBP > 90th centile)	
Predictor	**N (%)**	**AOR$^{\Psi}$ (95% CI)**	**N (%)**	**AOR$^{\Psi}$ (95% CI)**	**N (%)**	**AOR$^{\Psi}$ (95% CI)**	**N (%)**	**AOR$^{\Psi}$ (95% CI)**
Gender								
Male*	5 (0.7)	1.00	10 (1.5)	1.00	41 (5.8)	1.00	6 (0.8)	1.00
Female	10 (1.5)	1.37 (0.50-3.79)	10 (1.5)	1.12 (0.47-2.70)	33 (4.7)	0.89 (0.51-1.55)	8 (1.1)	1.18 (0.31-4.45)
Age tertiles (years)								
4.0-7.9*	3 (0.7)	1.00	4 (0.9)	1.00	25 (5.3)	1.00	4 (0.9)	1.00
8.0-9.9	5 (1.1)	1.50 (0.21-10.50)	5 (1.1)	1.07 (0.17-5.66)	25 (5.3)	1.00 (0.51-1.96)	4 (0.9)	0.92 (0.28-3.08)
10.0-15.0	7 (1.5)	3.21 (0.62-16.56)†	11 (2.4)	2.95 (0.76-11.48)	24 (5.1)	1.00 (0.55-2.26)	6 (1.3)	1.36 (0.50-3.71)
Birth weight								
> 2500g *	11 (1.2)	1.00	19 (2.1)	1.00	48 (5.1)	1.00	9 (1.0)	1.00
≤ 2500g	0 (0)§	0.43 (0.02-7.31)	0 (0)§	0.24 (0.01-4.05)	6 (5.9)	1.17 (0.50-2.85)	1 (1.0)	1.03 (0.13-8.21)
BMI SD quartiles								
-4.8 to -0.8*	4 (1.2)	1.00	6 (1.8)	1.00	0 (0)	1.00	1 (0.3)	1.00
-0.7 to 0.1	1 (0.3)	0.44 (0.04-5.27)	6 (1.8)	0.83 (0.24-2.96)	0 (0)	-	2 (0.6)	1.45 (0.01-3.94)
0.2 to 0.7	6 (1.7)	1.81 (0.25-13.10)	7 (2.1)	1.31 (0.31-5.57)	0 (0)	-	4 (1.1)	2.35 (0.31-5.90)
0.8 to 6.9	4 (1.2)	1.00 (0.89-3.59)	1 (0.3)	0.15 (0.01-2.05)	74 (5.3)	-	7 (2.0)	**5.78 (1.24-26.73)**†
Isolation								
Least isolation*	1 (0.3)	1.00	7 (2.1)	1.00	22 (6.2)	1.00	1 (0.3)	1.00
Low-mid isolation	6 (1.4)	1.77 (0.16-19.18)	5 (1.1)	0.20 (0.05-0.87)	27 (6.0)	0.81 (0.27-2.42)	10 (2.2)	4.00 (0.81-19.77)
High-mid isolation	6 (2.3)	5.90 (0.74-47.32)	4 (1.6)	0.49 (0.11-2.24)	6 (2.4)	0.35 (0.11-1.09)	2 (0.8)	2.20 (0.19-25.40)
Highest isolation	2 (0.6)	2.42 (0.22-26.58)	4 (1.3)	0.44 (0.11-1.82)	19 (5.4)	0.60 (0.17-2.13)	1 (0.3)	0.95 (0.07-4.62)
Social disadvantage								
Least disadvantage*	2 (0.6)	1.00	7 (2.1)	1.00	20 (5.9)	1.00	7 (2.1)	1.00
Low-mid disadvantage	6 (1.7)	1.79 (0.06-9.65)	6 (1.6)	0.95 (0.26-3.40)	20 (5.2)	0.75 (0.34-1.67)	4 (1.0)	0.66 (0.25-1.72)
High-mid disadvantage	4 (1.1)	1.19 (0.30-4.73)	5 (1.6)	0.95 (0.08-2.43)	13 (3.7)	0.62 (0.22-1.71)	2 (0.6)	0.32 (0.09-1.08)
Highest disadvantage	3 (0.9)	1.00 (0.21-4.69)	2 (0.6)	**0.17 (0.05-0.57)**	21 (6.4)	1.38 (0.26-3.67)	1 (0.3)	0.16 (0.05-2.52)†

* Referent group

† Trend $p < 0.05$

§ 0.5 added to cells to allow analysis

ψ Adjusted where appropriate for ethnicity, age, gender, birth weight, BMI SD, systolic BP, diastolic BP, isolation category and disadvantage category.

Abbreviations: ACR, albumin:creatinine; ARIA, Accessibility and Remoteness Index of Australia; AOR, adjusted odds ratio; BMI, body mass index; HPF, high power field; RBC, red blood cell; SBP, systolic blood pressure; SD, standard deviation; SEIFA, Socio-Economic Indexes For Areas.

Definitions: Persistent marker = marker found at both baseline and follow-up; least isolation, ARIA score 0-1.1; low-mid isolation, ARIA score 1.2-2.4; high-mid isolation, ARIA score 2.5-4.9; highest isolation, ARIA score 5.0-14.0; least disadvantage, SEIFA score 989-1103; low-mid disadvantage, SEIFA score 960-988; high-mid disadvantage, SEIFA score 836-959; highest disadvantage, SEIFA score 680-835.

6.6: References

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CHAPTER 7: PERSISTENT MARKERS OF CHRONIC KIDNEY DISEASE IN AUSTRALIAN INDIGENOUS AND NON-INDIGENOUS CHILDREN: A SIX-YEAR FOLLOW-UP STUDY

7.1: Abstract

Background: Indigenous people world-wide have a two to fifty-fold increased risk for end-stage kidney disease (ESKD), but there is a paucity of data on the natural history and risk for early chronic kidney disease (CKD) in Indigenous populations.

Methods: Aboriginal and non-Aboriginal children were enrolled from primary schools throughout New South Wales, Australia. Urinalysis, height, weight, blood pressure, birth weight and socio-demographic status were measured at baseline and two and four-year follow up. Markers of CKD were albuminuria, ACR $\geq$ 3.4 mg/mmol, haematuria $\geq$25 RBC/uL ($\geq$1+), obesity, BMI $\geq$ 2 standard deviations, and systolic and diastolic hypertension, blood pressure $\geq 95^{th}$ percentile.

Findings: 2266 children (55.1% Aboriginal, 51.0% male, mean age 8.9 years $\pm$ SD 2.0 years) were enrolled at baseline. There were 1432 children (63%) re-tested at two-year follow up, and 1506 children (67%) re-tested at four year follow-up. Prevalence of baseline CKD markers was frequent (5-7%), but most abnormalities at baseline were transient. Besides persistent obesity (5.0%), persistence of CKD markers at final follow-up were infrequent; haematuria (1.9%), albuminuria (2.4%), systolic hypertension (1.5%) and diastolic hypertension (0.2%). There was no difference in prevalence of persistent markers of CKD between Aboriginal and non-Aboriginal children.

Interpretation: Over four year follow-up, Australian Indigenous children have no increased risk for early evidence of CKD. More than 70% of baseline markers are transient, with persistent markers being uncommon. Our findings suggest the increased risk for ESKD in Indigenous adults is not manifest until young adulthood, and so is potentially preventable.

7.2: Introduction

Chronic and end-stage kidney disease (ESKD) is of epidemic proportions in Indigenous populations. Native American Indians, Canadian Indians and Indigenous Australians have a two to nine times increased risk of end-stage kidney disease when compared to their non-Indigenous countrymen, although the disparity is much greater within subgroups of Indigenous populations ([1])([2])([3]). ESKD occurs up to 10 years earlier in Indigenous people, who also have an excess of co-morbid illness resulting in decreased survival. Particularly among diabetic patients, Indigenous people have an accelerated course to ESKD once CKD occurs. Indigenous people are less likely to be listed for transplantation, and wait longer for grafts, also resulting in poorer survival ([4]).

Little is known about the early causal pathways leading to these health disparities. Other studies have documented disease end-points in high-risk, geographically isolated, and disadvantaged communities (1,2,4), but have not accounted for the likely multi-determinant causes, including socio-demographic confounders. There are no studies describing the natural history of early chronic kidney disease markers in Indigenous children compared with non-Indigenous children. The aim of our study was to determine the prevalence of persistent markers of chronic kidney disease in Australian Aboriginal and non-Aboriginal children, and whether ethnicity, geographic remoteness and social disadvantage predict for persistent markers of chronic kidney disease.

7.3: Methods

Selection of participants: Government-run primary schools were approached for testing from urban, coastal, rural and remote locations in areas where Aboriginal people are known to live across the state of New South Wales. This state has the highest Aboriginal population in Australia. To maximise power, sampling was done to obtain equal numbers of Aboriginal and non-Aboriginal children, and in similar proportions from urban, coastal, rural and remote areas. All primary schools in remote communities were approached and other areas were sampled if greater than twenty Aboriginal children in the relevant age range attended. We attempted to enrol all Aboriginal students from participating schools, and to age and gender match them with a random sample of non-Aboriginal students. Participation rates for both Aboriginal and non-Aboriginal students from each school were 85-100%.

Aboriginal status was determined using the Australian Bureau of Statistics best practice recommendations, asking the Standard Indigenous Question on the consent form "Is your child of Aboriginal or Torres Strait Islander origin?" ([5]). All Aboriginal children in the participating primary schools were offered testing for height, weight, blood pressure and urinary dipstick abnormalities. We aimed to recruit equal numbers of boys and girls, Aboriginal and non-Aboriginal children, and approximately equal numbers of children from each 12 month age group.

Aboriginal community engagement: Consultation with local Aboriginal Medical Services and consent from community leaders was undertaken prior to commencement of the study. Approval was obtained from the Ethics Committees of the Children's Hospital at Westmead, the University of Sydney, New South Wales Area Health Services and the New South Wales Department of Education and Training. Informed consent was obtained for each child and, in accordance with NHMRC Guidelines for Ethical Conduct in Aboriginal and Torres Strait Islander Research ([6]), data were collected onto a standardised form and de-identified for storage and analysis before being returned to each community after the study visit. Permission to publish data was also obtained from each community.

Measurement of markers of chronic kidney disease: Markers of chronic kidney disease measured were haematuria, albuminuria, obesity and systolic and diastolic hypertension. Risk factors known and thought to be associated with the development of these markers in

Aboriginal and non-Aboriginal people were also recorded, including age, gender, growth parameters, birth weight and environmental health determinants: measures of geographic isolation and social disadvantage.

A morning clean catch specimen was collected from each child, with dipstick analysis for haematuria, and albuminuria performed at the survey site on fresh specimens using a Bayer Clinitek 50 machine ([7]). Leukocytes and nitrites were also recorded for later adjustment for abnormalities of presumed urinary tract infection. Girls older than eight years who were found to have haematuria were questioned about menses, and if appropriate, collection was performed at another time. According to Kidney Disease Outcomes Quality Initiative (K/DOQI) definitions, haematuria was defined as greater than or equal to 25 RBC per microlitre (1+), and albuminuria as albumin:creatinine (ACR) greater than or equal to 3.4 mg/mmol ([8]).

Birth weight was provided by the parent/carer by recall or from the child's health record. Height was measured in stocking feet to the nearest 0.1cm with a SECA 220 telescopic portable stadiometer ([9]) that was calibrated between screening visits. Weight was measured in stocking feet and in school uniform on digital scales to the nearest 0.01 kg. Body mass index (BMI) standard deviation z-scores (SD) were calculated using an age and sex-adjusted program ([10]). Blood pressure was measured on the right arm with the child sitting, using an aneroid sphygmomanometer and the largest cuff to encircle the arm and cover at least three-quarters of the length of the upper arm ([11]). In children less than 13 years, diastolic pressure was measured at the point of muffling (Korotkov 4). For older children the point of disappearance was used (Korotkov 5) ([12]). Systolic and diastolic hypertensions were defined as blood pressure greater than the 95th percentile for age and gender (12).

Follow-up measurements were performed two and four years after baseline testing at the primary or new high school on all available children, and the frequency of persistent chronic kidney disease markers (markers detected at baseline, at two-year and at four-year follow-up, or in children with only a baseline and final test, markers detected at both baseline and follow-up) was ascertained.

Standardisation of urban, coastal, rural and remote locality was made using the Accessibility and Remoteness Index of Australia (ARIA++), with each subject given an Index score according

to their postcode of residence ([13]). Using geographical information system (GIS) capabilities, distances, services and population density for each locality are converted to a continuous variable with values ranging from zero for high accessibility, to 18 for extreme remoteness ([14]). ARIA++ values for this NSW study ranged from 0 to 14, and for categorical analysis the scores were grouped into quartiles. Isolation categories (and ARIA++ score range) used were: Least isolation (0-1.1), low-mid isolation (1.2-2.4), high-mid isolation (2.5-4.9) and highest isolation (5.0-14.0).

To determine the level of social and economic well being of areas studied, the Socio-Economic Indexes for Areas 2001 ([15]) Index of Disadvantage was applied to subjects at the level of collection district of residence. This is the smallest geographic area for which the Index is available, and includes approximately 200 households. The Index of Disadvantage is a continuous score, and is based upon characteristics such as low income, lower level of education, high unemployment, and unskilled jobs. It has been standardised to a mean of 1000, and a standard deviation of 100 across all collection districts in Australia, ie, 95% of scores are between 800 and 1200. Higher scores indicate higher socio-economic status (SES) and least disadvantage. For categorical analysis, the scores were grouped into quartiles: Highest disadvantage (680-835), high-mid disadvantage (836-960), low-mid disadvantage (961-988) and least disadvantage (989-1103).

Data analysis: Comparisons between Aboriginal and non-Aboriginal children at final follow-up were made by gender, age groups, birth weight quartiles, body mass index SD quartiles, and categories of isolation and disadvantage using the chi-squared test. Comparisons between children at final follow-up and children with only baseline or baseline and two-year follow-up were also made according to these categories using the chi-squared test. Adjusted relative risks for baseline and persistent markers of chronic kidney disease in Aboriginal compared with non-Aboriginal children (referent group) were determined using logistic regression, with 95% confidence intervals. Adjusted relative risks for other potential predictors of persistent chronic kidney disease markers (gender, age, birth weight, body mass index, geographic isolation and social disadvantage) were determined using logistic regression, with the lowest risk category for each predictor being the referent group, with 95% confidence intervals. Analyses were adjusted where appropriate for ethnicity, age, gender, body mass index SD, birth weight and categories

of isolation and disadvantage. Adjustment was made in all analyses for the effect of cluster sampling by school.

Tests for interactions between ethnicity, gender, age, categories of isolation, disadvantage and other significant variables in the final model were performed. Significance was set at a p-value of <0.05 for main effects and interactions. Statistical analysis was completed using SAS ([16]) and SPSS software ([17]).

We planned to collect data at baseline from 1000 Aboriginal and 1000 non-Aboriginal children which were sufficient to detect differences in prevalence of markers of chronic kidney disease between the two groups of 2.9 versus 1.1%, 5.5 versus 2.9%, 8.2 versus 6.0%, and 9.4 versus 7.2% at 80% power for haematuria, albuminuria, obesity and systolic hypertension respectively.

7.4: Results

*Baseline recruitment and follow-up (**figure 7.4.1**)* From February 2002 to June 2004, 2266 children were enrolled from 37 primary schools across New South Wales. There were 1248 (55.1%) Aboriginal children, 51% were male, and the mean age was 8.9 years (± SD 2.0 years). A more detailed description of baseline characteristics has been reported elsewhere ([18]). At two-year follow-up from March 2004 to December 2006, there were 1432 (63.0%) children available for re-testing; 773 (54.0%) were Aboriginal, 50.4% were male, and the mean age was 10.5 years (± SD 2.0 years). At four year follow-up from February 2006 to December 2007, 1506 children (66.5%) were re-tested, 1248 (55.1%) were Aboriginal, 51.0% were male, and the mean age was 13.3 years (± SD 3.2 years).

*Characteristics of the Aboriginal and non-Aboriginal children at final follow-up (**table 7.4.1**)* At final follow-up, there were proportionally more Aboriginal children in the youngest age groups and from the areas of highest isolation and disadvantage (all $p<0.0001$). This was also the case at baseline (18). There were more Aboriginal children with lower birth weights at final follow-up ($p=0.001$). When comparing the overall group at final follow-up to those children without a final follow-up, there were significantly more children from the older age groups who had no final follow-up ($p<0.0001$). There were no differences in ethnicity, gender, birth weight, BMI SD and isolation and disadvantage categories between children at final follow-up and those children without a final follow-up.

*Prevalence of baseline and persistent markers of chronic kidney disease in Aboriginal and non-Aboriginal children (**table 7.4.2**)* Markers of chronic kidney disease at baseline were frequent; haematuria (5.5%), albuminuria (7.3%), obesity (7.1%), systolic hypertension (3.0%) and diastolic hypertension (1.9%). There was no increased risk of baseline markers in Aboriginal children as compared with non-Aboriginal children, with the exception of haematuria, 7.1% versus 3.6% (adjusted OR 2.25, 95% CI 1.37-3.69, $p=0.001$).

At four-year follow-up, the overall prevalence of persistent markers was much less frequent; haematuria (1.9%), albuminuria (2.4%), obesity (5.0%), systolic hypertension (1.5%) and diastolic hypertension (0.2%). There was no increased risk for any persistent marker in Aboriginal children when compared to non-Aboriginal children, even after adjustment for geographic remoteness and social disadvantage.

*Physiological and environmental predictors of persistent markers of chronic kidney disease (**table 7.4.3**)*

Females had a four times increased risk of persistent haematuria when compared to males (adjusted RR 4.31, 95% CI 1.61-11.63, p=0.001). There was an increasing risk for persistent systolic hypertension with increasing BMI SD (trend p<0.0001), and the highest BMI SD quartile had a 19 times increased risk for persistent systolic hypertension when compared to the lowest BMI SD quartile (adjusted RR 19.05, 95% CI 2.54-43.09, p<0.0001). There were no other predictors for persistent markers of chronic kidney disease in these children, in particular, persistent markers were not predicted by lower birth weight, geographic remoteness or social disadvantage.

*Association between persistent markers of chronic kidney disease (**figure 7.4.2**)* This figure demonstrates the clustered association between persistent CKD markers, systolic hypertension, diastolic hypertension and obesity. All children with persistent diastolic hypertension had persistent obesity, and most had persistent systolic hypertension. Half the children with persistent systolic hypertension had persistent obesity.

There were no interactions found between environmental health determinants of geographic isolation and social disadvantage and ethnicity, age, gender or other covariates in any model.

7.5: Discussion

This study is the first population-based follow-up of risk for chronic disease in Indigenous children and youth. It also includes a non-Indigenous comparator group, and measures and adjusts for social disadvantage and geographic isolation. Non-Indigenous comparators are essential in eliciting the magnitude of increased risk for Indigenous children against the background population rates, and measurement of socio-demographic factors is important in adjusting for the potentially confounded relationship between health, isolated living and social disadvantage. This four-year follow-up study has shown that persistent markers of chronic kidney disease are infrequent, and there is no increased risk for persistent markers in Aboriginal children when compared to non-Aboriginal children, even after adjustment for social disadvantage and geographic isolation.

Our cross-sectional survey of this cohort showed that baseline markers of chronic disease were frequent in Aboriginal and non-Aboriginal elementary school-aged children, and that at a single test, Aboriginal children have twice the risk of haematuria as non-Aboriginal children. Other Indigenous studies have a similarly high cross-sectional prevalence of haematuria and albuminuria in children ([19]) ([20]). These studies are from extremely disadvantaged communities with high rates of end-stage kidney and cardiovascular disease. Without follow-up testing, or comparative data from a non-Indigenous group, the assumption has been that these frequent one-off markers lead to the high states of disease seen in adulthood, and that ethnically-based biological effects are causative ([21]). Our follow-up results show that more than 70% of baseline urinary and blood pressure abnormalities in Australian Aboriginal and non-Aboriginal children and youth are transient. Semi-quantitative single estimations of urinary blood and protein in children vary according to posture, illness, exercise and time of day ([22]). A higher rate of transient haematuria may reflect the higher incidence of transient disease seen in Indigenous children, such as post-infectious glomerulonephritis ([23]). The persistence of these markers are infrequent in our cohort, and do not occur more frequently in Aboriginal children. The finding that young females are more at risk of persistent haematuria is novel, and may be influenced by a growing percentage of menstruating females within the cohort, although we attempted to test these young women at a different time. Further investigation and longer-term follow-up of these children is underway to determine the underlying cause of this association.

Obesity is the only frequent persistent marker of chronic kidney disease in these children, although no more so in Aboriginal children. Persistent obesity of 5.0% found in our study is similar to national rates of obesity in Australian elementary school-aged children of 6% ([24]). Increasing BMI and persistent obesity were significantly associated with persistent systolic and diastolic hypertension. These children with clustering of CKD markers are also particularly at risk for early onset diabetes and cardiovascular disease ([25])([26]).

This follow-up study was challenging because of high rates of school absenteeism and family mobility, however our follow-up rate at four years improved upon our two-year follow-up rate due to better community liaison and engagement with Aboriginal Area Health Workers. The group lost to follow-up was not significantly different to those who we were able to follow, apart from a higher proportion of older children lost who were absent or no longer at school. This may have introduced ascertainment bias, but our follow-up rate of 70% is high, given the nature and setting of the cohort. The regression analyses for risk of chronic kidney disease markers in Aboriginal children were adjusted for age to account for these imbalances.

The study was adequately powered to find small differences in risk for markers of chronic kidney disease if they existed between Aboriginal and non-Aboriginal children. Measurement of the main predictor of risk, Aboriginal status, was performed using best practice recommendations (5). Measurement of social disadvantage and geographic isolation was made using standardised systems that have been applied reliably in geographically and ethnically similar population-based samples ([27]). We accept that unmeasured confounding from individual-level socio-economic factors remains as a study bias ([28]). With further data collection, multi-level analyses could be used to identify, measure and correct for ecological bias when spatially-aggregated measures are applied to individual data, an approach we will use for future follow-up ([29]). Parentally recalled birth weight has been shown as a reliable proxy for recorded birth weight in population-based research ([30]).

Have we omitted or misclassified outcome measures of early chronic kidney disease in these children? Albuminuria is the strongest predictor of death, cardiovascular disease and end-stage renal disease in Aboriginal adults ([31])([32]). Spot ACR, at the cut-off used in this study, has good receiver operator curve characteristics for detecting pathological albuminuria ([33]). Blood pressure was measured using appropriate cuff sizes, with repeat measures performed in

hypertensive children. Obesity was determined using BMI standard deviations, which has been validated for use in this age group of children ([34]), and our prevalence of obesity is comparable to national surveys (24). Measurement of outcomes such as central obesity, blood lipid, glucose and insulin levels would have been desirable for evidence of pre-diabetes and the metabolic syndrome ([35]), however measuring all possible risk factors was beyond the practicalities and community acceptance for such a large school-based screening study. Painful and embarrassing procedures would have been counter-productive to the success of our follow-up recruitment rates.

Within New South Wales, Australia, there is no increased risk for persistent markers of chronic kidney disease in Aboriginal children. This suggests that the increased risk for chronic kidney disease experienced by Aboriginal adults in Australia is not yet established in this age group, and social health determinants are likely to be influential in the later development of this increased risk. These results also show that a one-off measurement of markers of chronic kidney disease in children is misleading as most abnormalities are transient. Persistent obesity clusters closely with persistent hypertension, and its frequency suggests it should be addressed from a primary school age. These results provide useful information for primary health care practitioners, paediatricians, nephrologists, policy-makers and families.

Figure 7.4.1: Flow diagram of subjects and CKD markers at baseline, two-year and four-year follow-up

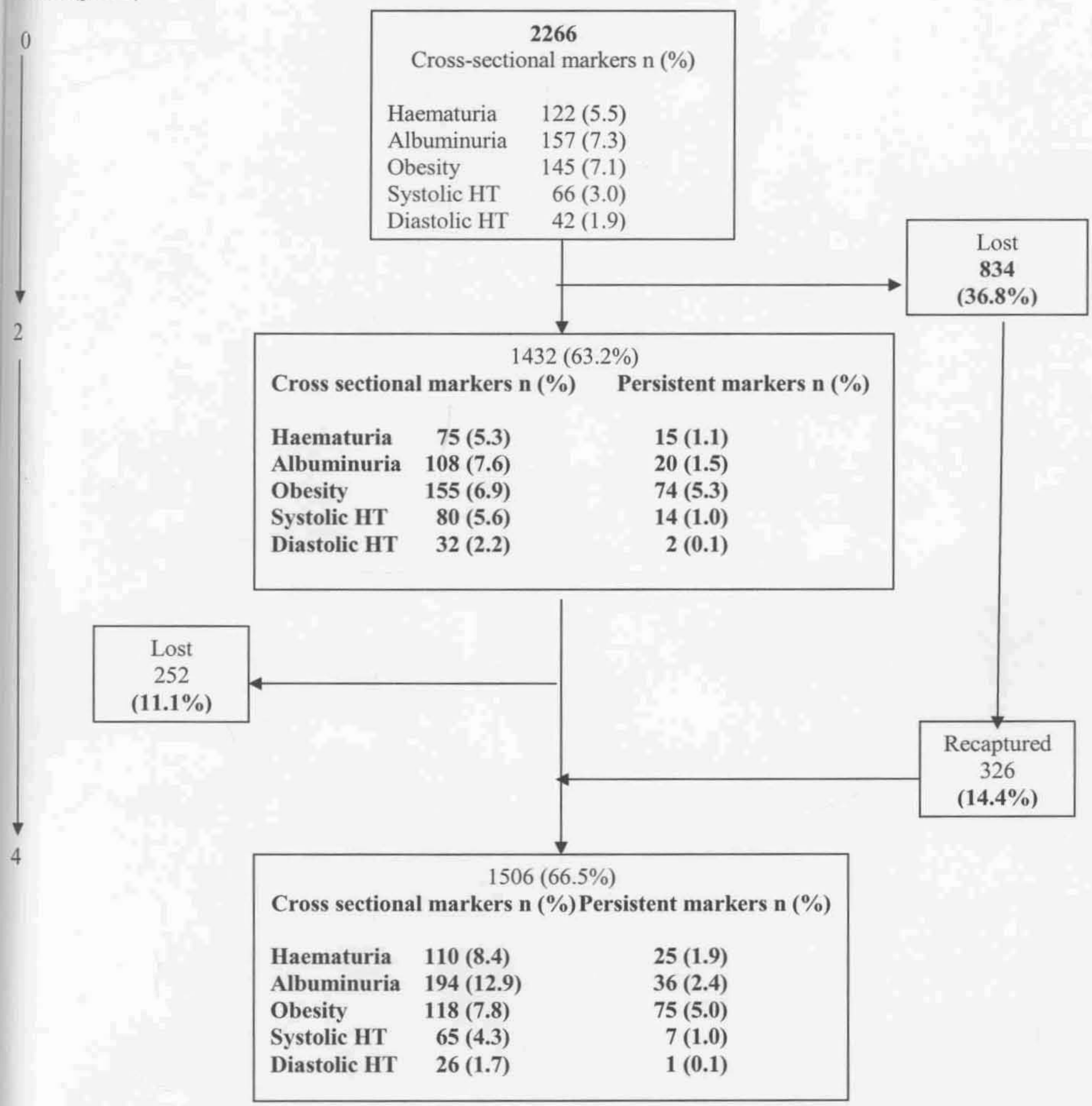


Table 7.4.1: Baseline characteristics of children at four-year follow-up stratified by ethnicity

Variable	All Subjects N=1506	%	Aboriginal N=807	%	Non-Aboriginal N=699	%	P
Gender							
Male	775	51.5	410	50.8	365	52.2	0.59
Female	731	48.5	397	49.2	334	47.8	
Age groups (years)							
4-5.9	211	9.3	95	11.8	47	6.7	<0.0001
6-6.9	281	12.4	119	14.7	83	11.9	
7-7.9	330	14.6	138	17.1	100	14.3	
8-8.9	336	14.8	134	16.6	101	14.4	
9-9.9	351	15.5	103	12.8	140	20.0	
10-10.9	361	15.9	104	12.9	112	16.0	
11-14.8	396	17.5	114	14.1	116	16.6	
Birth weight quartiles (g)*							
412-2920	258	25.0	138	30.1	120	20.9	0.001
2921-3316	266	25.8	120	26.2	146	25.4	
3317-3685	255	24.7	108	23.6	147	25.6	
3686-5272	253	24.5	92	20.1	161	28.0	
BMI SD quartiles*							
-4.8 to -0.8	357	23.9	207	25.8	150	21.8	0.30
-0.7 to 0.1	369	24.7	195	24.3	174	25.3	
0.2 to 0.7	390	26.2	200	24.9	190	27.6	
0.8 to 6.9	375	25.2	200	24.9	175	25.4	
Geographic Isolation (ARIA score)							
Least isolation (0-1.1)	410	27.2	206	25.5	204	29.2	<0.0001
Low-mid isolation (1.2-2.4)	424	28.2	220	27.3	204	29.2	
High-mid isolation (2.5-4.9)	329	21.8	149	18.5	180	25.8	
Highest isolation (5.0-14.0)	343	22.8	232	28.7	111	15.9	
Social Disadvantage (SEIFA score)							
Least disadvantage (989-1103)	548	24.2	273	21.9	275	27.0	<0.0001
Low-mid disadvantage (960-988)	585	25.8	287	23.0	298	29.3	
High-mid disadvantage (836-960)	576	25.4	334	26.8	242	23.8	
Highest disadvantage (680-835)	557	24.6	354	28.4	203	19.9	

Abbreviations: ARIA, Accessibility and Remoteness Index of Australia; BMI, body mass index; SD, standard deviation; SEIFA, Socio-Economic Indexes For Areas.
*Indicates where data does not equal column totals.

Table 7.4.2: Prevalence of baseline and persistent markers of chronic kidney disease in Aboriginal and non-Aboriginal children

	Baseline				Persistent			
nic kidney disease markers	**All**	**Non-Aboriginal (referent category)**	**Aboriginal**	**p**	**All**	**Non-Aboriginal (referent category)**	**Aboriginal**	**p**
aturia (≥ 25 RBC per HPF,1+)								
nts (%)	122	36 (3.6)	86 (7.1)		25	12 (2.0)	13 (1.8)	
usted RR Ψ	(5.5)	1.00	2.25 (1.37-3.69)*	0.001	(1.9)	1.00	0.92 (0.50-2.45)	0.81
minuria (ACR mg/mmol)								
nts (%)	157	63 (6.5)	94 (8.1)		36	17 (2.4)	19 (2.4)	
usted RRΨ	(7.3)	1.00	1.37 (0.93-2.01)	0.11	(2.4)	1.00	0.97 (0.53-2.01)	0.92
ity (BMI≥2SD)								
nts (%)	145	63 (6.7)	82 (7.4)		75	30 (4.3)	45 (5.6)	
usted RRΨ	(7.1)	1.00	1.10 (0.76-1.44)	0.52	(5.0)	1.00	1.32 (0.82-2.11)	0.25
lic hypertension (SBP>95th								
le)								
nts (%)	66	26 (2.6)	40 (3.2)		23	7 (1.0)	16 (2.0)	
usted RRΨ	(3.0)	1.00	1.26 (0.77-2.09)	0.36	(1.5)	1.00	2.00 (0.82-5.00)	0.12
tolic hypertension (DBP>95th								
ile)								
nts (%)	42	15 (1.5)	27 (2.2)		3	1 (0.1)	2 (0.2)	
usted RRΨ	(1.9)	1.00	1.47 (0.78-2.80)	0.23	(0.2)	1.00	1.74 (0.15-19.2)	0.65

* $p<0.05$

ΨAdjusted for age, gender, birth weight, BMI SD, systolic BP, diastolic BP, isolation category and disadvantage category.

Definitions: Persistent marker, marker found at both baseline and follow-up.

Abbreviations: ACR, albumin:creatinine; BMI, body mass index; DBP, diastolic blood pressure; RR, relative risk; SBP, systolic blood pressure; SD, standard deviation.

Table 7.4.3: Physiological and environmental predictors of persistent markers of chronic kidney disease

	Haematuria		Albuminuria		Obesity		Systolic Hypertension	
Predictor	**N (%)**	**ARR‡ (95% CI)**	**N (%)**	**ARR‡ (95% CI)**	**N (%)**	**ARR‡ (95% CI)**	**N (%)**	**ARR‡ (95% CI)**
Gender								
Male*	5 (0.7)	1.00	14 (1.8)	1.00	43 (5.5)	1.00	10 (1.3)	1.00
Female	20 (3.1)	4.31 (1.61-11.63)	22 (3.0)	1.69 (0.86-3.33)	32 (4.4)	0.78 (0.49-1.25)	13 (1.8)	1.39 (0.61-3.18)
Birth weight								
> 2500 *	15 (1.7)	1.00	24 (2.4)	1.00	46 (4.6)	1.00	19 (1.9)	1.00
≤ 2500g	2 (2.4)	1.39 (0.31-6.16)	2 (2.0)	0.83 (0.19-3.54)	6 (5.9)	1.32 (0.55-3.17)	1 (1.0)	0.52 (0.07-3.92)
BMI SD quartiles								
-4.8 to -0.8*	8 (2.6)	1.00	10 (2.8)	1.00	-	-	1 (0.3)	1.00
-0.7 to 0.1	3 (0.9)	0.34 (0.09-1.34)	11 (3.0)	1.07 (0.45-2.54)	-	-	0 (0.0)	0.49 (0.02-14.50)
0.2 to 0.7	8 (2.3)	0.89 (0.33-2.39)	8 (2.1)	0.73 (0.28-1.87)	-	-	3 (0.8)	2.77 (0.29-26.72)
0.8 to 6.9	6 (1.9)	0.71 (0.24-2.06)	7 (1.9)	0.66 (0.25-1.75)	-	-	19 (5.1)	19.05 (2.54-43.09)†
Isolation								
Least isolation*	9 (2.4)	1.00	12 (2.9)	1.00	19 (4.6)	1.00	7 (1.7)	1.00
Low-mid isolation	11 (2.6)	1.07 (0.44-2.61)	7 (1.7)	0.56 (0.22-1.43)	26 (6.1)	1.35 (0.73-2.48)	12 (2.8)	1.67 (0.65-4.28)
High-mid isolation	2 (1.1)	0.46 (0.10-2.16)	7 (2.1)	0.72 (0.28-1.86)	9 (2.7)	0.58 (0.26-1.32)	2 (0.6)	0.35 (0.07-1.70)
Highest isolation	3 (0.9)	0.36 (0.10-1.32)	10 (2.9)	0.99 (0.42-2.33)	21 (6.1)	1.35 (0.71-2.55)	23 (1.5)	0.34 (0.07-1.63)
Social disadvantage								
Least disadvantage*	8 (2.3)	1.00	9 (2.6)	1.00	19 (5.5)	1.00	7 (2.0)	1.00
Low-mid disadvantage	4 (0.9)	0.40 (0.12-1.33)	11 (2.6)	0.98 (0.40-2.40)	19 (4.4)	0.79 (0.41-1.53)	9 (2.1)	1.04 (0.38-2.81)
High-mid disadvantage	8 (2.7)	1.17 (0.43-3.16)	6 (1.6)	0.60 (0.21-1.70)	18 (4.8)	0.86 (0.44-1.66)	3 (0.8)	0.39 (0.10-1.51)
Highest disadvantage	5 (2.0)	0.86 (0.28-2.65)	10 (2.8)	1.08 (0.43-2.68)	19 (5.4)	0.97 (0.50-1.86)	4 (1.1)	0.55 (0.16-1.90)

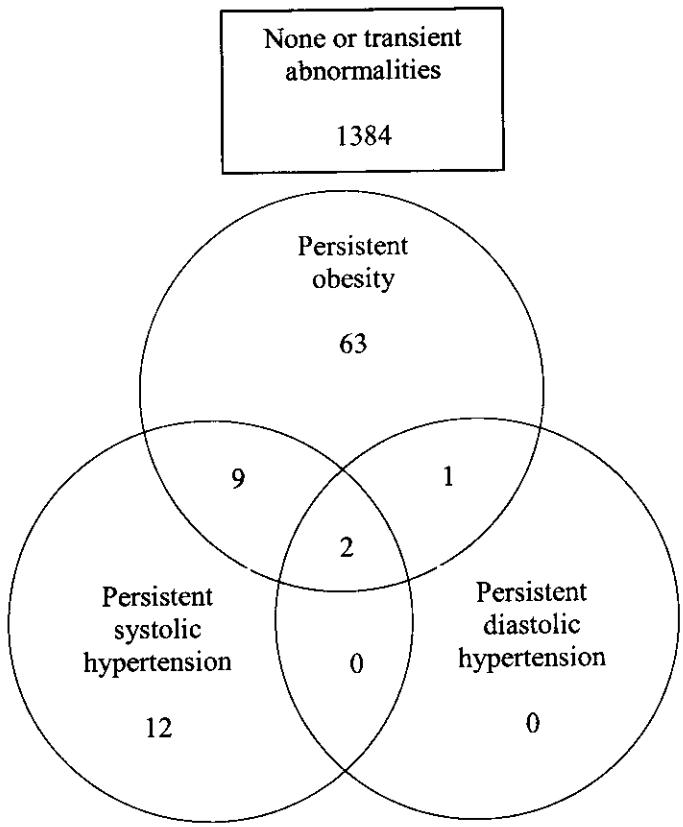
*Referent category

† Trend $p < 0.05$

‡Adjusted for ethnicity, age, gender, body mass index, birth weight, blood pressure and categories of isolation and disadvantage.

Abbreviations: ARR, adjusted relative risk; BMI, body mass index; SD, standard deviation.

Figure 7.4.2: Association between persistent markers of chronic kidney disease – systolic hypertension, diastolic hypertension, obesity.



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CHAPTER 8: DISCUSSION

8.1: Discussion

The literature describing ESKD in Indigenous people is plentiful; however the vast majority concentrates on a few remote groups and lacks non-Indigenous comparators. When compared to Caucasians and national populations, the risk for all-cause ESKD is universally greater among the Indigenous groups of the USA, Canada, Australia, New Zealand and Venezuela. Most of this excess risk is due to a higher incidence of diabetic ESKD. The reasons for this interaction between diabetes and risk for ESKD in Indigenous populations has not yet been properly explored through examination of physiological as well as environmental differences. Other non-Indigenous, disadvantaged groups with higher rates of ESKD, such as African Americans, share these socio-demographic risk factors, and have comparable rates of ESKD to Indigenous people.

Of the few comparative studies describing risk for ESKD in Indigenous people compared to non-Indigenous people, there are no observational or prospective studies available, resulting in a lack of information on the early causal chain to these disease outcomes. Most comparative studies are retrospective registry and hospital record reviews, with the inherent bias of misclassification of Indigenous status, under-ascertainment of ESKD through recording of treated cases only, and lack of measurement of socio-demographic risk factors for chronic and end-stage kidney disease. Many community-based or tribal studies lack an adequate non-Indigenous comparator who shares the socio-demographic risk for the area. The results of these studies are not readily applied to the broader Indigenous community. For all of the countries included in this review, the majority of Indigenous people reside in urban areas, where local non-Indigenous comparators are available and population-based prospective studies are possible.

What this study adds

The cross-sectional studies reported in this thesis are the first to describe the prevalence of early markers of chronic kidney and cardiovascular disease in a population-based sample of Aboriginal children as compared with non-Aboriginal children. They also describe the association between risk for markers of chronic disease and socio-demographic determinants of health. This research is the first to describe the natural history of chronic kidney disease in Indigenous people, and to define important risk factors so that preventative measures and better research may be developed.

The study on the diagnostic test accuracy is the first to assess the validity of proteinuria dipsticks in detecting baseline and persistent albuminuria in Aboriginal and non-Aboriginal children, and in subsets of children at higher risk of chronic kidney disease. This is important research for informing primary-care, paediatric and other physicians who work in remote Indigenous and other communities.

The prospective results are the first to describe the prevalence of more important persistent markers of chronic kidney disease in Aboriginal and non-Aboriginal children, and the risk for disease after accounting for socio-demographic differences.

Results – baseline (cross-sectional data, chapters 3 & 4)

Early markers of chronic kidney disease

The overall prevalence of baseline abnormalities was frequent; haematuria was 5.5%, proteinuria 7.3%, and albuminuria 7.3%. Only haematuria was more frequent in Aboriginal children (7.1% versus 3.6%, p=0.002). Socio-economic disadvantage and geographic isolation were neither significant nor consistent risk factors for any marker of chronic kidney disease.

Early markers of cardiovascular disease

Risk factors measured for cardiovascular disease (obesity, albuminuria and systolic and diastolic hypertension) are already common in young children. Obesity was detected in 7.1%, albuminuria in 7.3%, systolic hypertension in 7.2% and diastolic hypertension in

5.9%, with no differences in the prevalence of these risk factors between Aboriginal and non-Aboriginal children. Hypertension was less common with increasing social disadvantage, even after adjustment for body mass index (trend $p<0.02$). Increasing body mass index standard deviation was strongly associated with systolic and diastolic hypertension (both $p<0.0001$).

Results – prospective (two-year follow-up data, chapters 5 & 6)

Dipstick detection of albuminuria

Proteinuria dipsticks had a sensitivity of 62% and specificity of 97% at baseline. In predicting persistent albuminuria, sensitivity was 75%, specificity 93%. Accuracy of dipsticks did not vary with ethnicity, gender or body mass index. Accuracy was less in younger children (4.0-7.9 years), and in children with haematuria.

Persistent markers of chronic kidney disease at first follow-up

Besides persistent obesity (5.3%), overall persistence of risk factors for chronic kidney disease was low (systolic hypertension 1.1%, diastolic hypertension 0.2%, haematuria 1.1%, and albuminuria 1.5%). While there were more Aboriginal than non-Aboriginal children with baseline haematuria (7.1% versus 3.6%, $p=0.002$), after adjustment for age, gender, birth weight and socio-demographic status, there were no differences in risk for the more important persistent chronic kidney disease markers between Aboriginal and non-Aboriginal children.

Results - prospective (four-year follow-up data, chapter 7)

Persistent markers of chronic kidney disease at final follow-up

Prevalence of baseline CKD markers was frequent, but most abnormalities found at baseline were transient. Besides persistent obesity (5.0%), persistence of CKD markers at final follow-up were infrequent; haematuria (1.9%), albuminuria (2.4%), systolic hypertension (1.5%) and diastolic hypertension (0.2%). After adjustment for socio-demographic inequities, there was no difference in prevalence of persistent markers of CKD between Aboriginal and non-Aboriginal children.

Conclusions

The frequency of early markers of chronic kidney and cardiovascular disease at a single test in New South Wales primary-school aged Aboriginal and non-Aboriginal children is high. The frequency of the more important persistent markers of chronic disease is low, besides obesity, which remains high. This highlights the importance of follow-up testing in the detection of chronic disease markers, as 70-80% of abnormalities at a single test will not persist. It also highlights the importance of intervening early in young obese children, who are likely to remain obese without intervention.

At a single test, Aboriginal children from New South Wales, Australia have a higher prevalence of haematuria, however they have no higher risk of any other marker. This may reflect the higher rates of certain transient diseases in Aboriginal children, such as post-infectious glomerulonephritis. These Aboriginal children have no higher risk of the more important persistent markers of chronic kidney disease when compared to non-Aboriginal children. Social disadvantage and geographic isolation carried no higher risk of chronic disease in these children.

The performance characteristics of proteinuria dipsticks make them suitable for albuminuria screening in Aboriginal and other higher risk groups of children, and they are particularly useful for detecting children who will have persistent albuminuria.

Future directions

This work has established the natural history of early markers of chronic kidney and cardiovascular disease in primary-school aged Aboriginal and non-Aboriginal children from New South Wales, Australia, and shown that Aboriginal children and youth have no increased risk for chronic disease when compared to non-Aboriginal children. Most abnormalities are transient, and follow-up testing is important. Proteinuria dipsticks are a cheap, portable and reliable method of detecting baseline and persistent albuminuria in all children.

This is important information in determining the causal chain of events towards development of end-stage kidney disease. These findings suggest that these Aboriginal children are not 'born into' a higher risk of chronic kidney disease, and that the three-fold higher risk for end-stage disease experienced by New South Wales Aboriginal adults is not yet manifest in Aboriginal children. This implies that higher risk of chronic kidney disease develops in early adulthood, and that ongoing comparative studies are needed to determine the contribution made by socio-demographic disadvantage to risk of disease. The ARDAC Second Phase Study will follow this cohort of children for a further six years (2008-2013), with additional anthropometric, laboratory and individual-level socio-demographic data in order to document the natural history of chronic kidney disease in Aboriginal young adults.

APPENDIX 1: PARENT INFORMATION SHEET

Centre for Kidney Research
NHMRC Centre for Clinical Research Excellence in Renal Medicine

Phone: + 61 2 9845 3037
Fax: + 61 2 9845 3038
Email: ckr@chw.edu.au
Website:www.kidney-research.org

Parent information sheet

The History of Renal Disease in Aboriginal Children in NSW (ARDAC study)

Investigators

Dr Jonathan C Craig	Phone: 9845 3431
Dr Elisabeth Hodson	Phone: 9845 3430
Dr Leigh Haysom	Phone: 9845 3041
Ms Rita Williams	Phone: 9845 3019
Ms Rhonda Sharples	Phone: 9845 3019
Prof L Paul Roy	Phone: 9845 3037
(Centre for Kidney Research)	Phone: 9845 3037

We know that many Aboriginal people develop complete kidney failure and require kidney dialysis treatment or a kidney transplant. Research in the Northern Territory has shown that many Aboriginal children have blood in their urine, suggesting that they could develop kidney problems when they get older. In addition research in Aboriginal adults suggests that, if kidney disease is detected early, treatment can be offered that may prevent kidney failure.

In NSW we do not know whether many Aboriginal children have blood in their urine or whether Aboriginal children are more likely than non-Aboriginal children to have blood in their urine. We believe it is important to find this out so we would like to carry out a research project to test urine specimens from Aboriginal and non-Aboriginal children in different areas in New South Wales. We hope the information we obtain from this study will help to determine how common such early signs of kidney problems are in Aboriginal children and in non-Aboriginal children in NSW.

We would like to ask you if you will let your child take part in the kidney testing study at your school. This will involve a urine test, measuring blood pressure and recording your child's height and weight. No blood tests will be taken as part of this study. We will send the results of the tests to you. We can also send the results of the tests, if they are abnormal, to your own doctor if you give us permission to do this.

If you would like your child to take part in the study, please fill out the consent form and Sections A and B on the data collection form and give it to your child to bring back to the school. We may not be able to test all those who have agreed to take part in the study as we are only able to test about 200 children from each of the areas, where we are doing the study.

We will make sure that all the information collected in this study is kept confidential. All information will be entered into a database, which is accessed only by the staff at the Centre for Kidney Research at The Children's Hospital at Westmead. Also it is a Hospital rule that confidential information kept on computer databases will be deleted and paper copies will be shredded after 15 years. The results of the study will be provided to the Aboriginal communities and will not be published without their permission.

Please remember that, if you don't want to, you do not have to let your child take part in the kidney testing study at your school.

If you have any concerns about how this study will be carried out, please do not hesitate to discuss them with Rita Williams, one of the investigators (Tel: 02 9845 3019) or with Anne O'Neill (Tel: 02 9845 1316), the Secretary of the Ethics Committee of the Children's Hospital at Westmead, that has approved this project.

APPENDIX 2: SCHOOL PRINCIPAL INFORMATION SHEET

Centre for Kidney Research
NHMRC Centre for Clinical Research Excellence in Renal Medicine

Phone: + 61 2 9845 3037
Fax: + 61 2 9845 3038
Email: ckr@chw.edu.au

Website: www.kidney-research.org

Dear Principal

Research Project: Antecedents of Renal Disease in Aboriginal Children

It is now widely recognised that there is an epidemic of renal disease among Aboriginal people throughout Australia. Aboriginal people are 8 to 13 times more likely to develop renal failure, and they do so at an earlier age than other Australians. Recent evidence from the Northern Territory and elsewhere suggests that if renal disease is diagnosed early, effective prevention strategies can be introduced to delay or in some cases prevent progression to the need for dialysis. In surveys performed in the Northern Territory, it is clear that a significant number of Aboriginal children already have evidence of renal disease.

Currently the extent to which this problem also affects children in New South Wales remains unclear. In 2002 the staff of the Centre for Kidney Research at the Children's Hospital at Westmead surveyed 1000 children (500 Aboriginal children with 500 non-Aboriginal children as a comparison group) in urban, rural and coastal settings to determine how many Aboriginal children had abnormal urine tests, that could indicate a risk of kidney disease, and to find out how frequently these abnormalities were found in Aboriginal children compared with non-Aboriginal children. Preliminary analysis of the data suggests that the number of Aboriginal children with abnormalities on urine testing is higher than the number of non Aboriginal children. However we need further data to confirm this. We have received funding through an NHMRC Centre for Clinical Research Excellence grant to continue the survey in New South Wales schools. We hope that we can also restudy children initially studied in 2002 and 2003 during the following 4 years to determine what happens to these children in the short term.

We would like to invite students in your school to take part in the survey.

If you agree that your school can participate, the process will be as follows:

1. An explanation sheet and consent form will be sent home for parents or guardians of Aboriginal and non-Aboriginal children.

2. If they agree to participate, a urine container will be sent home with the child.

3. On the screen day, the child will bring a sample of urine in the container provided. If they forget, the sample can be collected at the school if the child is old enough to do this

without help. The child will have their blood pressure taken and their height and weight recorded. For statistical purposes the name, date of birth and address of the child will also be recorded. This information will be entered into a secure database with strict privacy considerations and only aggregated data will be reported.

4. In the event that a child does show early signs of kidney disease, the information will be sent to the child's parent or guardian so that the child can be taken to the family's doctor of choice. Other families will be notified that the study revealed normal results.

We hope that your school will be able to join our survey. We ask that this proposal be discussed with the Aboriginal Education Assistant and teachers in your school and a copy of this letter be given to them. For further information please don't hesitate to contact the undersigned.

With kind regards
Yours sincerely

Dr Elisabeth Hodson
Head, Department of Nephrology

Rita Williams
Senior Aboriginal Health Education Officer

Dr Leigh Haysom
PhD Fellow

APPENDIX 3: CONSENT FORM

Centre for Kidney Research
NHMRC Centre for Clinical Research Excellence in Renal Medicine

Phone: + 61 2 9845 3037
Fax: + 61 2 9845 3038
Email: ckr@chw.edu.au
Website: www.kidney-research.org

Investigators: Dr Jonathan C Craig, Dr Elisabeth Hodson, Ms Rita Williams, Dr Leigh Haysom, Prof L Paul Roy

CONSENT FORM

Antecedents of Renal Disease in Aboriginal Children in NSW (ARDAC study)

I have read and understood the Information Sheet, and give my consent for ..... to participate in this research study.

I understand that I am free to withdraw from the study at any time and this decision will not otherwise affect my child's care.

I give permission for the results of the tests, if abnormal:-

1. to be sent to my doctor_____
(insert name & address)

2. to be sent to the Aboriginal Medical Service

3. to be sent to my local Aboriginal Health Education Officer

(please circle your choices)

NAME OF CHILD: ..... (Please print)

NAME OF PARENT OR CARER: .....(Please print)

RELATIONSHIP TO CHILD:.....(Please print)

SIGNATURE OF PARENT OR GUARDIAN .....

APPENDIX 4: DATA FORM

A. Child's details

1. Child's name: _____
2. Date of Birth: _____/ _____/ _____
3. Sex: Male / Female (please circle)
4. Birth weight (if known): _____grams OR _____ lbs ___ oz
5. Address: _____

   _____

   _____ Post code _____
6. Aboriginal or Torres Strait Islander / Non-Aboriginal (please circle)

B Parent's Carer's/Guardian's details:

5. Mother/Father/Carer/Guardian: _____
6. Contact phone No (optional): ( ) _____
   (The parents of any child whose results are abnormal and needs immediate action will be notified via phone)
7. Mobile phone number (optional):_____

C. Clinical details

8. Date screened: ___/ ___/ _____
9. Screened by: _____
10. Height: _____ (cm)
11. Weight: _____ (kg)
12. Urine test result: Blood: Negative / Positive / trace + ++ +++ ++++

    Protein: Negative / Positive / trace + ++ +++ ++++
13. Blood pressure: _____
14. Action taken: _____

    _____
15. Other notes: _____

    _____

APPENDIX 5: SUPPORTING DATA FOR CHAPTER 2

Search strategy

The following search strategy was used to identify all epidemiological studies for inclusion in the literature review "Epidemiology of end-stage renal disease in Indigenous people" from these databases:

1. Medline and Premedline (1966 – present)
2. EMBASE (1980 – present)
3. All EBM Reviews including Cochrane databases
4. CINAHL/ATSI/Rural Health databases (1988 – present)

The following MESH and text terms were used to identify Indigenous people

Exp Oceanic ancestry group/ or exp American native continental ancestry group/ or exp Alaskan native/ or exp inuits
Aborigin$.tw
Koori$.tw
Torres Strait Islander$.tw
Maori$.tw
Pacific Islander$.tw
Manitoba.tw
James Bay Cree$.tw
Pima$.tw
Navajo$.tw
Gila River$.tw
Eskimo$.tw
Yanomami$.tw
Metis$.tw
First Nation$.tw

The following MESH and text terms were used to identify studies of end-stage kidney disease

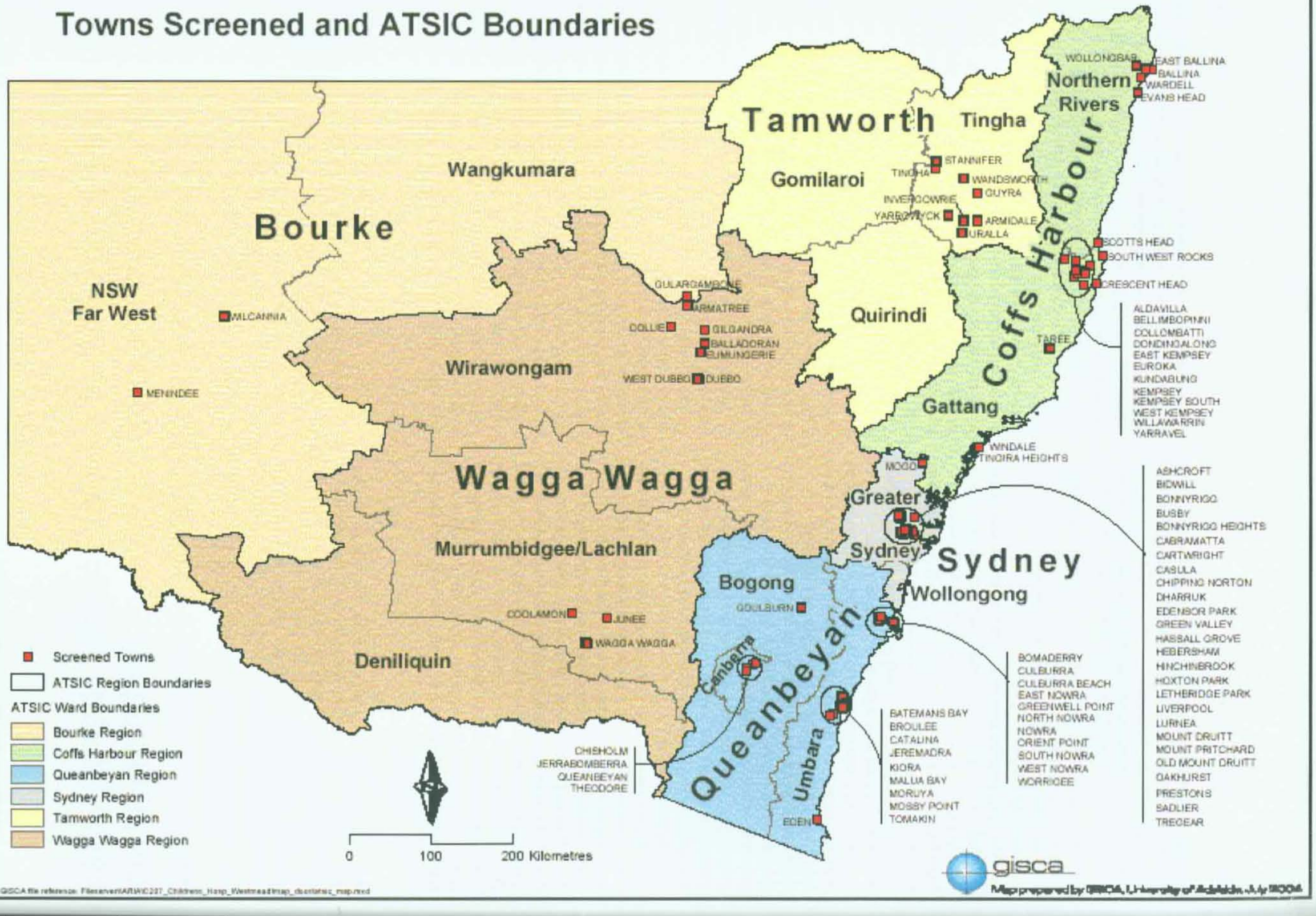
Exp Renal Replacement Therapy/ or exp Renal Dialysis/ or exp peritoneal dialysis/ or exp kidney failure/ or kidney failure, chronic/
(Haemodialysis or hemodialysis).tw
peritoneal dialysis.tw
dialysis.tw
(haemofiltrat$ or hemofiltrat$).tw
(CAPD or CCPD or APD).tw
(ESRD or ESRF or ESKD or ESKF).tw
kidney graft$.tw

renal graft$.tw
kidney transplant$.tw
renal transplant$.tw
renal insufficienc$.tw
chronic kidney disease$.tw
chronic renal disease$.tw
end stage renal disease$.tw
(end stage kidney failure or end stage renal failure or chronic renal failure).tw

The following MESH and text terms were combined with the above to identify studies of frequency and aetiology

Review.pt
Meta analysis.pt
Systematic$ and (review$ or overview$).tw
Exp cohort-studies/
Exp case control studies/
Exp risk/ or exp risk factors/
Odds.tw and ratio$.tw
Relative.tw and risk.tw
Case.tw and control$.tw

Towns Screened and ATSIC Boundaries



Early chronic kidney disease in Aboriginal and non-Aboriginal Australian children: remoteness, socioeconomic disadvantage or race?

L Haysom[1], R Williams[2], E Hodson[3], LP Roy[4], D Lyle[5] and JC Craig[6]

[1]Centre for Kidney Research, The Children's Hospital at Westmead and The School of Public Health, University of Sydney, Sydney, Australia; [2]Centre for Kidney Research, The Children's Hospital at Westmead, Sydney, Australia; [3]Department of Nephrology, The Children's Hospital at Westmead and Clinical Associate, The School of Public Health, University of Sydney, Sydney, Australia; [4]Department of Nephrology, The Children's Hospital at Westmead, Sydney, Australia; [5]Department of Rural Health, University of Sydney, Sydney, Australia and [6]Department of Clinical Epidemiology, The School of Public Health, University of Sydney and Centre for Kidney Research, The Children's Hospital at Westmead, Sydney, Australia

Indigenous people suffer substantially more end-stage kidney disease (ESKD), especially Australian Aboriginals. Previous work suggests causal pathways beginning early in life. No studies have shown the prevalence of early markers of chronic kidney disease (CKD) in both Indigenous and non-Indigenous children or the association with environmental health determinants – geographic remoteness and socioeconomic disadvantage. Height, weight, blood pressure, and urinary abnormalities were measured in age- and gender-matched Aboriginal and non-Aboriginal children from elementary schools across diverse areas of New South Wales, Australia. Hematuria was defined as ⩾25 red blood cells/μl (⩾1+), proteinuria ⩾0.30 g/l (⩾1+), and albuminuria (by albumin:creatinine) ⩾3.4 mg/mmol. Remoteness and socioeconomic status were assigned using the Accessibility and Remoteness Index of Australia and Socio-Economic Indexes For Areas. From 2002 to 2004, 2266 children (55% Aboriginal, mean age 8.9 years) were enrolled from 37 elementary schools. Overall prevalence of hematuria was 5.5%, proteinuria 7.3%, and albuminuria 7.3%. Only baseline hematuria was more common in Aboriginal children (7.1 versus 3.6%; $P = 0.002$). At 2-year follow-up, 1.2% of Aboriginal children had persistent hematuria that was no different from non-Aboriginal children ($P = 0.60$). Socioeconomic disadvantage and geographical isolation were neither significant nor consistent risk factors for any marker of CKD. Aboriginal children have no increase in albuminuria, proteinuria, or persistent hematuria, which are more important markers for CKD. This suggests ESKD in Aboriginal people may be preventable during early adult life.

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Correspondence: *L Haysom, Centre for Kidney Research, The Children's Hospital at Westmead, Locked Bag 4001, Westmead NSW 2145, Australia. E-mail: LeighH@chw.edu.au*

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Indigenous minorities have almost universally poorer health outcomes than non-Indigenous majority populations worldwide. This is particularly true for kidney disease.[1–3] Australian Aboriginal and Torres Strait Islander people (hereafter referred to as Aboriginal) are eight times more likely to develop end-stage kidney disease (ESKD) than non-Aboriginal people and are 10 years younger on average. They are only half as likely to be listed for transplantation and have almost 30% lower graft and 8% lower patient survival 5 years post-transplantation.[1] This pattern of excessive burden due to increased prevalence and poorer outcomes once ESKD occurs is also found in the Inuit and Native Canadians in Canada,[2] Native Americans in the USA,[3] and in the Maori people of New Zealand.[1]

Why Indigenous peoples have such an excess risk of ESKD is largely unknown. The three main causes of ESKD in Aboriginal people are diabetic nephropathy, primary glomerulonephritis, and hypertension.[4] A much larger proportion of ESKD in Aboriginal Australians is attributed to diabetic nephropathy (47%) as compared with non-Aboriginal Australians (17%); however, the ESKD excess is not explained solely by differences in diabetic prevalence or comorbidities.[1] The causal chain contributing to chronic kidney disease (CKD) may start at or before birth, with maternal factors,[5] low birth weight and reduced nephron mass[6,7] rendering the kidney more vulnerable to diabetes and hypertension. Marked regional differences in ESKD have been noted between Aboriginal populations[8] and in ethnically homogeneous countries such as Japan, suggesting socio-demographic influences rather than genetic predisposition are responsible.[9] Environmental factors such as isolated living and socioeconomic disadvantage may play the more important role in the development of CKD.[8]

Current knowledge about the risk factors for CKD in Aboriginal people in Australia is mainly limited to adult-based research that comes from areas of high remoteness and socioeconomic disadvantage in Northern Australia. This

lacks non-Aboriginal control groups or adjustment for variability in locality and sociodemographics.[10] The aims of our study were to determine whether the increased risk of CKD in Aboriginal adults is evident in childhood, and to determine whether environmental health determinants could explain any difference in observed risk.

RESULTS

Baseline characteristics

From February 2002 to June 2004, 2266 children were enrolled from 37 elementary schools across New South Wales (Table 1). There were 1248 (55.1%) Aboriginal and 1018 (44.9%) non-Aboriginal children; 51% were male subjects, and the mean age was 8.9 years (±3.8 years). There were proportionally more Aboriginal children in the youngest age group (4–6 years), in the lowest weight s.d. quartile (both $P<0.0001$) and in the lowest systolic ($P<0.0001$) and diastolic blood pressure quartiles ($P=0.02$). Aboriginal children were more likely to live within the categories of highest isolation and disadvantage, and in the most remote region ($P<0.0001$). There were no differences between the groups for gender, birth weight, height s.d., and body mass index s.d. quartiles.

Design effect estimates for the impact of cluster sampling by school were small for all markers of CKD: 1.10 for hematuria, 1.20 for proteinuria, and 1.28 for albuminuria.

Background prevalence of ESKD from the areas sampled was 1170 cases per million Aboriginal population compared with 740 cases per million non-Aboriginal population, with a relative risk of ESKD in Aboriginal people of 1.58 (1.21–2.00), $P=0.001$.

Prevalence of markers of CKD

The overall prevalence of hematuria was 5.5%, proteinuria 7.3%, and albuminuria 7.3% (Table 2).

Risk factors for markers of CKD

Aboriginality. Aboriginal children were more likely to have hematuria at baseline testing than non-Aboriginal children, and this association was more significant after adjustment for environmental health determinants and other covariates (adjusted odds ratios (OR) 2.25, 95% confidence interval (CI) 1.37–3.69, $P=0.001$) (Table 2). Even after adjustment, there were no differences in the frequency of proteinuria (adjusted OR 0.93, 95% CI 0.68–1.27, $P=0.65$) or albuminuria (adjusted OR 1.37, 95% CI 0.93–2.01, $P=0.11$) between the Aboriginal and non-Aboriginal children.

Persistent and non-persistent hematuria. At 2-year follow-up, the overall prevalence of hematuria was 5.4%. At follow-up, 9/731 (1.2%) Aboriginal children had persistent hematuria, compared with 6/643 (0.9%) non-Aboriginal children ($P=0.60$). There was also no difference in the frequency of persistent and non-persistent hematuria between the Aboriginal and non-Aboriginal children ($P=0.51$).

Geographical isolation. Children from low-mid isolation areas had a relatively low prevalence of hematuria (unadjusted OR 0.36, 95% CI 0.18–0.71, $P=0.002$) compared with the least isolated-referent category, which did not change appreciably with adjustment; however, there was no evidence of a linear trend in the association between isolation and frequency of hematuria (trend $P=0.05$, non-trend $P<0.05$) (Table 3). There was no association between prevalence of proteinuria and isolation category. There appeared to be an inconsistent relationship between isolation category and frequency of albuminuria detected, with the most isolated children having the lowest prevalence of albuminuria, especially after adjustment for race and other environmental health determinants (race adjusted OR 0.49, 95% CI 0.26–0.90, $P=0.01$). There was, however, no evidence of a linear trend between isolation and frequency of albuminuria (trend $P=0.19$).

Social disadvantage. No association between social disadvantage categories and markers of CKD was found (Table 4). There was a trend for higher risk of proteinuria in less disadvantaged children ($P=0.004$).

Region. No association between regional categories and markers of CKD was found. There was an increasing trend in risk for proteinuria from urban to remote regions ($P=0.04$), but deviation from trend was also significant ($P<0.05$).

There were no interactions found between environmental health determinants and race, age, gender, or other covariates in any model.

DISCUSSION

Aboriginal children are no more likely to have early urinary markers of CKD than non-Aboriginal children. There was a higher prevalence of hematuria at baseline testing in Aboriginal children, but there were no differences in the rates of persistent hematuria between Aboriginal and non-Aboriginal children. We were unable to show any consistent clear association between proposed environmental determinants of health – social disadvantage and isolation – and markers of early CKD. Race is often used incorrectly as a proxy for many risk factors in health that are indicators of disadvantage, including geographical remoteness and socioeconomic status.[11] We measured all these potential risk factors in our study and have shown that neither racial nor environmental risk factors appear predictive of early CKD. Importantly, the association between environment and markers of CKD was not altered by adjustment for Aboriginal status. This is the first study designed to differentiate the relative contributions of race and environmental health determinants on early markers of CKD.

Our results are surprising as we expected to find an increased prevalence of CKD, especially albuminuria, in Aboriginal children and particularly in remote communities. This hypothesis is largely based on studies of adult Aboriginal people. In remote Aboriginal communities in the Northern Territory of Australia, where the incidence of ESKD is the highest in Australia and the world (1000–2500 cases per million population annually), microalbuminuria and overt albuminuria in Aboriginal adults are highly prevalent (23 and 30%, respectively). Over 1–8 years follow-up, albuminuria

Table 1 | Baseline sociodemographic and clinical characteristics

Variable	All subjects n=2266	%	Aboriginal % (n=1248)	Non-Aboriginal % (n=1018)	P-value
Gender					
Male	1155	51.0	50.8	51.2	0.86
Female	1111	49.0	49.2	48.8	
Age groups (years)					
4–5.9	211	9.3	11.3	6.8	<0.0001
6–6.9	281	12.4	13.6	10.9	
7–7.9	329	14.5	15.2	13.7	
8–8.9	337	14.9	14.8	14.9	
9–9.9	351	15.5	13.5	18.0	
10–10.9	361	15.9	13.8	18.6	
11–14.8	396	17.5	17.8	17.1	
Birth weight quartiles (g)[a]					
412–2920	217	25.7	29.6	22.1	0.08
2921–3316	210	24.9	23.1	26.4	
3317–3685	210	24.9	24.4	25.3	
3686–5272	208	24.6	22.9	26.2	
Height s.d. quartiles[a]					
−4.8–−0.7	563	25.1	26.9	22.8	0.12
−0.8–0.1	564	25.1	24.6	25.7	
0.2–1.0	558	24.8	24.7	25.0	
1.1–4.8	562	25.0	23.8	26.6	
Weight s.d. quartiles[a]					
−6.6—0.5	560	24.9	28.3	20.8	<0.0001
−0.4–0.3	560	24.9	24.3	25.7	
0.4–1.2	567	25.2	21.7	29.7	
1.3–13.3	559	24.9	25.7	23.9	
BMI s.d. quartiles[a]					
−4.8–−0.8	560	24.9	26.9	22.5	0.08
−0.7–0.1	562	25.0	24.0	26.3	
0.2–0.7	566	25.2	24.0	26.7	
0.8–6.9	558	24.8	25.1	24.6	
Isolation category (ARIA score)					
Least isolation (0–1.1)	610	26.9	25.9	28.2	<0.0001
Low-mid isolation (1.2–2.4)	639	28.2	27.2	29.4	
High-mid isolation (2.5–4.9)	521	23.0	19.4	27.4	
Highest isolation (5.0–14.0)	496	21.9	27.5	15.0	
Disadvantage category (SEIFA score)					
Least disadvantage (989–1103)	548	24.2	21.9	27.0	<0.0001
Low-mid disadvantage (960–988)	585	25.8	23.0	29.3	
High-mid disadvantage (836–960)	576	25.4	26.8	23.8	
Highest disadvantage (680–835)	557	24.6	28.4	19.9	
Region					
Urban	370	16.3	16.1	16.6	<0.0001
South coast	364	16.1	15.4	16.9	
North coast	497	21.9	20.8	23.3	
Rural	599	26.4	24.4	29.0	
Remote	436	19.2	23.3	14.2	
Systolic BP quartiles (mm Hg)[a]					
62–92	562	25.1	28.2	21.4	<0.0001
93–100	608	27.2	26.6	27.9	
101–108	542	24.2	21.6	27.5	
109–170	525	23.5	23.6	23.3	
Diastolic BP quartiles (mm Hg)[a]					
28–53	522	23.2	25.6	20.5	0.02
54–58	618	27.6	27.9	27.3	
59–64	585	26.2	24.6	28.1	
65–98	512	22.9	21.8	24.2	

ARIA++, Accessibility and Remoteness Index of Australia; BMI, body mass index; BP, blood pressure; s.d., standard deviation; SEIFA, Socio-Economic Indexes For Areas.
[a]Indicates where data does not total 2266.

Table 2 | Prevalence of chronic kidney disease markers in aboriginal and non-aboriginal children

	Overall	Non-Aboriginal (referent category)	Aboriginal	*P*-value
Hematuria				
Events (%)	122 (5.5)	36 (3.6)	86 (7.1)	
Unadjusted OR		1.00	2.02 (1.30–3.13)	0.002
Adjusted OR[a]		1.00	2.25 (1.37–3.69)	0.001
Proteinuria				
Events (%)	161 (7.3)	75 (7.6)	86 (7.0)	
Unadjusted OR		1.00	0.93 (0.65–1.32)	0.67
Adjusted OR[a]		1.00	0.93 (0.68–1.27)	0.65
Albuminuria (ACR mg/mmol)				
Events (%)	157 (7.3)	63 (6.5)	94 (8.1)	
Unadjusted OR		1.00	1.27 (0.87–1.84)	0.22
Adjusted OR[a]		1.00	1.37 (0.93–2.01)	0.11

ACR, albumin:creatinine; BMI, body mass index; BP, blood pressure; OR, odds ratios; RBC, red blood cells; s.d., standard deviation.
Definitions: Hematuria ⩾25 RBC per HPF (1+); proteinuria ⩾0.30 g/L (1+); albuminuria, albumin:creatinine (ACR) ⩾3.4 mg/mmol.
[a]Adjusted for age, gender, birth weight, height s.d., weight s.d., BMI s.d., systolic BP, diastolic BP, isolation category, disadvantage category, and region.

Table 3 | Association between chronic kidney disease markers and geographical isolation

	Lowest isolation (referent category)	Low-mid isolation	High-mid isolation	Highest isolation	Trend *P*-value
Hematuria					
Events (%)	34 (5.7)	15 (2.4)	40 (7.9)	33 (6.8)	0.05*
Unadjusted OR	1.00	0.36 (0.18–0.71)	1.26 (0.75–2.10)	1.07 (0.49–2.37)	
Adjusted OR[a]	1.00	0.31 (0.14–0.66)	1.26 (0.73–2.16)	0.99 (0.46–2.16)	
Race adjusted OR[b]	1.00	0.29 (0.13–0.63)	1.31 (0.77–2.23)	0.84 (0.38–1.85)	
Proteinuria					
Events (%)	41 (6.9)	58 (9.3)	28 (5.5)	34 (7.0)	0.48*
Unadjusted OR	1.00	1.78 (0.89–3.59)	0.96 (0.46–2.00)	1.24 (0.58–2.62)	
Adjusted OR[a]	1.00	1.62 (0.78–3.39)	0.99 (0.46–2.14)	1.16 (0.53–2.55)	
Race adjusted OR[b]	1.00	1.63 (0.78–3.42)	0.99 (0.46–2.13)	1.17 (0.54–2.57)	
Albuminuria					
Events (%)	45 (7.9)	47 (7.5)	42 (8.3)	23 (5.2)	0.19
Unadjusted OR	1.00	0.82 (0.48–1.40)	0.96 (0.62–1.50)	0.59 (0.27–1.27)	
Adjusted OR[a]	1.00	0.63 (0.35–1.13)	0.87 (0.58–1.31)	0.52 (0.28–0.97)	
Race adjusted OR [b]	1.00	0.62 (0.35–1.11)	0.88 (0.59–1.32)	0.49 (0.26–0.90)	

ACR, albumin:creatinine; BMI, body mass index; BP, blood pressure; OR, odds ratios; RBC, red blood cells; s.d., standard deviation.
Definitions: Hematuria ⩾25 RBC per HPF (1+); proteinuria ⩾0.30 g/l (1+); albuminuria, albumin:creatinine (ACR) ⩾3.4 mg/mmol.*Non-trend $P < 0.05$.
[a]Adjusted for age, gender, height s.d., weight s.d., BMI s.d., systolic BP, diastolic BP, disadvantage category, and region.
[b]Adjusted for race, age, gender, height s.d., weight s.d., BMI s.d., systolic BP, diastolic BP, disadvantage category, and region.

was strongly predictive of CKD, although this association was not followed from childhood.[10] The current prevalence of albuminuria (albumin:creatinine > 3.4 mg/mmol) in those aged 5–19 years from this community is 7.6%, similar to the rate seen in our Aboriginal (8.1%) and non-Aboriginal participants (6.5%).[12] However, the lack of non-Aboriginal control groups and the socioeconomic similarities in these remote settings forces a presumption of race as the major contributor. This study has found no significant differences in albuminuria or proteinuria between Aboriginal and non-Aboriginal children across New South Wales, even when controlling for levels of isolation, disadvantage, and region. From a sociodemographic perspective, when compared with lower risk determinants, areas of remoteness, high isolation, and high disadvantage carried no increased risk for CKD in this cohort.

The higher prevalence of hematuria in the Aboriginal children, which was even more significantly associated with race after adjustment for environmental confounders, was not due to a higher number of menstruating Aboriginal female subjects as these children were identified at screening and tested on another occasion. An excess of hematuria in cross-sectional studies has been found in Aboriginal children from remote communities with high rates of post-infectious glomerulonephritis.[13] In a population of Aboriginal children aged 5–19 years screened from remote Northern Territory communities, the rate of asymptomatic hematuria (7.7%) was similar to that in our Aboriginal cohort (7.1%) (26). In non-diabetic Indigenous adults, a higher prevalence of hematuria has been associated with familial factors,[14,15] mesangioproliferative glomerulonephritis,[16] and immunoglobulin A nephropathy.[17] In Aboriginal children with

Table 4 | Association between chronic kidney disease markers and social disadvantage

	Least disadvantage (referent category)	Low-mid disadvantage	High-mid disadvantage	Highest disadvantage	Trend *p*-value
Hematuria					
Events (%)	32 (6.0)	25 (4.4)	32 (5.7)	33 (6.0)	0.78
Unadjusted OR	1.00	0.73 (0.28–1.91)	0.95 (0.40–2.24)	0.99 (0.47–2.12)	
Adjusted OR[a]	1.00	0.55 (0.21–1.41)	0.82 (0.35–1.93)	0.76 (0.34–1.72)	
Race adjusted OR[b]	1.00	0.59 (0.22–1.57)	0.79 (0.33–1.91)	0.72 (0.30–1.73)	
Proteinuria					
Events (%)	53 (9.9)	43 (7.6)	34 (6.0)	31 (5.6)	0.004
Unadjusted OR	1.00	0.75 (0.41–1.39)	0.58 (0.32–1.05)	0.54 (0.27–1.06)	
Adjusted OR[a]	1.00	0.57 (0.21–1.58)	0.53 (0.22–1.28)	0.57 (0.27–1.24)	
Race adjusted OR[b]		0.57 (0.21–1.58)	0.53 (0.22–1.28)	0.58 (0.27–1.23)	
Albuminuria					
Events (%)	43 (8.1)	42 (7.5)	41 (8.2)	31 (5.6)	0.18
Unadjusted OR	1.00	0.93 (0.53–1.63)	1.02 (0.67–1.57)	0.68 (0.40–1.16)	
Adjusted OR[a]	1.00	0.80 (0.39–1.68)	0.87 (0.46–1.65)	0.68 (0.42–1.11)	
Race adjusted OR[b]	1.00	0.82 (0.38–1.74)	0.86 (0.45–1.66)	0.66 (0.40–1.10)	

ACR, albumin:creatinine; BMI, body mass index; BP, blood pressure; OR, odds ratios; s.d., standard deviation.
Definitions: Hematuria ≥ 25 RBC per HPF (1+); proteinuria ≥ 0.30 g/L (1+); albuminuria, albumin:creatinine (ACR) ≥ 3.4 mg/mmol.
[a]Adjusted for age, gender, height s.d., weight s.d., BMI s.d., systolic BP, diastolic BP, isolation category, and region.
[b]Adjusted for race, age, gender, height s.d., weight s.d., BMI s.d., systolic BP, diastolic BP, isolation category, and region.

hematuria, ESKD outcomes have not yet been demonstrated[18] and prospective studies are needed. At 2-year follow-up, there were no differences in the rates of persistent and non-persistent hematuria between Aboriginal and non-Aboriginal children.

What are the possible reasons in this study for the lack of differentiation in risk for CKD between Aboriginal and non-Aboriginal children from socio-demographically diverse environments? The study had an adequate sample size; even with larger numbers any increase in risk would be small. The precision in risk for albuminuria is already narrowly defined, with the upper limit of any 95% CI being 2.3. Cluster sampling bias appeared minimal and adjustment for this bias made little difference to the summary estimates.

Measurement of the main predictors of risk (Aboriginal status and categories of isolation, disadvantage, and region) was performed using standardized systems.[19–21] There is no easy solution to the misclassification bias introduced when spatially aggregated measures are applied to individual data, and there is no method available to identify and measure ecological bias. These standards, however, have been used reliably in geographically and ethnically similar population-based samples.[8,22] High levels of disadvantage in some areas of lowest isolation demonstrate the disparities between environmental determinants of health,[23] emphasizing the importance of using more than one measure, across urban to very remote regions as we have done. Family history of CKD and other environmental determinants such as physician availability are also important potential predictors, but collection of this information either before or at the time of testing was not possible. We determined the regional prevalence of Aboriginal ESKD patients for the study period to be almost twice as much as non-Aboriginal ESKD patients. This is consistent with the difference in ESKD rates for Aboriginal and non-Aboriginal people across New South Wales.[8] This disparity has not been reflected in our study findings for risk of CKD in Aboriginal children. These data suggest that CKD in Aboriginal people starts in later childhood and early adulthood, and that a window of opportunity for prevention exists.

It is unlikely there was error in recording the outcome, as measurement of proteinuria was performed using both standard machine dipstick analysis, but confirmed with a more precise albumin:creatinine. Early morning protein:creatinine correlates well with 24 h urinary protein in children with normal renal function.[24] Spot albumin:creatinine has been shown to have very good receiver operator characteristic curves for detecting pathological albuminuria at the cutoff used in this study.[25] Unfortunately, the test performance for proteinuria screening tests in low prevalence populations has not been validated. Semiquantitative, one-off estimations of urinary protein in children vary according to posture, exercise, illness, and time of day.[25] Measurement error would have been reduced by repeat testing; however, this was not possible in this study. Prospective testing to demonstrate persistent markers is likely to be of more importance, and we look forward to reporting the results of prospective testing over 6 years in this cohort.

Have we misclassified or omitted outcome measures for early CKD? Proteinuria was found to be the strongest risk factor for ESKD in the largest community-based study of mass screening, with an adjusted relative risk of 14.9.[26] Creatinine measurement in a healthy pediatric sample is unlikely to be helpful in determining risk for CKD. Renal ultrasound added little to the evaluation of high-risk Aboriginal children and adults with asymptomatic proteinuria or hematuria.[12]

This study indicates that within New South Wales, there is no increased risk of early CKD in healthy elementary

school-aged Aboriginal children when compared with non-Aboriginal children. In addition, the environmental determinants of health measured here are not associated with the markers for CKD studied in these children. Our findings suggest, whereas the causal pathways for ESKD in Aboriginal people may exist in childhood or earlier, an increased risk for CKD is not yet apparent. There is opportunity for primary preventative measures addressing health-seeking behaviors, access to health care, and lifestyle factors such as smoking, obesity, diet, and alcohol abuse in Aboriginal children and young adults, and these are likely to make a significant impact on CKD development.[27]

These are preliminary findings based upon cross-sectional data. This information is novel, and has not been reported previously. Of even greater importance will be the reporting of the longitudinal data currently being collected on this cohort. This will provide unique and valuable information on the natural history of CKD in Aboriginal and non-Aboriginal children across different levels of socio-demographic risk.

MATERIALS AND METHODS

Selection of participants

Government-run elementary schools were approached for testing from urban, coastal, rural, and remote locations across the state of New South Wales. This state has the highest Aboriginal population in Australia. Non-government schools (private and denominational) have very few Aboriginal enrolments, and were not considered for recruitment. To maximize power, sampling was carried out to obtain equal numbers of Aboriginal and non-Aboriginal children, and in similar proportions from urban, coastal, rural, and remote areas. All elementary schools in remote communities were approached and other areas were sampled if more than 20 Aboriginal children in the relevant age range attended.

Aboriginal status was determined using the Australian Bureau of Statistics best practice recommendations, asking the Standard Indigenous Question on the consent form 'Is your child of Aboriginal or Torres Strait Islander origin?'.[19] All Aboriginal children in the participating elementary schools were offered testing for height, weight, blood pressure, and urinary dipstick abnormalities. Non-Aboriginal children were matched for gender and age (nearest birthday) using class lists. We aimed to recruit equal numbers of boys and girls, Aboriginal and non-Aboriginal children, and approximately equal numbers of children from each 12-month-age group.

Aboriginal community engagement

Consultation with local Aboriginal Medical Services and consent from community leaders were undertaken before commencement of the study. Approval was obtained from the Ethics Committees of the Children's Hospital at Westmead, the University of Sydney, New South Wales Area Health Services, and the New South Wales Department of Education and Training. Informed consent was obtained for each child and, in accordance with NHMRC Guidelines for Ethical Conduct in Aboriginal and Torres Strait Islander Research,[28] data were collected onto a standardized form and de-identified for storage and analysis before being returned to each community after the study visit. Permission to publish data was also obtained from each community.

Measurement of markers of CKD and associated risk factors

Markers of CKD measured were hematuria, proteinuria, and albuminuria. Risk factors known or thought to be associated with the development of CKD in Aboriginal people were also recorded, including age, gender, growth parameters, birth weight, blood pressure, and environmental health determinants: categories of isolation, disadvantage, and region.

A morning clean catch specimen of urine was collected from each child, with dipstick analysis for hematuria, proteinuria, and albuminuria performed at the survey site on fresh specimens using a Bayer Clinitek 50 machine.[29] Leukocytes and nitrites were also recorded for later adjustment for abnormalities of presumed urinary tract infection. Girls older than 8 years who were found to have hematuria were questioned about menses, and, if appropriate, collection was performed at another time. Follow-up urinalysis was performed 2 years after baseline testing on all available children, and the frequency of persistent hematuria (hematuria at baseline and 2 year follow-up) and transient hematuria (hematuria detected at either baseline or 2 year follow-up) was also ascertained.

Hematuria was defined as $\geqslant$25 red blood cells per microliter (1+), proteinuria as $\geqslant$0.30 g/l (1+), and albuminuria as albumin:creatinine $\geqslant$ 3.4 mg/mmol.

Standardization of urban, coastal, rural, and remote locality was made using the Accessibility and Remoteness Index of Australia, with each subject given an Index score according to their postcode of residence.[20] Using geographical information system capabilities, distances, services, and population density for each locality are converted to a continuous variable with values ranging from zero for high accessibility, to 18 for extreme remoteness.[30] Accessibility and Remoteness Index of Australia values for this NSW study ranged from 0 to 14, and for categorical analysis the scores were grouped into quartiles. Isolation categories (and Accessibility and Remoteness Index of Australia score range) used were least isolation (0–1.1), low-mid isolation (1.2–2.4), high-mid isolation (2.5–4.9), and highest isolation (5.0–14.0). Locality was also classified by region (in order of increasing remoteness by Accessibility and Remoteness Index of Australia score): urban, south coast, north coast, rural, and remote.

To determine the level of social and economic well-being of areas studied, the Socio-Economic Indexes for Areas 2001[21] Index of Disadvantage was applied to subjects at the level of collection district of residence. This is the smallest geographic area for which the Index is available. The Index of Disadvantage is a continuous score, and is based upon characteristics such as low income, lower level of education, high unemployment, and unskilled jobs. It has been standardized to a mean of 1000, and a s.d. of 100 across all collection districts in Australia, that is, 95% of scores are between 800 and 1200. Higher scores indicate higher socioeconomic status and least disadvantage. For categorical analysis, the scores were grouped into quartiles: highest disadvantage (680–835), high-mid disadvantage (836–960), low-mid disadvantage (961–988), and least disadvantage (989–1103).

Birth weight was provided by the parent/carer by recall or from the child's health record. Height was measured in stocking feet to the nearest 0.1 cm with an SECA 220 telescopic portable stadiometer[31] that was calibrated between screening visits. Weight was measured in stocking feet and in school uniform on digital scales to the nearest 0.01 kg. Body surface area, body mass index, height, and weight s.d. z-scores were calculated using an age and sex-adjusted program.[32] Blood pressure was measured on the right arm with the child sitting, using an aneroid sphygmomanometer and the largest

cuff to encircle the arm and cover at least three-quarters of the length of the upper arm.[33] In children less than 13 years, diastolic pressure was measured at the point of muffling (Korotkov 4). For older children the point of disappearance was used (Korotkov 5).[34] For children with diastolic and/or systolic blood pressure greater than the 90th centile for age and sex, two further blood pressures were recorded after resting the child, and the lowest blood pressure according to the systolic reading was recorded in mm Hg.[35]

Data analysis

Proportions of CKD markers (hematuria, proteinuria, and albuminuria) and associated risk factors (age, gender, birth weight, systolic and diastolic blood pressure, height s.d., weight s.d., body mass index s.d., and category of isolation, disadvantage, and region) were compared between Aboriginal and non-Aboriginal groups using the χ^2 test. Rates of persistent and non-persistent (transient) hematuria were compared between Aboriginal and non-Aboriginal children using the χ^2 test. The Mantel extension test was used to determine linear trends across categories and quartiles. OR for markers of CKD by isolation category, disadvantage category, and region were determined using logistic regression, with 95% CIs. Analyses were adjusted for age, gender, diastolic and systolic blood pressure, height s.d., weight s.d., body mass index s.d., and categories of isolation, disadvantage, and region. Where appropriate, analyses were then further adjusted for Aboriginal race. Adjustment was made in all analyses for the effect of cluster sampling by school.

The Hosmer and Lemeshow test for goodness of fit was applied in the multivariate models. Tests for interactions between race, gender, age, categories of isolation, disadvantage and region, and other significant variables in the final model were performed. Significance was set at a $P<0.05$ for main effects and for interactions. Statistical analysis was completed using SAS[36] and SPSS software.[37]

Data on the incidence of ESKD was supplied by the Australia and New Zealand Dialysis and Transplant Registry to determine the background prevalence of ESKD in the areas sampled.[38] As point prevalence data are not available from the Registry, we used incidence data for each postcode for the years 1967–2004 to calculate ESKD prevalence for Aboriginal and non-Aboriginal people. Presuming Aboriginal and non-Aboriginal population numbers accessed from the Australian Bureau of Statistics 2001 census were relatively stable over these 37 years, prevalence was calculated as total ESKD events over this time period, divided by the population and multiplied by the time period.[19] This incidence density figure was multiplied by the duration of disease (approximated at 20 years) to give point prevalence.

We planned to collect data from 1000 Aboriginal and 1000 non-Aboriginal children, which were sufficient to detect differences in prevalence of markers of CKD between the two groups of 2.9 versus 1.1%, 4.0 versus 1.8%, 5.5 versus 2.9 at 80% power for hematuria, proteinuria, and albuminuria, respectively.

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ORIGINAL ARTICLE

Cardiovascular risk factors in Australian indigenous and non-indigenous children: A population-based study

Leigh Haysom,[1,2] Rita E Williams,[1] Elisabeth M Hodson,[1,3] Pamela Lopez-Vargas,[1] L Paul Roy,[3] David M Lyle[4] and Jonathan C Craig[1,2]

[1]Centre for Kidney Research, and [3]Department of Nephrology, The Children's Hospital at Westmead, and [2]The School of Public Health, [4]Department of Rural Health, University of Sydney, Sydney, Australia

Aim: Indigenous people have a two- to tenfold increased risk of premature death from cardiovascular disease. We aimed to determine whether some key risk factors for cardiovascular disease occur more commonly in Aboriginal than non-Aboriginal Australian children.

Methods: Children were enrolled from primary schools throughout New South Wales, the state with the highest number of Aboriginal people. Associations between ethnicity, gender, birthweight, socio-demographic status and hypertension, obesity, baseline and persistent albuminuria were determined.

Results: A total of 2266 children (55% Aboriginal) were enrolled. Mean age was 8.9 years (±3.8 years). Obesity (body mass index ≥2 standard deviations) was detected in 7.1%, systolic hypertension (blood pressure >90th percentile) in 7.2%, diastolic hypertension in 5.9%, baseline albuminuria (albumin : creatinine ≥3.4 mg/mmol) in 7.3% and persistent albuminuria in 1.5% with no differences between Aboriginal and non-Aboriginal children. Hypertension was less common with increasing social disadvantage (trend $P < 0.02$). Increasing body mass index standard deviation was strongly associated with systolic and diastolic hypertension (both $P < 0.0001$).

Conclusions: Many risk factors for cardiovascular disease are already common in young children but not more prevalent in Aboriginal than in non-Aboriginal children. In all children, overweight and obesity have the strongest association with hypertension, but social disadvantage appears protective for hypertension. Our findings suggest that risk for cardiovascular health disparities seen in indigenous adults manifests beyond childhood and that a window of opportunity exists to prevent some of these outcomes.

Key words: epidemiology; hypertension; obesity.

Key Points

1. No difference in risk for cardiovascular disease between indigenous and non-indigenous children.
2. Some of the difference in risk found in indigenous adults must manifest beyond childhood.
3. A window of opportunity therefore may exist to prevent these outcomes.

Correspondence: Dr Leigh Haysom, Centre for Kidney Research, The Children's Hospital at Westmead, Corner Hawkesbury Road and Hainsworth Street, Locked Bag 4001, Westmead NSW 2145, Australia. Fax: +61 29845 3038; email: leighh@chw.edu.au

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Disclosures

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Cardiovascular disease is the leading cause of premature death in indigenous people world-wide, and there is an increasing disparity in rates of cardiovascular deaths between indigenous and White people populations that is pronounced by middle age. Recent data for American Indian and Alaskan Natives show the cardiovascular death rate in 45- to 55-year-olds is twice that of White people in the United States with a 4.1% annual increase, compared with a 1.7% annual decrease in White people.[1] By age 40, Aboriginal Australians are 10 times more likely to die of ischaemic heart disease compared with non-Aboriginal Australians.[2]

The causal pathways to these health disparities are poorly researched and are likely to be multideterminant because of differences in physiological and socio-economic risk factors. Overall rates of obesity and hypertension in American Indian and Alaskan native adults are higher than White people in the United States and the disparity widens with age.[3] Australian Aboriginals more than 15 years of age are 1.5 times more likely to be overweight or hypertensive.[4] Diabetes prevalence is twice the national rate in American Indians and Alaskan natives and more than four times the national rate in remote Aboriginal Australians.[3,5] Albuminuria presents early as part of the metabolic syndrome complex in Aboriginal Australians and Native Americans,[6,7] and it robustly predicts cardiovascular morbidity and death.[6] This increased burden of risk factors found in indigenous adults contributes to the widening gap in cardiovascular

health outcomes between Indigenous and non-Indigenous people and to a tendency for disease at a much younger age.[6,7] The social and environmental inequalities that Indigenous people are born and raised with, such as the lack of access to health care, inadequate health-care delivery and social disadvantage, are also likely to contribute to these outcomes.[8]

There are no population-based studies in ethnically and socioeconomically diverse children evaluating the early prevalence of risk factors for cardiovascular disease. This study aimed to determine whether established risk factors for cardiovascular disease (obesity, hypertension and albuminuria) are more prevalent in Aboriginal than non-Aboriginal Australian children and whether these risk factors are associated with physiological determinants of ethnicity, gender and birthweight, and environmental health determinants of geographical isolation and social disadvantage.

Methods

Selection of participants

Government-run primary schools were selected from urban, coastal, rural and remote locations known for their high Aboriginal population across the state of New South Wales. This state has the highest proportion of Aboriginal people. To maximise power, sampling was carried out to obtain equal number of Aboriginal and non-Aboriginal children and in similar proportions from urban, coastal, rural and remote areas. All primary schools in remote communities were approached, and other areas were sampled if greater than 20 Aboriginal children in the relevant age range attended.

Aboriginal status was determined by using the Australian Bureau of Statistics best practice recommendations, asking the standard indigenous question 'Is your child of Aboriginal or Torres Strait Islander origin?' on the consent form.[9] All Aboriginal children in the participating primary schools were offered measurement of height, weight, blood pressure and urinary abnormalities. We aimed to recruit equal number of boys and girls, equal number of Aboriginal and non-Aboriginal children and approximately equal number of children from each 12-month age group.

Aboriginal community engagement

Consultation with local Aboriginal Medical Services was undertaken and consent from community leaders was obtained prior to commencement of the study. Approval was obtained from the Ethics Committees of the Children's Hospital at Westmead, the University of Sydney, New South Wales Area Health Services and the New South Wales Department of Education and Training. Informed consent was obtained for each child in accordance with National Health and Medical Research Council Guidelines for Ethical Conduct in Aboriginal and Torres Strait Islander Research.[10] Data were collected onto a standardised form and de-identified for storage and analysis before being returned to each community after the study visit. Permission to publish data was also obtained from each community.

Measurement of birthweight, growth parameters and blood pressure

Birthweight was provided by the parent/carer by recall or from the child's health record. Height was measured in stocking feet to the nearest 0.1 cm with a Seca 220 telescopic portable stadiometer (Seca, Hamberg, Germany)[11] that was calibrated between screening visits. Weight was measured on digital scales to the nearest 0.01 kg, with the child in stockinged feet and in school uniform. Body mass index (BMI), height and weight standard deviation (SD) z-scores were calculated by using an age- and gender-adjusted programme based upon international normative data.[12] Blood pressure was measured on the right arm with the child sitting, by using an aneroid sphygmomanometer and the largest cuff to encircle the arm and cover at least three-quarters of the length of the upper arm.[13] In children less than 13 years old, diastolic pressure was measured at the point of muffling (Korotkoff 4). For older children, the point of disappearance was used (Korotkoff 5).[14] For children with diastolic and/or systolic blood pressure greater than the 90th percentile for age and gender (using normative data from Australian children, including Aboriginal children), two further blood pressures were recorded after resting the child, and the lowest blood pressure according to the systolic reading was recorded in mmHg.[15]

Measurement of albuminuria

A morning clean catch specimen of urine was collected from each child, with dipstick analysis for albuminuria performed at the survey site on fresh specimens using a Bayer Clinitek 50 machine and Albustix dipsticks (Bayer Healthcare, Pymble, Australia).[16] Leukocytes and nitrites were also recorded for later adjustment for abnormalities of presumed urinary tract infection. Girls older than 8 years who were found to have haematuria were questioned about menses and, if appropriate, collection was performed at another time. Because albuminuria is often transient, follow-up urinalysis was performed 2 years after baseline testing on all available children, and the frequency of persistent albuminuria (albuminuria detected at baseline and follow-up) and non-persistent or transient albuminuria (albuminuria detected at either baseline or follow-up) was also ascertained.

Measurement of environmental health determinants

Standardisation of urban, coastal, rural and remote locality was made by using the Accessibility and Remoteness Index of Australia (ARIA++), with each subject given an index score according to their postcode of residence.[17] Using geographical information systems capabilities, distances, services and population density for each locality are converted to a continuous variable with values ranging from 0 for high accessibility to 18 for extreme remoteness.[18] ARIA++ values for this New South Wales study ranged from 0 to 14, and, for categorical analysis, the scores were grouped into quartiles. Isolation categories (and ARIA++ score range) used were least isolation (0–1.1), low-mid isolation (1.2–2.4), high-mid isolation (2.5–4.9) and highest isolation (5.0–14.0).

To determine the level of social and economic well-being of areas studied, the Socio-Economic Indexes for Areas 2001[19]

Index of Disadvantage was applied to subjects at the level of collection district of residence. This is the smallest geographic area for which the Index is available and includes approximately 200 households. The Index of Disadvantage is a continuous score and is based upon characteristics such as low income, lower level of education, high unemployment and unskilled jobs. It has been standardised to a mean of 1000 and an SD of 100 across all collection districts in Australia; that is, 95% of scores are between 800 and 1200. Higher scores indicate higher socio-economic status (SES) and least disadvantage. For categorical analysis, the scores were grouped into quartiles: Highest disadvantage (680–835), high-mid disadvantage (836–960), low-mid disadvantage (961–988) and least disadvantage (989–1103).

Data analysis

Cardiovascular risk factors considered were systolic and diastolic hypertension (blood pressure greater than the 90th percentile for age and gender), obesity (BMI SD ≥2), albuminuria at baseline [albumin : creatinine (ACR) greater than or equal to 3.4 mg/mmol] and persistent albuminuria (albuminuria at both baseline and at 2-year follow-up). Potential predictors of cardiovascular risk factors were Aboriginal status, female gender, low birthweight (≤2500 g), higher isolation categories (ARIA score 1.2–14.0) and higher disadvantage categories (socio-economic indexes for areas score 680–988). Categories of gender, age group, systolic and diastolic blood pressure percentiles, isolation and disadvantage, quartiles of birthweight, height SD, weight SD, BMI SD and cardiovascular risk factors were compared between Aboriginal and non-Aboriginal groups by using the chi-squared test. The association between predictors and cardiovascular risk factors was determined by using odds ratios and 95% confidence intervals with the presumed lowest risk category of predictor as the referent group. Logistic regression was used to adjust for differences in ethnicity, age, gender, diastolic and systolic blood pressure, BMI SD and categories of isolation and disadvantage. The Mantel extension test was used to determine linear trends across categories and quartiles. Adjustment was made in all analyses for the effect of cluster sampling by school. Tests for interactions between ethnicity, gender, age, categories of isolation and disadvantage and other significant variables in the final model were performed. Significance was set at a P value of <0.05. Statistical analysis was completed by using SAS (SAS Institute, Cary, NC, USA)[20] and SPSS (Chicago, IL, USA) software.[21]

With data collection planned from 1000 Aboriginal and 1000 non-Aboriginal children, the study was adequately powered to detect differences in prevalence of albuminuria, hypertension and obesity between the two groups of 5.5 vs. 2.9%, 12.0 vs. 10.0% and 9.0 vs. 7.0% given a two-tailed significance of less than 0.05.

Results

Baseline characteristics

From February 2002 to June 2004, 2266 children were enrolled from 37 primary schools across New South Wales. There were 1248 (55.1%) Aboriginal and 1018 (44.9%) non-Aboriginal children, 51% were male and the mean age was 8.9 years (± 3.8 years). There were proportionally more Aboriginal children in the youngest age group (4–6 years), in the lowest weight SD quartile, in the most isolated area and in the most disadvantaged category (all $P < 0.0001$). There were no differences between the groups for gender, birthweight, height SD, BMI SD quartiles and blood pressure percentile categories. At 2-year follow-up, there were 1334 children available for urinalysis. Twenty children (1.5%) had persistent albuminuria and 157 children (11.8%) had transient albuminuria (albuminuria at either baseline or at follow-up) (Table 1).

Prevalence of cardiovascular risk factors

The observed frequencies of outcomes of interest were systolic hypertension (7.2%), diastolic hypertension (5.9%), obesity (7.1%), baseline albuminuria (7.3%) and persistent albuminuria (1.5%).

Physiological predictors of cardiovascular risk factors

Aboriginal children were no more likely to have cardiovascular risk factors than non-Aboriginal children. At baseline testing, girls were at higher risk of albuminuria than boys (adjusted odds ratio 1.81, 95% confidence interval 1.46–2.15, $P = 0.001$). There were no differences in rates of persistent and transient albuminuria between boys and girls ($\chi^2 = 2.12$, $P = 0.15$) nor between Aboriginal and non-Aboriginal children ($\chi^2 = 0.15$, $P = 0.70$). When compared with higher birthweight, low birthweight was not associated with any cardiovascular risk factor. None of these physiological determinants were associated with obesity or hypertension (Table 2).

Environmental predictors of cardiovascular risk factors

There was a trend for higher risk of systolic and diastolic hypertension in less disadvantaged children (trend $P = 0.01$ and 0.02, respectively). There were no significant trends across isolation categories for any cardiovascular risk factor. None of these environmental determinants were associated with albuminuria or obesity (Table 2).

Association between cardiovascular risk factors

Increasing systolic blood pressure percentiles were associated with diastolic hypertension, and increasing diastolic blood pressure percentiles were associated with systolic hypertension (both trend $P < 0.0001$). There was a strong association between increasing BMI SD and risk of systolic and diastolic hypertension (both trend $P < 0.0001$). Compared with children in the lowest BMI SD quartile, the adjusted risk of systolic and diastolic hypertension for children in the highest BMI SD quartile was 12.37 (6.17–24.78) and 5.05 (2.74–9.32), respectively, both $P < 0.0001$. Conversely, higher systolic and diastolic blood pressure percentiles were strongly associated with obesity (both trend $P < 0.0001$). There was a trend for lower risk of albuminuria in children with higher BMI SD (trend $P = 0.005$).

Table 1 Baseline characteristics

Variable	All subjects		Aboriginal		Non-Aboriginal	
	n = 2266	%	*n* = 1248	%	*n* = 1018	%
Gender (*P* = 0.86)						
Male	1155	51.0	634	50.8	521	51.2
Female	1111	49.0	614	49.2	497	48.8
Age groups (year) (*P* < 0.0001)						
4–5.9	211	9.3	142	11.3	69	6.8
6–6.9	281	12.4	170	13.6	111	10.9
7–7.9	329	14.5	189	15.2	140	13.7
8–8.9	337	14.9	185	14.8	152	14.9
9–9.9	351	15.5	168	13.5	183	18.0
10–10.9	361	15.9	172	13.8	189	18.6
11–14.8	396	17.5	222	17.8	174	17.1
Birthweight quartiles (g)* (*P* = 0.08)						
412–2920	217	25.7	119	29.6	98	22.1
2921–3316	210	24.9	92	23.1	118	26.4
3317–3685	210	24.9	98	24.4	112	25.3
3686–5272	208	24.6	92	22.9	116	26.2
Height SD quartiles* (*P* = 0.12)						
–4.8 to –0.7	563	25.1	334	26.9	229	22.8
–0.8 to 0.1	564	25.1	306	24.6	258	25.7
0.2 to 1.0	558	24.8	305	24.7	253	25.0
1.1 to 4.8	562	25.0	295	23.8	267	26.6
Weight SD quartiles* (*P* < 0.0001)						
–6.6 to–0.5	560	24.9	351	28.3	209	20.8
–0.4 to 0.3	560	24.9	301	24.3	259	25.7
0.4 to 1.2	567	25.2	269	21.7	298	29.7
1.3 to 13.3	559	24.9	319	25.7	240	23.9
BMI SD quartiles* (*P* = 0.08)						
–4.8 to –0.8	560	24.9	333	26.9	227	22.5
–0.7 to 0.1	562	25.0	298	24.0	264	26.3
0.2 to 0.7	566	25.2	298	24.0	268	26.7
0.8 to 6.9	558	24.8	311	25.1	247	24.6
Isolation category (ARIA score) (*P* < 0.0001)						
Least isolation (0–1.1)	610	26.9	323	25.9	287	28.2
Low-mid isolation (1.2–2.4)	639	28.2	340	27.2	299	29.4
High-mid isolation (2.5–4.9)	521	23.0	242	19.4	279	27.4
Highest isolation (5.0–14.0)	496	21.9	343	27.5	153	15.0
Disadvantage category (SEIFA score) (*P* < 0.0001)						
Least disadvantage (989–1103)	548	24.2	273	21.9	275	27.0
Low-mid disadvantage (960–988)	585	25.8	287	23.0	298	29.3
High-mid disadvantage (836–959)	576	25.4	334	26.8	242	23.8
Highest disadvantage (680–835)	557	24.6	354	28.4	203	19.9
Systolic BP percentiles* (*P* = 0.09)						
<50th	1258	56.2	711	57.7	547	54.4
50th to 90th	817	36.5	426	34.6	391	38.9
>90th	162	7.2	95	7.7	67	6.7
Diastolic BP percentiles* (P = 0.34)						
<50th	1410	63.0	793	64.4	617	61.4
50th to 90th	696	31.2	370	30.0	326	32.4
>90th	131	5.9	69	5.6	62	6.2

*Indicates where data does not total 2266. ARIA, Accessibility and Remoteness Index of Australia; BMI, body mass index; BP, blood pressure; SD, standard deviation; SEIFA, Socio-Economic Index for Areas.

Table 2 Physiological and environmental predictors of cardiovascular risk factors

Predictor	Systolic hypertension		Diastolic hypertension		Albuminuria		Obesity	
	n (%)	AOR‡ (95% CI)	*n* (%)	AOR‡ (95% CI)	*n* (%)	AOR‡ (95% CI)	*n* (%)	AOR‡ (95% CI)
Aboriginality								
Non-Aboriginal†	67 (6.7)	1.00	62 (6.2)	1.00	63 (6.5)	1.00	63 (6.7)	1.00
Aboriginal	95 (7.7)	1.22 (0.87–1.57)	69 (5.6)	0.94 (0.57–1.31)	94 (8.1)	1.37 (0.93–2.01)	82 (7.4)	1.10 (0.76–1.44)
Gender								
Male†	76 (6.7)	1.00	70 (6.1)	1.00	59 (5.4)	1.00	72 (7.0)	1.00
Female	86 (7.8)	1.34 (0.99–1.69)	61 (5.6)	0.88 (0.50–1.25)	98 (9.4)	1.81 (1.46–2.15)*	73 (7.2)	1.03 (0.69–1.37)
Birthweight								
> 2500†	100 (7.8)	1.00	80 (6.3)	1.00	94 (7.7)	1.00	86 (7.3)	1.00
≤2500 g	11 (8.7)	1.10 (0.43–1.76)	5 (4.0)	0.63 (0.33–1.63)	6 (5.0)	0.58 (0.25–1.53)	7 (6.0)	0.77 (0.32–1.81)
Isolation								
Least isolation†	34 (5.6)	1.00	19 (3.1)	1.00	45 (7.9)	1.00	44 (7.8)	1.00
Low-mid isolation	71 (11.3)	2.20 (1.38–3.51)	62 (9.9)	3.75 (2.14–6.55)	47 (7.5)	0.91 (0.58–1.42)	45 (7.9)	1.01 (0.66–1.56)
High-mid isolation	25 (4.9)	0.89 (0.50–1.49)	34 (6.7)	2.24 (1.23–4.01)	42 (8.3)	1.04 (0.67–1.64)	27 (5.7)	0.70 (0.41–1.17)
Highest isolation	32 (6.5)	1.20 (0.72–1.95)	16 (3.2)	1.04 (0.52–2.06)	23 (5.2)	0.61 (0.36–1.09)	29 (6.5)	0.83 (0.50–1.36)
Social disadvantage								
Least disadvantage†	55 (10.2)	1.00	33 (6.1)	1.00	43 (8.1)	1.00	34 (6.9)	1.00
Low-mid disadvantage	43 (7.4)	0.70 (0.46–1.10)	47 (8.1)	1.37 (0.84–2.23)	42 (7.5)	0.87 (0.66–1.37)	27 (5.0)	0.89 (0.57–1.39)
High-mid disadvantage	30 (5.3)	0.51 (0.30–0.83)	31 (5.5)	0.96 (0.59–1.54)	41 (8.2)	1.00 (0.70–1.62)	44 (8.5)	1.22 (0.76–2.00)
Highest disadvantage	34 (6.2)	0.59 (0.35–0.95)*	20 (3.6)	0.62 (0.36–1.05)*	31 (5.6)	0.70 (0.46–1.11)	40 (8.1)	1.20 (0.72–1.89)

*Trend $P < 0.05$. †Referent category. ‡Adjusted for ethnicity, age, gender, BMI, birthweight, blood pressure and categories of isolation and disadvantage. Definitions: Systolic hypertension, systolic blood pressure > 90th percentile; diastolic hypertension, diastolic blood pressure > 90th percentile; albuminuria, albumin : creatinine (ACR) ≥ 3.4 mg/mmol; obesity, BMI ≥ 2 SD; least isolation, ARIA score 0–1.1; low-mid isolation, ARIA score 1.2–2.4; high-mid isolation, ARIA score 2.5–4.9; highest isolation, ARIA score 5.0–14.0; least disadvantage, SEIFA score 989–1103; low-mid disadvantage, SEIFA score 960–988; high-mid disadvantage, SEIFA score 836–959; highest disadvantage, SEIFA score 680–835. ACR, albumin : creatinine; AOR, adjusted odds ratio; ARIA, Accessibility and Remoteness Index of Australia; BMI, body mass index; CI, confidence interval; SD, standard deviation; SEIFA, Socio-Economic Index for Areas.

Compared with children in the lowest BMI SD quartile, the adjusted risk of albuminuria for children in the highest BMI SD quartile was 0.51 (0.32–0.82), $P = 0.001$ (Table 3).

There were no interactions found between ethnicity, age, gender, isolation and disadvantage categories, or other covariates in any model.

Discussion

Aboriginal children in New South Wales have no increased prevalence of traditional cardiovascular risk factors (hypertension, albuminuria and obesity) when compared with non-Aboriginal children. Ethnicity is prone to misuse as a proxy of disadvantage,[22,23] although it is likely that the socio-demographic factors associated with being Aboriginal contribute cumulatively to the poor cardiovascular health of Aboriginal adults. Such factors include lower income and education levels, geographical isolation, limited access to health care and diseconomies of scale due to sparsely distributed populations.[24] This is one of the few studies that differentiate the contributions of ethnicity and environmental health determinants towards risk of cardiovascular disease in children. We have found that ethnicity is not associated with increased cardiovascular risk, even after adjustment for differences in socio-demographic status.

The lack of non-indigenous control groups and the socio-economic similarities in studies of Indigenous adults from non-population-based, remote community settings force the presumption that indigenous status is the major contributor of disease.[25] However, in Aboriginal communities with the highest rates of cardiovascular death in Australia,[26] a similar prevalence of albuminuria to our study findings has been found on cross-sectional testing of the children. The frequency of albuminuria (ACR > 3.4 mg/mmol) in those aged 5–19 years from such communities was 7.6%, which is not different to the baseline rate seen in our Aboriginal (8.1%) and non-Aboriginal (6.5%) children. Accepting that much of this albuminuria is likely to be only transient,[27] at 2-year follow-up, we found no significant differences in transient or persistent albuminuria between Aboriginal and non-Aboriginal children.

Study design issues are unlikely to explain the reasons for a lack of differentiation in risk for cardiovascular disease between Aboriginal and non-Aboriginal children from socio-demographically diverse environments. The study was adequately powered in terms of sample size for the cardiovascular risk factors. Adjustment for cluster sampling bias made little difference to the summary estimates. Measurement of the ethnic and environmental predictors of risk was performed by using standardised systems.[8,16,18] We accept that unmeasured

Table 3 Association between cardiovascular risk factors

Cardiovascular risk factors	Systolic hypertension AOR (95% CI)‡	Diastolic hypertension AOR (95% CI)‡	Albuminuria AOR (95% CI)‡	Obesity AOR (95% CI)‡
Systolic BP centiles				
≥50th†	–	1.00	1.00	1.00
51st–90th	–	5.36 (3.18–9.02)	0.98 (0.70–1.38)	3.65 (2.36–5.66)
>90th	–	29.11 (16.59–51.09)*	0.55 (0.25–1.22)	15.41 (9.32–25.49)*
Diastolic BP centiles				
≤50th†	1.00	–	1.00	1.00
51st–90th	3.95 (2.65–5.87)	–	0.65 (0.44–0.95)	3.01 (2.05–4.43)
>90th	54.80 (34.0–88.0)*	–	0.73 (0.35–1.53)†	8.75 (5.31–14.44)*
Albuminuria (ACR mg/mmol)				
<3.4	1.00	1.00	–	1.00
≥3.4	0.61 (0.27–1.35)	1.06 (0.52–2.16)	–	0.45 (0.18–1.11)
BMI SD quartiles				
−4.8 to −0.8	1.00	1.00	1.00	–
−0.7 to 0.1	2.50 (1.14–5.49)	1.88 (0.95–3.74)	0.67 (0.44–1.04)	–
0.2 to 0.7	4.26 (2.04–8.91)	2.67 (1.40–5.12)	0.65 (0.42–1.02)	–
0.8 to 6.9	12.37 (6.17–24.78)*	5.05 (2.74–9.32)*	0.51 (0.32–0.82)*	–

*Trend $P < 0.05$. †Referent category. ‡Adjusted for ethnicity, age, gender, body mass index, birthweight, blood pressure and categories of isolation, disadvantage and region. Definitions: Systolic hypertension, systolic blood pressure > 90th percentile; diastolic hypertension, diastolic blood pressure >90th percentile; albuminuria, albumin : creatinine (ACR) ≥ 3.4 mg/mmol; obesity, BMI ≥ 2 SD. ACR, albumin : creatinine; AOR, adjusted odds ratio; BMI, body mass index; BP, blood pressure; CI, confidence interval; SD, standard deviation.

confounding from individual-level socio-economic factors remains as a study bias. With further data collection, multilevel analyses could be used to identify, measure and correct for ecological bias when spatially aggregated measures are applied to individual data.[28] The standards used in this study, however, have been applied reliably in geographically and ethnically similar samples.[29,30] Parentally recalled birthweight has been shown as a reliable proxy for recorded birthweight in population-based research.[31,32]

It is unlikely that there was an error in recording the outcomes. Blood pressure was measured by using appropriate cuff sizes, particularly for obese and older children, and repeat measures were performed in hypertensive children. Spot ACR has been shown to have good receiver operator characteristic curves for detecting pathological albuminuria at the cut-off used in this study.[33] Obesity was determined by using BMI SD, which has been validated for use in this age group of children.[34] Overall prevalence of obesity of 7.1% in our cohort is comparable with 6% for Australian children.[35] Waist circumference has been shown to be more predictive of cardiovascular risk in indigenous adults,[36] and measurement of outcomes such as central obesity, blood lipid, glucose, HbA1C and insulin levels would have been desirable for evidence of metabolic syndrome.[37] Measuring all possible cardiovascular risk factors was beyond the practicalities of such a large school-based screening study and painful or embarrassing procedures would have been counter-productive to the current success of our follow-up recruitment rates.

Overweight and obesity were most significantly associated with hypertension. Without early intervention, these obese and hypertensive pre-pubertal children are at high risk for diabetes and cardiovascular disease in adulthood and are likely to have shorter life expectancies than their parents.[38,39] The increasing risk for hypertension in socially advantaged children seems contradictory to other studies.[40,41] Our study sampled children from where Aboriginal populations reside, in areas of the lowest SES.[42] The highest SES quartile in our cohort (indicating lesser disadvantage) correlates with mid-range SES categories in other comparative studies.[43,44] Our findings are consistent with these studies that show that the prevalence of disease risk factors follows a bell-shaped curve across different socio-economic environments. Lowest risk occurs at either extreme of SES, while highest risk occurs in mid-range SES categories.[43,44]

Girls were found to be at increased risk of albuminuria at baseline, even after adjustment for presumed urinary tract infection and testing menstruating females at another time. Transient proteinuria is a common cause of albuminuria in this age group[26], and most of the albuminuria found in these children was transient. At 2-year follow-up, there was no difference in rates of persistent and transient albuminuria between boys and girls.

Low birthweight was not associated with any cardiovascular disease risk factor but has been associated with higher risk of hypertension in children from observational studies with well- and poorly defined study bases.[45,46] A systematic review of 55 studies showed that birthweight had little association to blood-pressure levels in later life. Being currently overweight had a much more relevant and significant association with hypertension,[41] as we have shown in our study.

Microalbuminuria is an established marker with obesity as part of the metabolic syndrome in adults;[32] however, our finding that children in higher BMI SD quartiles have no increased risk for albuminuria is not new and has been found even in children with insulin resistance.[47] Measurement error may also contribute to a spurious increase in risk for albuminuria in

underweight children. An overestimation of microalbuminuria by ACR may result in these children with low muscle mass as a result of a combination of normal excretion of urinary albumin with a low urinary creatinine excretion.[48] Whether albuminuria is predictive of cardiovascular disease in youth, as it is in adults, remains to be proven.

This study indicates that, within New South Wales, there is no increase in prevalence of these risk factors for cardiovascular disease in **primary**-school aged Aboriginal children when compared with non-Aboriginal children. Children who are obese and those from areas of mid-range SES are at higher risk of developing cardiovascular disease. This suggests that some of the difference in cardiovascular risk for Indigenous people manifests beyond childhood and may therefore result from broader social inequalities. It also suggests that a window of opportunity exists to develop strategies that deal with obesity and underlying social disparities for all children, which in turn may prevent some of the cardiovascular disease inequality in Aboriginal adults.

What This Study Adds

1 Population-based data on the prevalence of risk factors for cardiovascular disease from a large cohort of Indigenous and non-Indigenous children.
2 Measurement and adjustment for the confounded relationship between socio-demographic factors and risk for cardiovascular disease.
3 This large population-based study has found no difference in risk for cardiovascular disease between Indigenous and non-indigenous children, after accounting for socio-demographic differences.

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ORIGINAL ARTICLE

Diagnostic accuracy of urine dipsticks for detecting albuminuria in indigenous and non-indigenous children in a community setting

Leigh Haysom · Rita Williams · Elisabeth Hodson · Pamela Lopez-Vargas · L. Paul Roy · David Lyle · Jonathan C. Craig

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Abstract Albuminuria predicts cardiovascular and end-stage kidney disease in indigenous populations. Early detection in indigenous children may identify those who could benefit from early treatment. Community-based detection of albuminuria needs to be performed using a reliable, inexpensive, and widely available test, such as a proteinuria dipstick. Dipstick accuracy for detecting albuminuria in a community setting has not been evaluated. We assessed the accuracy of Multistix 10 SG dipsticks to detect baseline albuminuria and predict for persistent albuminuria at a 2-year follow-up in a population-based cohort of Australian Aboriginal and non-Aboriginal elementary-school-aged children. Variability in the accuracy of dipsticks in subgroups of higher risk children was analyzed using the relative diagnostic odds ratio (RDOR). Using Multistix 10 SG dipsticks, index-test-positive cases were defined as ≥0.30 g/L (1+) proteinuria and index-test-negative cases as <0.30 g/L (negative or trace) proteinuria. Referent-test-positive cases were defined as spot albumin: creatinine (ACR) ≥3.4 mg/mmol, and referent-test-negative cases as ACR <3.4 mg/mmol. There were 2,266 children (55.1% Aboriginal, 51.0% boys, mean age 8.9 years) enrolled. At the 2-year follow-up, 1,432 (63.0%) children were retested (54.0% Aboriginal, 50.5% boys, mean age 10.5 years). Prevalence of baseline albuminuria was 7.3%, and persistent albuminuria was 1.5%. Dipsticks had a sensitivity of 62% and specificity of 97% at baseline. In predicting persistent albuminuria, sensitivity was 75% and specificity 93%. Accuracy did not vary with ethnicity, gender, or body mass index. Accuracy was less in younger children (4.0–7.9 years), and in those with hematuria. The performance characteristics of Multistix dipsticks make them suitable for albuminuria detection in Aboriginal and other higher-risk groups of children. More than two thirds of children detected at a single test will have transient rather than persistent albuminuria. Multistix dipsticks are particularly useful for detecting children who will have persistent albuminuria.

Keywords Proteinuria · Albuminuria · Diagnostic test · ACR · Aboriginal · Children

L. Haysom (✉) · R. Williams · E. Hodson · P. Lopez-Vargas · J. C. Craig
Centre for Kidney Research,
The Children's Hospital at Westmead,
Locked Bag 4001,
Westmead, NSW 2145, Australia
e-mail: LeighH@chw.edu.au

L. Haysom · J. C. Craig
School of Public Health, University of Sydney,
Sydney, NSW, Australia

L. P. Roy
Pediatrics, The Children's Hospital at Westmead,
Westmead, NSW, Australia

D. Lyle
Department of Rural Health, University of Sydney,
Sydney, NSW, Australia

Introduction

Morbidity and premature mortality from chronic disease are a much greater burden for indigenous than for non-indigenous populations. Cardiovascular disease is the leading cause of premature death in indigenous people from 45 years of age, which is 20 years earlier than in non-indigenous populations. Death rates from cardiovascular disease in indigenous people are two- to tenfold higher than in non-indigenous people [1]. In 2005, there were record

numbers of new cases of kidney-failure patients entering dialysis or transplant programs across the world [2, 3], and indigenous people were vastly overrepresented in this group [2, 4] Indigenous Australians are, on average, eight times more likely than non-indigenous Australians of the same age and gender to develop end-stage kidney disease (ESKD) [5]. ESKD occurs almost 10 years earlier in indigenous people, at a median age of 51, versus 60 years in non-indigenous people [6]. With treatments now available to reduce the rate of progression of these chronic diseases, health interest groups have called for governments to commence national programs for early identification of those at greatest risk [2, 3, 7, 8].

Albuminuria presents early in indigenous populations, with high background rates of cardiovascular and kidney disease [9, 10]. Even after adjustment for other traditional risk factors, albuminuria strongly predicts all-cause mortality, cardiovascular morbidity, cardiovascular mortality, and ESKD [8]. In Australian Aboriginal communities, an albuminuria secondary prevention program has demonstrated significant reduction in mortality and morbidity from cardiovascular and chronic kidney disease [11]. A program aimed at early detection and monitoring of albuminuria in Aboriginal children should provide an inexpensive, portable, point-of-care, diagnostic service given the remoteness of many indigenous communities [12]. Urine dipsticks for spot albumin:creatinine have been shown to be accurate in diagnosing albuminuria [13]; however, their cost prohibits them as a screening instrument. Inexpensive urine dipsticks for proteinuria could serve this purpose, but there are currently no data on their accuracy to detect albuminuria in children in community-based settings.

The aims of our study were to evaluate the accuracy of Multistix proteinuria dipsticks for detecting albuminuria in Aboriginal children, to determine whether accuracy varies with subject characteristics, and to determine the predictive ability of dipsticks to identify those children with persistent albuminuria over 2 years of follow-up, who are at greatest risk of chronic disease.

Methods

The Standards for Reporting of Diagnostic Accuracy (STARD) checklist was adopted for the reporting of these data [14].

Selection of participants Government-run elementary schools were approached for testing from urban, coastal, rural, and remote locations across the state of New South Wales. This state has the highest Aboriginal population in Australia [15]. Nongovernment schools (private and denominational) have very few Aboriginal enrollments and were not considered for recruitment. To maximize power and generalizability, consecutive sampling was done to obtain equal numbers of Aboriginal and non-Aboriginal children, boys and girls, and in similar proportions from urban, coastal, rural, and remote areas. All elementary schools in remote communities were approached, and other areas were sampled if greater than 20 Aboriginal children in the relevant age range attended.

Aboriginal status was determined using the Australian Bureau of Statistics best-practice recommendations, asking the Standard Indigenous Question on the consent form "Is your child of Aboriginal or Torres Strait Islander origin?" [15]. All Aboriginal children in the participating elementary schools were offered testing. Non-Aboriginal children were matched for gender and age from the same class. We aimed to recruit equal numbers of boys and girls, Aboriginal and non-Aboriginal children, and equal numbers of children from each 12-month age group.

Approval was obtained from the Ethics Committees of the Children's Hospital at Westmead, the University of Sydney, New South Wales Area Health Services, and the New South Wales Department of Education and Training. Informed consent was obtained for each child and, in accordance with National Health and Medical Research Council (NHMRC) Guidelines for Ethical Conduct in Aboriginal and Torres Strait Islander Research [16], data was collected onto a standardized form and deidentified for storage and analysis before being returned to each community after the study visit. Permission to publish data was also obtained from each community.

Multistix proteinuria dipstick (index test) The Multistix-10 SG reagent dipstick (Bayer Diagnostics Manufacturing Ltd., Bridgend, South Wales, UK) costs approximately US $0.80 per stick and detects urine protein by the protein error of indicators principle. At a constant pH, the development of any green color is due to the presence of protein. The color is then read spectrophotometrically by the Bayer Clinitek 50 urinalysis machine within four proteinuria categories: negative/trace (protein<0.30 g/L), 1+ (protein 0.30 g/L), 2+ (protein 1 g/L), 3+ (protein 3 g/L), and 4+ (≥ 20 g/L) (Bayer Healthcare, Bayer Australia Ltd).

Spot urine albumin:creatinine dipstick (referent test) The Clinitek (Bayer Australia Ltd. Pymble, NSW, Australia) dipstick detects urine albumin and creatinine concentrations at an approximate cost of US $3.80 per stick. Urine albumin is measured by dye binding of albumin with sulphonephthalein dye, resulting in a color shift at a constant pH. This is referred to as the protein error of pH indicators. Urine creatinine complexes with copper and the copper–creatinine complex reacts with hydroperoxide and a dye to produce a color change. Color changes are then read

spectrophotometrically by the Bayer Clinitek 50 urinalysis machine as a ratio of albumin:creatinine concentration within three categories: normal/no pathological albuminuria (ACR < 3.4 mg/mmol), microalbuminuria (ACR 3.4–33.9 mg/mmol), and macroalbuminuria (ACR > 33.9 mg/mmol). This method has been validated as a referent standard test for verifying albuminuria in children [17].

Sample collection and handling All children were given verbal instructions by the study nurse about the method of urine collection. Parent/carer assistance was provided in the younger age group. A morning clean-catch urine specimen was collected from each child into a sterile container and analyzed immediately with the index and referent tests by the nurse at the survey site. Girls older than 8 years who were found to have hematuria were questioned about menses, and if this was present, collection was performed at another time.

Definition of positivity All samples were tested according to the manufacturer's instructions (Clinitek 50 User's Guide, Bayer Corporation, Elkhart, IN, USA) by the index and referent tests at the same time point by the study nurse. A computer printout of results at the following cutoffs was produced by the urinalysis machine at the end of each test. Kidney Disease Outcomes Quality Initiative (KDOQI) recommendations for cut-off values were used to define proteinuria, albuminuria, and hematuria [17]. Test-positive cases were defined as ≥ 0.30 g/L proteinuria (Multistix dipstick 1+), and test-negative cases were defined as < 0.30 g/L proteinuria (Multistix dipstick negative or trace). Referent-test-positive cases were defined as albumin:creatinine (ACR) ≥ 3.4 mg/mmol at initial testing (baseline albuminuria present) and referent-test-negative cases as ACR < 3.4 mg/mmol at initial testing (no baseline albuminuria).

Because albuminuria can be a benign transient phenomenon in the pediatric age group [18], we also assessed test performance of Multistix dipsticks in predicting persistent albuminuria, with referent-test-positive cases classified as children with spot urine ACR ≥ 3.4 mg/mmol at both initial testing and 2-year follow-up. Referent-test-negative cases were then defined as ACR < 3.4 mg/mmol at both initial testing and 2-year follow-up, or a combination of positive and negative tests at baseline and follow-up (none or transient albuminuria). Hematuria was defined as ≥ 25 red blood cells per microliter (RBC/μl) (Multistix dipstick 1+) at baseline testing and no hematuria as < 25 RBC/μl (Multistix dipstick negative or trace) at baseline testing. Albuminuria in association with suspected urinary tract infection (leucocytes and/or nitrites on Multistix dipstick testing) and macroalbuminuria (ACR ≥ 34 mg/mmol) were found in less than 1% of children. These children were included in the analyses.

Precision of the referent and index tests was assessed by the study nurse using quality control calibration materials at each screening center prior to testing any samples. All positive and negative control calibrations fell within the acceptable cutoffs designated by the manufacturer (Bayer HealthCare, Bayer Corporation, Elkhart, IN, USA), based upon national and international precision goals derived from biological variation and international consensus data on performance criteria [19, 20].

Statistical methods

For albuminuria at baseline and for persistent albuminuria, comparisons between the index and referent tests for the entire cohort and subgroups were represented in two-by-two contingency tables. Indicators of test performance derived from these tables were sensitivity, specificity, and relative diagnostic odds ratios (RDOR) with 95% confidence intervals (CI). The diagnostic OR is the ratio of the odds of albuminuria in proteinuria dipstick positives relative to the odds of albuminuria in proteinuria dipstick negatives. The value of the diagnostic OR ranges from zero to infinity, with higher values indicating better discriminatory test performance [21]. The RDOR compares this ratio of test performance in at-risk subgroups (Aboriginal children, boys, older children, children with hematuria, and normal weight and overweight/obese children) against the presumed lower-risk referent group (non-Aboriginal children, girls, younger children, children without hematuria, and underweight children) with 95% CI for proportions calculated using exact binomial methods. Age was divided into tertiles, with younger children defined as 4.0–7.7 years at baseline and 6.0–9.4 years at the 2-year follow-up. Older children were defined as 7.8–14.8 years at baseline and 9.5–15.4 at the 2-year follow-up. Underweight was defined as body mass index (BMI) standard deviation (SD) <1, overweight and obese as BMI SD >1, and normal weight as BMI SD −1 to +1 [22]. Statistical analyses were completed using SAS (SAS Institute Inc., Cary. NC, USA) and SPSS (SPSS Inc. Chicago, IL, USA).

Results

Participants From February 2002 to September 2004, 2,266 healthy children were enrolled in this study from 37 elementary schools across New South Wales, including 1,248 (55.1%) Aboriginal children. Overall, 51.0% were boys, and the mean age was 8.9 (± 2.0 years). There were proportionally more Aboriginal children in the youngest age tertile (37.4% versus 28.5%, X^2 20.01, 2 df, $p<0.0001$), with no significant differences between Aboriginal and

non-Aboriginal children for gender and BMI categories. There were significantly more Aboriginal children with hematuria at baseline testing compared with non-Aboriginal children (7.1% versus 3.6%, X^2 12.31, 1 df, p=0.002). A more detailed description of subject characteristics at baseline is available elsewhere [23]. At 2-year follow-up from March 2004 to December 2006, there were 1,432 (63.0%) children available for retesting; 773 (54.0%) were Aboriginal, 50.4% were boys, and mean age was 10.5 (± 2.0 years). When comparing the overall group at follow-up to those children lost to follow-up, there were significantly more children from the oldest age group who were lost to follow-up compared with younger age groups (p<0.0001). There were no differences in ethnicity, gender, or BMI SD between children at follow-up and those children lost to follow-up.

Figures 1 and 2 show the process of patient recruitment, order of tests, and crude test results. Of the 2,266 children enrolled at baseline, 53 (2.3%) would not provide a urine sample on the test day, and 78 (3.4%) did not receive an ACR due to equipment failure at the study site. Of the 1,432 (63%) children available for 2-year follow-up testing, 74 (5.2%) did not have either an initial Multistix dipstick test or initial ACR, and 17 (1.2%) did not receive a follow-up ACR.

The prevalence of baseline albuminuria was 7.3%, and persistent albuminuria (at the 2-year follow-up) was 1.5%. There was no significant difference in the prevalence of baseline or persistent albuminuria between Aboriginal and non-Aboriginal children (8.1% versus 6.5%, X^2 1.97, 1 df, p=0.16 and 1.4% versus 1.5%, X^2 0.03, 1 df, p=0.86). Baseline and follow-up data for the cohort have been described in more detail elsewhere [23].

Accuracy for baseline albuminuria Table 1 shows the accuracy of the Multistix dipstick for the diagnosis of albuminuria at baseline. Overall sensitivity was 62% (55–70%) and overall specificity was 97% (96–98%). There were no significant differences in the accuracy of Multistix dipsticks in detecting baseline albuminuria in Aboriginal compared with non-Aboriginal children (RDOR 0.97, 95% CI 0.42–2.25, p=0.62), girls compared with boys (RDOR 0.53, 95% CI 0.23–1.23, p=0.56), and overweight/obese and normal-weight children compared with underweight children (RDOR<0.5), although there was a trend toward

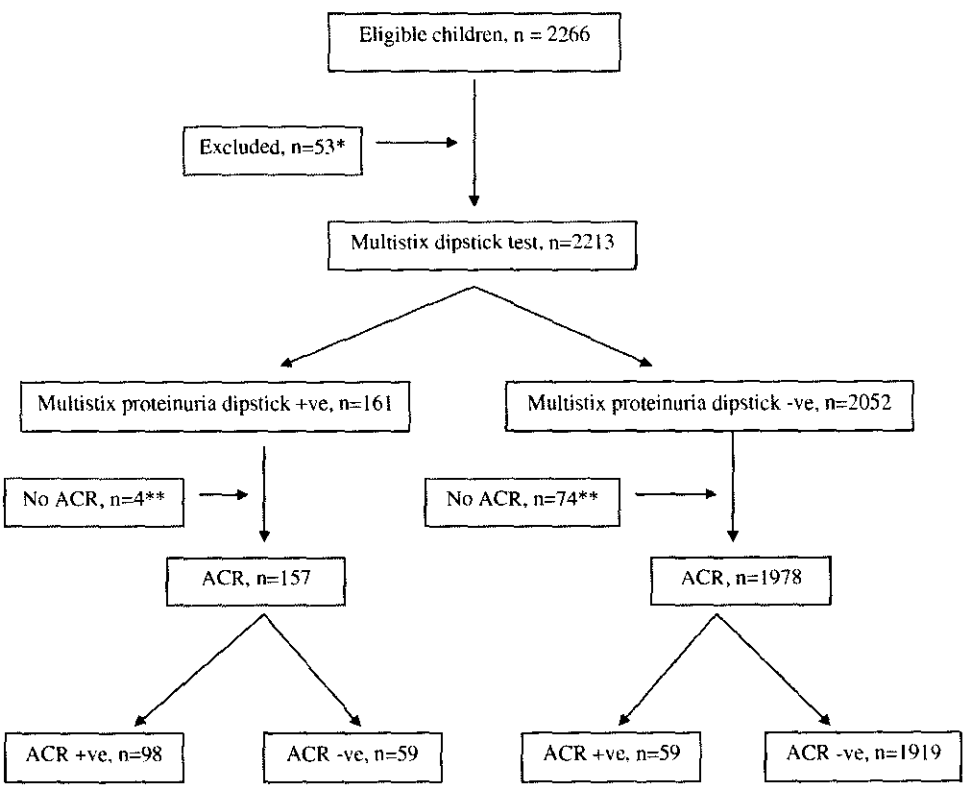

Fig. 1 Recruitment and testing of children at baseline

*Child refused to void
**Equipment failure

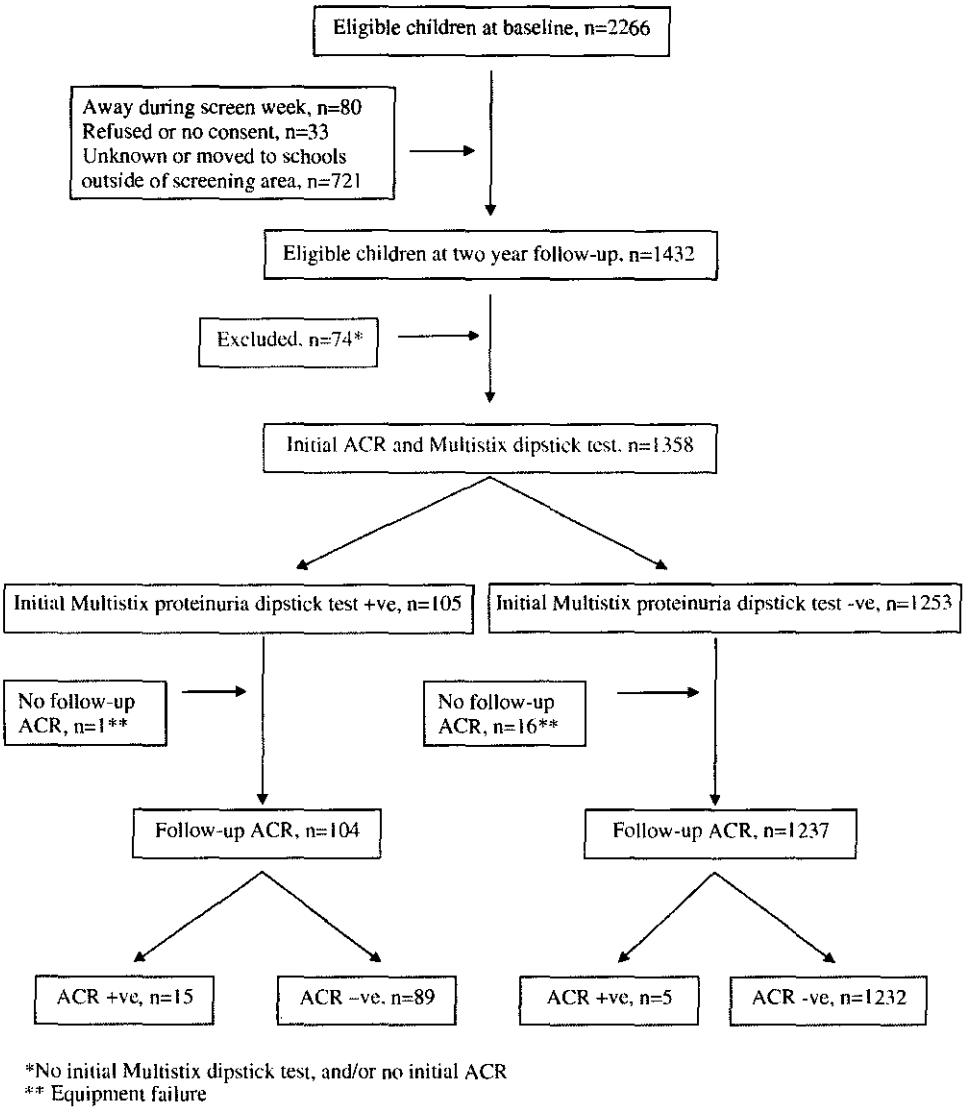

Fig. 2 Recruitment and testing of children at the 2-year follow-up

*No initial Multistix dipstick test, and/or no initial ACR
** Equipment failure

lower accuracy with increasing BMI (trend $p=0.01$). Multistix dipsticks were more accurate in diagnosing baseline albuminuria in older children (8.0–15.0 years) compared with the youngest age tertile (4.0–7.9 years), RDOR>4, trend $p=0.01$ and in children with hematuria compared with children without hematuria (RDOR 7.51, 95% CI 2.27–24.82, $p=0.01$).

Accuracy for persistent albuminuria Table 2 shows the results of Multistix dipsticks in predicting persistent albuminuria. Overall sensitivity was 75% (53–89%), and overall specificity was 93% (92–94%). There were no significant differences in the accuracy of Multistix dipsticks in predicting persistent albuminuria in Aboriginal compared with non-Aboriginal children (RDOR 0.81, 95% CI 0.10–6.60, $p=0.82$), girls compared with boys (RDOR 1.05, 95% CI 0.13–8.55, $p=0.36$), older children (8.0–15.0 years) compared with the youngest age tertile (4.0–7.9 years), RDOR<0.9, trend $p=0.31$, and overweight/obese and normal-weight children compared with underweight children, although there was a trend toward better accuracy with increasing BMI (RDOR>1.6, trend $p=0.01$). Multistix dipsticks were substantially less accurate in predicting persistent albuminuria in children with hematuria compared with children without hematuria (RDOR 0.03, 95% CI 0.001–0.93, $p=0.02$).

Absolute accuracy Table 3 shows the absolute accuracy per 1,000 children tested using ACR and Multistix dipsticks. Out of a hypothetical cohort of 1,000 children, with 73

Table 1 Accuracy of Multistix dipsticks in detecting albuminuria at baseline (prevalence 7.3%)

Characteristics	Prevalence albuminuria %	TP	TN	FP	FN	Sensitivity % (95% CI)	Specificity % (95% CI)	Relative diagnostic odds ratio (95% CI)
Whole cohort	7.3	98	1919	59	59	62 (55–70)	97 (96–98)	NA
Ethnicity								
Non–Aboriginal[a]	6.5	42	877	31	21	67 (54–77)	97 (95–98)	1.00
Aboriginal	8.1	56	1042	28	38	60 (49–69)	97 (96–98)	0.97 (0.42–2.25)
Gender								
Male[a]	5.4	38	1014	24	21	64 (52–75)	98 (97–98)	1.00
Female	9.4	60	905	35	38	61 (51–70)	96 (95–97)	0.53 (0.23–1.23)
Age tertiles (years)								
4.0–7.9[a]	6.0	12	633	14	29	29 (19–40)	98 (97–99)	1.00
8.0–9.9	7.2	37	658	20	16	70 (59–79)	97 (96–98)	4.07 (1.31–12.68)
10.0–15.0	8.8	49	628	25	14	78 (68–85)	98 (97–99)	4.70 (1.54–14.36)
Other sediment								
Hematuria absent[a]	6.8	83	1823	58	55	60 (52–68)	97 (96–98)	1.00
Hematuria present	16.5	15	9	1	4	79 (57–91)	99 (94–100)	7.51 (2.27–24.82)
BMI SD								
Underweight[a]	11.1	31	299	13	8	80 (68–88)	96 (94–97)	1.00
Normal weight	7.2	57	1237	36	42	58 (50–65)	97 (96–98)	0.52 (0.18–1.53)
Overweight/obese	4.8	10	364	10	9	53 (34–69)	97 (96–98)	0.45 (0.11–1.92)

BMI body mass index, *FN* false negative, *FP* false positive, *SD* standard deviation, *TN* true negative, *TP* true positive.
Definitions: Albuminuria, ACR ≥ 3.4 mg/mmol; hematuria ≥ 25 red blood cells per high-power field (1+); underweight, BMI SD < −1; normal weight, BMI SD −1 to +1; overweight and obese, BMI SD > +1
[a] Referent group

Table 2 Accuracy of Multistix dipsticks in detecting persistent albuminuria (prevalence 1.5%)

Characteristics	Prevalence albuminuria %	TP	TN	FP	FN	Sensitivity % (95% CI)	Specificity % (95% CI)	Relative diagnostic odds ratio (95% CI)
Whole cohort	1.5	15	1232	89	5	75 (53–89)	93 (92–94)	NA
Ethnicity								
Non-Aboriginal[a]	1.4	7	576	43	2	78 (45–94)	93 (91–95)	1.00
Aboriginal	1.5	8	656	46	3	73 (43–90)	93 (91–95)	0.81 (0.10–6.60)
Gender								
Male[a]	1.5	7	640	35	3	70 (40–89)	95 (93–96)	1.00
Female	1.5	8	592	54	2	80 (49–94)	92 (89–94)	1.05 (0.13–8.55)
Age tertiles (years)								
6.0–9.4[a]	0.9	3	412	20	1	75 (31–95)	95 (94–96)	1.00
9.5–11.4	1.1	4	415	31	1	80 (38–96)	93 (92–94)	0.87 (0.04–21.23)
11.5–15.4	2.4	8	405	38	3	73 (44–90)	91 (90–92)	0.46 (0.03–6.74)
Other sediment[b, c]								
Hematuria absent[a]	1.5	15	1190	77	4	78 (56–90)	94 (93–95)	1.00
Hematuria present	1.9	0	41	12	1	25 (21–27)	77 (76–79)	0.03 (0.001–0.93)
BMI SD								
Underweight[a]	1.8	3	204	21	1	70 (31–93)	91 (90–92)	1.00
Normal weight	1.9	11	740	53	4	72 (48–88)	93 (93–94)	1.59 (0.17–15.15)
Overweight/obese	0.3	1	281	15	0	75 (20–97)	95 (94–96)	2.46 (0.10–108.09)

[a] Referent group
[b] 0.5 was added to all cells to obtain an estimate that deals with the zero cell
[c] Hematuria absent or present at baseline
BMI body mass index, *FN* false negative, *FP* false positive, *TN* true negative, *TP* true positive, *SD* standard deviation.
Definitions: Albuminuria, ACR ≥ 3.4 mg/mmol; hematuria ≥ 25 red blood cells per high-power field (1+); underweight, BMI SD < −1; normal weight, BMI SD −1 to +1; overweight and obese, BMI SD> +1

Table 3 Absolute accuracy per 1,000 children screened by Multistix dipsticks (assuming a point prevalence of 7.3% for albuminuria at baseline and 1.5% for persistent albuminuria)

Target condition	Number detected with ACR	Number detected with dipstick	Difference	Number excluded with ACR	Number excluded with dipstick	Difference
Baseline albuminuria	73	45	28	927	899	28
Persistent albuminuria	15	11	4	985	916	69

ACR albumin:creatinine

having baseline albuminuria (a prevalence of 7.3%), Multistix dipsticks would correctly identify 45 children with albuminuria at the expense of 20 false positives and 28 false negatives. At 2-year follow-up, 15 children will have persistent albuminuria. Multistix dipsticks would identify 11, at the expense of 60 false positives (including those with transient albuminuria) and four false negatives.

Discussion

In this first large-scale community-based cohort study of the test performance of urine dipsticks in detection of albuminuria in indigenous children, we show that Multistix dipsticks are accurate for cross-sectional detection and very accurate for detecting children with persistent albuminuria. We also show that accuracy does not vary with ethnicity. Multistix dipsticks are an inexpensive, convenient, and portable diagnostic method for albuminuria detection.

Many of the design features of this study suggest the results are valid and generalizable. This was a prospective evaluation of dipstick urinalysis testing for albuminuria in a consecutive series of children from a clinically relevant and generalizable population. The children tested at follow-up were similar in demographic characteristics to the original population-based cohort at baseline. Many previous studies have used diseased cases with controls for dipstick evaluation, which leads to an overestimate of the true test performance (spectrum bias) [24–26]. There was no verification bias in our study, because all children received both the dipstick and referent tests. The study nurse was not blinded to the results of either test; however, interpretation of each was quantitative. The nurse had no information on the previous referent test result at the follow-up testing, and therefore, no significant effect from unblinding is expected [27, 28]. A single referent test was used, and there was no time interval or treatment between the dipstick and baseline referent tests. We accept that because some of the samples were collected at a time other than first-morning urine, some of the proteinuria detected would be orthostatic, particularly for adolescents. Persistence of proteinuria in these children at first-morning follow-up testing would make orthostatic proteinuria less likely.

Twenty-four-hour proteinuria is conventionally considered the gold standard for diagnosing albuminuria, but this method is unreliable due to collection errors and inconvenience [29, 30]. These problems are compounded in the pediatric population and in highly mobile, remote populations with limited access to health services, as seen in Aboriginal communities [12]. For these reasons, we used spot urine ACR as our surrogate referent test in this study. Replacement of 24-h urine protein by spot urine ACR for follow-up diagnostic purposes has been justified by substantial agreement between the two methods for all age groups with a wide spectrum of renal function and over the entire proteinuria range [13, 31–33]. There was no specific treatment for any child with albuminuria found at baseline before the follow-up referent test was performed, and we used predefined, standard cut-off values for index and referent-test positives and negatives [17].

We found that test performance varied with a number of subject characteristics. Multistix dipsticks were more accurate in detecting albuminuria in older children at baseline due to a low sensitivity, but this finding was not confirmed for the more important outcome of persistent albuminuria. However, this result may have been influenced by the disproportionate losses at follow-up between the oldest age group and the younger age groups. Dipsticks were less accurate for detecting albuminuria in children with higher BMI at baseline but more accurate in predicting persistent albuminuria in children with higher BMI at follow-up (again due to differences in sensitivity). Dipsticks were better at detecting albuminuria in the presence of hematuria, although hematuria worsened the prediction of persistent albuminuria at follow-up. These inconsistent findings in children with hematuria need to be interpreted cautiously. There are no comparable data from other studies, and these results are largely influenced by the continuity correction of 0.5, resulting in unstable estimates.

Long-term prospective studies are needed to determine the risk of ESKD in Aboriginal children and young adults with albuminuria and how the risks change in association with other comorbidities such as hypertension and diabetes.

Compared with the cost of relocation, dialysis and other treatments for sustaining an Aboriginal Australian on dialysis for an average survival period of 20 years [34], it may eventuate that health dollars and much psychological suffering could be saved through a primary prevention program, as has been proposed for other high-risk populations [35, 36]. Point-of-care testing for community risk assessment is culturally appropriate and widely accepted within Aboriginal communities [11, 12]. Our results support the use of Multistix dipsticks as a reliable, low-cost, diagnostic instrument for albuminuria in Aboriginal and other children.

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Conflict of interest statement There were no competing interests identified in the data collection or writing of this manuscript.

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Risk of CKD in Australian Indigenous and Nonindigenous Children: A Population-Based Cohort Study

Leigh Haysom, MD,[1,2] Rita Williams, BA,[1] Elisabeth Hodson, MD,[2,3] Pamela Lopez-Vargas, BN,[1] L. Paul Roy, MD,[4] David Lyle, MD, PhD,[5] and Jonathan C. Craig, MD, PhD[1,6]

Background: Aboriginal Australians have a 9-fold increased risk of end-stage renal disease. There is no information about the natural history and risk of chronic kidney disease (CKD) in Aboriginal and non-Aboriginal children.

Study Design: Using a prospective study design, we aimed to determine the prevalence of persistent markers and risk factors for CKD in Australian Aboriginal and non-Aboriginal children and whether Aboriginal children are at increased risk of persistent markers of CKD after accounting for sociodemographic differences.

Setting & Participants: Children were enrolled from elementary schools throughout New South Wales.

Predictor: Aboriginal (Aboriginal and Torres Strait Islander Australians) versus non-Aboriginal ethnicity.

Outcomes & Measurements: Urine analysis, height, weight, blood pressure, birth weight, and sociodemographic status were measured at baseline and 2-year follow-up. Albuminuria was defined as albumin-creatinine ratio of 3.4 mg/mmol or greater, hematuria as 25 or greater red blood cells/μL ($\geq$1+), obesity as body mass index of 2 SDs or greater, and systolic and diastolic hypertension as blood pressure greater than the 90th percentile.

Results: 2,266 children (55.1% Aboriginal; 51.0% boys; mean age, 8.9 $\pm$ 2.0 years [SD] years) were enrolled at baseline. Early markers and predictors of CKD at baseline were frequent: hematuria (5.5%), albuminuria (7.3%), obesity (7.1%), systolic hypertension (7.2%), and diastolic hypertension (5.8%). 1,432 children (63%) were available for retesting at 2-year follow-up (54.0% Aboriginal; 50.5% boys; mean age, 10.5 $\pm$ 2.0 years). Persistent obesity (5.3%) was frequent, but persistent markers of CKD were infrequent (systolic hypertension, 1.1%; diastolic hypertension, 0.2%; hematuria, 1.1%; and albuminuria, 1.5%). Although there were more Aboriginal than non-Aboriginal children with baseline hematuria (7.1% versus 3.6%; $P = 0.001$), after adjustment for age, sex, birth weight, and sociodemographic status, there was no increased risk of persistent hematuria, albuminuria, obesity, or hypertension in Aboriginal children.

Limitations: Persistent markers of CKD were much less frequent than anticipated, which may have affected study power. The group lost at follow-up was older children, which may have biased results.

Conclusions: Overall, only 20% of children found to have markers of early CKD had persistent abnormalities (diastolic and systolic hypertension, albuminuria, and hematuria) 2 years later, equivalent to a population point prevalence of 1% to 2% in children with a mean age of 10 years. Aboriginal children had greater rates of baseline and transient hematuria, but no increased risk of persistent markers of CKD, suggesting that adolescence and young adulthood is a critical time for preventative strategies.
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INDEX WORDS: Aboriginal; albuminuria; disadvantage; end-stage renal disease; follow-up; health determinants; hypertension; isolation; obesity; remoteness.

Morbidity and premature mortality from chronic kidney disease (CKD) are a much greater burden for indigenous than nonindigenous populations. Native American Indians have a 2 times greater incidence of end-stage renal disease (ESRD) compared with nonindigenous Americans, although the disparity is almost 4 times greater for Southwestern Native Americans.[1] Canadian Indians have 2½ times greater incidence of ESRD compared with the total

From the [1]Centre for Kidney Research, The Children's Hospital at Westmead and [2]The School of Public Health, University of Sydney; [3]Department of Nephrology, The Children's Hospital at Westmead; [4]The Children's Hospital at Westmead; [5]Department of Rural Health, University of Sydney; and [6]Department of Clinical Epidemiology, The School of Public Health, University of Sydney, Sydney, Australia.

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Address correspondence to Leigh Haysom, Centre for Kidney Research, The Children's Hospital at Westmead, Locked Bag 4001, Westmead NSW 2145, Australia. E-mail: leighh@chw.edu.au

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Canadian population.[2] Aboriginal and Torres Strait Islander Australians (hereafter referred to as Aboriginal) are 9 times more likely than non-Aboriginal Australians to develop ESRD.[3] ESRD occurs almost 10 years earlier in Australian Aboriginal people, at a median age of 51 versus 60 years in non-Aboriginal Australians.[4]

A much greater proportion of ESRD in Aboriginal Australians is attributed to diabetic nephropathy (47%) compared with non-Aboriginal Australians (17%), but little is known about the early causal pathways leading to these health disparities.[4] Most research to date has documented disease end points in high-risk communities,[1,2,4] with few studies measuring or adjusting for environmental risk factors that will also affect nonindigenous people, such as lack of access to health care and remote and lower standards of living.[5] There are several studies from high-risk indigenous communities describing the prevalence of early CKD markers,[6-8] but there are no population-based studies that document the persistence of early CKD markers in indigenous compared with nonindigenous children.

Our aim is to determine the prevalence of persistent markers and risk factors for CKD in Australian Aboriginal and non-Aboriginal children and whether Aboriginal children are at increased risk of CKD after accounting for sociodemographic differences.

METHODS

Selection of Participants

Government-run elementary schools were approached for testing from urban, coastal, rural, and remote locations across the state of New South Wales. This state has the largest Aboriginal population in Australia, and Aboriginal people within New South Wales have 3 times the risk of ESRD than non-Aboriginals.[3] To maximize power, sampling was performed to obtain equal numbers of Aboriginal and non-Aboriginal children and similar proportions from urban, coastal, rural, and remote areas. All elementary schools in remote communities were approached and other areas were sampled if more than 20 Aboriginal children in the relevant age range attended. We attempted to enroll all Aboriginal students from participating schools and match them for age and sex with a random sample of non-Aboriginal students.

Aboriginal status was determined by using the Australian Bureau of Statistics best practice recommendations, asking the Standard Indigenous Question on the consent form "Is your child of Aboriginal or Torres Strait Islander origin?"[9] All Aboriginal children in the participating elementary schools were offered testing for height, weight, blood pressure, and urinary abnormalities by means of dipstick. We aimed to recruit equal numbers of boys and girls, Aboriginal and non-Aboriginal children, and approximately equal numbers of children from each 12-month age group.

Aboriginal Community Engagement

Consultation with local Aboriginal Medical Services and consent from community leaders was undertaken before the start of the study. Approval was obtained from the Ethics Committees of the Children's Hospital at Westmead, University of Sydney, New South Wales Area Health Services, and New South Wales Department of Education and Training. Informed consent was obtained for each child, and in accordance with National Health and Medical Research Centre Guidelines for Ethical Conduct in Aboriginal and Torres Strait Islander Research,[10] data were collected by using a standardized form and de-identified for storage and analysis before being returned to each community after the study visit. Permission to publish data also was obtained from each community.

Measurement of Markers of CKD

Markers and predictors of CKD measured were hematuria, albuminuria, systolic and diastolic hypertension, and obesity. Risk factors known and believed to be associated with the development of these markers in Aboriginal and non-Aboriginal people also were recorded, including age, sex, growth parameters, birth weight, and environmental health determinants: measures of geographic isolation and social disadvantage.

A morning clean-catch urine specimen was collected from each child, with dipstick analysis for hematuria and albuminuria performed at the survey site on fresh specimens using a Bayer Clinitek 50 machine (Bayer Healthcare, Australia).[11] Leukocyte and nitrite levels also were recorded for later adjustment for abnormalities of presumed urinary tract infection. Girls older than 8 years who were found to have hematuria were questioned about menses, and, if appropriate, collection was performed at another time. According to Kidney Disease Outcomes Quality Initiative (KDOQI) definitions, hematuria was defined as dipstick 1+ or greater (equivalent to 25 red blood cells/μL; 1+), and albuminuria, as albumin-creatinine ratio of 3.4 mg/mmol or greater.[12]

Birth weight was provided by the parent/carer by recall or from the child's health record. Height was measured in stocking feet to the nearest 0.1 cm using a SECA 220 telescopic portable stadiometer (Ecomed, NSW, Australia)[13] that was calibrated between screening visits. Weight was measured in stocking feet and school uniform on digital scales to the nearest 0.01 kg. Body mass index (BMI) SD z score (SD) was calculated using an age- and sex-adjusted program.[14] Blood pressure was measured on the right arm with the child sitting, using an aneroid sphygmomanometer and the largest cuff to encircle the arm and cover at least three-quarters of the length of the upper arm.[15] In children younger than 13 years, diastolic pressure was measured at the point of muffling (Korotkov 4). For older children, the point of disappearance was used (Korotkov 5).[16] Systolic and diastolic hypertension was defined as blood pressure greater than the 90th percentile for age and sex.

Follow-up measurements were performed 2 years after baseline testing at the elementary or new high school for all available children, and the frequency of persistent CKD markers (markers detected at baseline and follow-up) was ascertained.

Standardization of urban, coastal, rural, and remote locality was made using ARIA++, a successor to the original Accessibility/Remoteness Index of Australia, with each subject given an index score according to their postcode of residence.[17] Using geographic information system capabilities, distances, services, and population density for each locality are converted to a continuous variable with values ranging from 0 for high accessibility to 18 for extreme remoteness. ARIA++ values for this NSW study ranged from 0 to 14, and for categorical analysis, scores were grouped into quartiles. Isolation categories (and ARIA++ score range) used were least isolation (0 to 1.1), low-mid isolation (1.2 to 2.4), high-mid isolation (2.5 to 4.9), and highest isolation (5.0 to 14.0).

To determine the level of social and economic well-being of areas studied, the Socio-Economic Indexes for Areas 2001[18] Index of Disadvantage was applied to subjects at the level of collection district of residence. This is the smallest geographic area for which the index is available and includes approximately 200 households. The Index of Disadvantage is a continuous score based on such characteristics as low income, lower level of education, high unemployment, and unskilled jobs. It has been standardized to a mean of 1,000 and an SD of 100 across all collection districts in Australia, ie, 95% of scores are 800 to 1,200. Higher scores indicate higher socioeconomic status and least disadvantage. For categorical analysis, scores were grouped into quartiles: highest disadvantage (680 to 835), high-mid disadvantage (836 to 960), low-mid disadvantage (961 to 988), and least disadvantage (989 to 1,103).

Data Analysis

Comparisons between children followed up and those with only baseline data were made according to ethnicity, sex, age groups, birth-weight quartiles, BMI SD quartiles, and categories of isolation and disadvantage by using χ^2 test. Odds ratios and relative risks for baseline and persistent markers of CKD in Aboriginal compared with non-Aboriginal children (referent group) were determined by using logistic regression with 95% confidence intervals (CIs). The relative risk between other potential predictors (sex, age, birth weight, BMI, geographic isolation, and social disadvantage) and persistent markers of CKD was determined by using logistic regression with 95% CIs. The presumed lowest risk category of each predictor was used as the referent group. The Mantel extension test was used to determine linear trends across categories. Analyses were adjusted for age, sex, BMI SD, birth weight, categories of isolation and disadvantage, and school by using a random-effects model.

Tests for interactions between ethnicity, sex, age, categories of isolation and disadvantage, and other significant variables in the final model were performed. Significance was set at P less than 0.05 for main effects and interactions. Statistical analysis was completed using SAS (SAS Institute, Cary, NC) and SPSS (SPSS Inc, Chicago, IL) software.

We planned to collect data at baseline from 1,000 Aboriginal and 1,000 non-Aboriginal children, which were sufficient to detect differences in prevalence of markers of CKD between the 2 groups of 2.9% versus 1.1%, 5.5% versus 2.9%, 8.2% versus 6.0%, and 9.4% versus 7.2% at 80% power for hematuria, albuminuria, obesity, and systolic hypertension, respectively. We anticipated a 60% to 70% follow-up rate, which would allow detection of differences in persistent markers between Aboriginal and non-Aboriginal children of 3.8% versus 1.5%, 3.2% versus 1.0%, 7.6% versus 5.3%, and 7.3% versus 5.0% at 80% power for hematuria, albuminuria, obesity, and systolic hypertension, respectively.

RESULTS

From February 2001 to June 2004, a total of 2,266 children were enrolled from 37 primary schools across New South Wales. Participation rates for both Aboriginal and non-Aboriginal students were 85% to 100%.

There were 1,248 (55.1%) Aboriginal children, 51% were boys, and mean age was 8.9 ± 2.0 (SD) years. A more detailed description of baseline characteristics has been reported elsewhere.[19]

Characteristics at 2-Year Follow-up

At 2-year follow-up from March 2004 to December 2006, there were 1,432 (63.0%) children available for retesting; 773 (54.0%) were Aboriginal, 50.4% were boys, and mean age was 10.5 ± 2.0 years (Table 1). Comparing the overall group at follow-up with children with only baseline data, there were significantly more children from the older age groups and urban areas who had no follow-up data ($P < 0.001$). There were no differences in ethnicity, sex, birth weight, BMI SD, and social disadvantage category between children at follow-up and children with only baseline data.

Prevalence of Baseline Markers of CKD in Aboriginal and Non-Aboriginal Children

Obesity (7.1%) and early markers of CKD at baseline were common: hematuria (5.5%), albuminuria (7.3%), systolic hypertension (7.2%), and diastolic hypertension (5.8%; Table 2). There was no increased risk of these early markers of CKD in Aboriginal compared with non-Aboriginal children, with the exception of hematuria (7.1% versus 3.6%; adjusted odds ratio, 2.25; 95% CI, 1.37 to 3.69; $P = 0.001$).

Table 1. Characteristics of Children at Baseline Stratified by Follow-up Status

Variable	Follow-up Data Available (n = 1,432)	%	Baseline Data Only Available (n = 834)	%	P
Ethnicity					
Aboriginal	773	54.0	475	57.0	0.2
Non-Aboriginal	659	46.0	359	43.0	
Sex					
Boys	723	50.5	432	51.8	0.5
Girls	709	49.5	402	48.2	
Age groups (y)					
4-5.9	144	10.1	67	8.0	<0.001
6-6.9	192	13.4	89	10.7	
7-7.9	237	16.6	93	11.2	
8-8.9	221	15.4	112	13.4	
9-9.9	231	16.1	120	14.4	
10-10.9	196	13.7	165	19.8	
11-14.8	211	14.7	188	22.5	
Birth weight quartiles (g)*					
412-2,920	259	25.6	86	21.1	0.3
2,921-3,316	255	25.2	107	26.2	
3,317-3,685	246	24.4	111	27.2	
3,686-5,272	250	24.8	104	29.4	
Body mass index SD quartiles*					
−4.8 to −0.8	355	25.0	205	24.9	0.9
−0.7 to 0.1	352	24.8	210	25.5	
0.2 to 0.7	363	25.5	203	24.6	
0.8 to 6.9	352	24.8	206	25.0	
Geographic isolation (ARIA++ score)					
Least (0-1.1)	358	25.0	252	30.2	<0.001
Low-mid (1.2-2.4)	453	31.6	186	22.3	
High-mid (2.5-4.9)	261	18.2	260	31.2	
Highest (5.0-14.0)	360	25.2	136	16.3	
Social disadvantage (SEIFA score)					
Least (989-1,103)	342	23.9	206	24.7	0.3
Low-mid (960-988)	385	26.9	200	24.0	
High-mid (836-960)	370	25.8	206	24.7	
Highest (680-835)	335	23.4	222	26.6	

Abbreviations: ARIA, Accessibility and Remoteness Index of Australia; SEIFA, Socio-Economic Indexes For Areas.
*Data do not equal column totals.

Prevalence of Persistent Markers of CKD in Aboriginal and Non-Aboriginal Children

At 2-year follow-up, the overall prevalence of persistent markers of CKD was much less frequent: hematuria (1.1%), albuminuria (1.5%), systolic hypertension (1.0%), and diastolic hypertension (0.1%; Table 2). Obesity remained relatively frequent at 5.3%. There was no increased risk of any persistent marker in Aboriginal compared with non-Aboriginal children.

Physiological and Sociodemographic Predictors for Persistent Markers of CKD

There was no increased risk of any persistent marker of CKD for girls compared with boys or for lower birth weight compared with higher birth weight (Table 3). Risk of persistent hematuria increased with increasing age (trend $P = 0.004$). Increasing age was not a risk factor for any other persistent marker of CKD. Risk of persistent systolic hypertension increased with increasing BMI SD (trend $P = 0.001$), and the highest BMI SD quartile was significantly associated with risk of persistent systolic hypertension (adjusted relative risk, 5.78; 95% CI, 1.24 to 26.73; $P = 0.03$). There was a decreasing risk of persistent systolic hypertension and persistent albuminuria with increasing social disadvantage (both trend $P < 0.02$). The quartile with the highest social disadvantage had a significantly

Table 2. Prevalence of Baseline and Persistent Markers of CKD in Aboriginal and Non-Aboriginal Children at 2-Year Follow-up

	Baseline Markers				Persistent Markers			
	Overall	Non-Aboriginal (referent category)	Aboriginal	*P*	Overall	Non-Aboriginal (referent category)	Aboriginal	*P*
Hematuria (dipstick ≥ 25 RBC/HPF)								
Events (%)	122 (5.5)	36 (3.6)	86 (7.1)		15 (1.1)	6 (0.9)	9 (1.2)	
Adjusted OR*		1.00	2.25 (1.37-3.69)	0.001		1.00	1.36 (0.29-6.36)	0.9
Albuminuria (ACR ≥ 3.4 mg/mmol)								
Events (%)	157 (7.3)	63 (6.5)	94 (8.1)		20 (1.5)	9 (1.4)	11 (1.5)	
Adjusted OR*		1.00	1.37 (0.93-2.01)	0.1		1.00	1.80 (0.70-4.65)	0.6
Obesity (BMI ≥ 2 SD)								
Events (%)	145 (7.1)	63 (6.7)	82 (7.4)		74 (5.3)	33 (5.1)	41 (5.4)	
Adjusted OR*		1.00	1.10 (0.76-1.44)	0.5		1.00	1.09 (0.67-1.78)	0.2
Systolic hypertension (SBP > 90th centile)								
Events (%)	162 (7.2)	67 (6.7)	95 (7.7)		14 (1.0)	6 (0.9)	8 (1.1)	
Adjusted OR*		1.00	1.22 (0.87-1.57)	0.3		1.00	1.25 (0.45-3.47)	0.7
Diastolic hypertension (DBP > 90th centile)								
Events (%)	131 (5.8)	62 (6.2)	69 (5.6)		2 (0.1)	1 (0.2)	1 (0.1)	
Adjusted OR*		1.00	0.94 (0.57-1.31)	0.6		1.00	—	—

Note: Persistent marker found at both baseline and follow-up.

Abbreviations: ACR, albumin-creatinine ratio; BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; HPF, high power field; OR, odds ratio; RBC, red blood cell; SBP, systolic blood pressure.

*Adjusted when appropriate for age, sex, birth weight, BMI SD, systolic blood pressure, diastolic blood pressure, isolation category, and disadvantage category.

lower risk of persistent albuminuria (adjusted relative risk, 0.17; 95% CI, 0.05 to 0.57; $P = 0.004$). There were no physiological or sociogeographic predictors of persistent obesity found.

There were no interactions found between environmental health determinants of geographic isolation and social disadvantage and ethnicity, age, sex, or other covariates in any model.

DISCUSSION

This is the first population-based cohort study describing the natural history of early CKD in indigenous children that includes a nonindigenous comparator group and measures and adjusts for social disadvantage and geographic isolation. Nonindigenous comparators are essential in deciding the level of increased risk of indigenous children against the background population rates, and measurement of sociodemographic factors is important in adjusting for the potentially confounded relationship between health, isolated living, and social disadvantage. In our prospective study of 2,266 children, 50% of whom are Aboriginal, during 2 years of follow-up, we show that persistent markers of CKD are infrequent and there is no increased risk of persistent markers in Aboriginal children compared with non-Aboriginal children, even after adjustment for social disadvantage and geographic isolation.

The follow-up data show that although baseline markers were frequent in Aboriginal and non-Aboriginal elementary school–aged children, most of these abnormalities were transient. At a single test, Aboriginal children had twice the risk of hematuria as non-Aboriginal children, but no increased risk of persistent hematuria. Other Australian indigenous studies had a similarly high cross-sectional prevalence of hematuria and albuminuria in children.[6,20] These studies were from extremely disadvantaged communities with the highest rates of ESRD and cardiovascular disease in the world. Without follow-up testing or comparative data from a nonindigenous group, the assumption is that these frequent one-off markers lead to the high states of disease seen in adulthood, and ethnically based biological effects are causative.[21] Our baseline results show that almost 80% of baseline urinary abnormalities are transient. Semiquantitative

Table 3. Physiological and Environmental Predictors of Persistent Markers of CKD

Predictor	Hematuria (dipstick ≥ 25 RBC/HPF)		Albuminuria (ACR ≥ 3.4 mg/mmol)		Obesity (BMI ≥ 2 SD)		Systolic Hypertension (SBP > 90th centile)	
	No. (%)	AOR* (95% CI)	No. (%)	AOR* (95% CI)	No. (%)	AOR* (95% CI)	No. (%)	AOR* (95% CI)
Sex								
Boys†	5 (0.7)	1.00	10 (1.5)	1.00	41 (5.8)	1.00	6 (0.8)	1.00
Girls	10 (1.5)	1.37 (0.50-3.79)	10 (1.5)	1.12 (0.47-2.70)	33 (4.7)	0.89 (0.51-1.55)	8 (1.1)	1.18 (0.31-4.45)
Age tertiles (y)								
4.0-7.9†	3 (0.7)	1.00	4 (0.9)	1.00	25 (5.3)	1.00	4 (0.9)	1.00
8.0-9.9	5 (1.1)	1.50 (0.21-10.50)	5 (1.1)	1.07 (0.17-5.66)	25 (5.3)	1.00 (0.51-1.96)	4 (0.9)	0.92 (0.28-3.08)
10.0-15.0	7 (1.5)	3.21 (0.62-16.56)‡	11 (2.4)	2.95 (0.76-11.48)	24 (5.1)	1.00 (0.55-2.26)	6 (1.3)	1.36 (0.50-3.71)
Birth weight (g)								
>2,500†	11 (1.2)	1.00	19 (2.1)	1.00	48 (5.1)	1.00	9 (1.0)	1.00
≤2,500	0 (0)§	0.43 (0.02-7.31)	0 (0)§	0.24 (0.01-4.05)	6 (5.9)	1.17 (0.50-2.85)	1 (1.0)	1.03 (0.13-8.21)
BMI SD quartiles								
−4.8 to −0.8†	4 (1.2)	1.00	6 (1.8)	1.00	0 (0)	1.00	1 (0.3)	1.00
−0.7 to 0.1	1 (0.3)	0.44 (0.04-5.27)	6 (1.8)	0.83 (0.24-2.96)	0 (0)	—	2 (0.6)	1.45 (0.01-3.94)
0.2 to 0.7	6 (1.7)	1.81 (0.25-13.10)	7 (2.1)	1.31 (0.31-5.57)	0 (0)	—	4 (1.1)	2.35 (0.31-5.90)
0.8 to 6.9	4 (1.2)	1.00 (0.89-3.59)	1 (0.3)	0.15 (0.01-2.05)	74 (5.3)	—	7 (2.0)	5.78 (1.24-26.73)†
Isolation								
Least†	1 (0.3)	1.00	7 (2.1)	1.00	22 (6.2)	1.00	1 (0.3)	1.00
Low-mid	6 (1.4)	1.77 (0.16-19.18)	5 (1.1)	0.20 (0.05-0.87)	27 (6.0)	0.81 (0.27-2.42)	10 (2.2)	4.00 (0.81-19.77)
High-mid	6 (2.3)	5.90 (0.74-47.32)	4 (1.6)	0.49 (0.11-2.24)	6 (2.4)	0.35 (0.11-1.09)	2 (0.8)	2.20 (0.19-25.40)
Highest	2 (0.6)	2.42 (0.22-26.58)	4 (1.3)	0.44 (0.11-1.82)	19 (5.4)	0.60 (0.17-2.13)	1 (0.3)	0.95 (0.07-4.62)
Social disadvantage								
Least†	2 (0.6)	1.00	7 (2.1)	1.00	20 (5.9)	1.00	7 (2.1)	1.00
Low-mid	6 (1.7)	1.79 (0.06-9.65)	6 (1.6)	0.95 (0.26-3.40)	20 (5.2)	0.75 (0.34-1.67)	4 (1.0)	0.66 (0.25-1.72)
High-mid	4 (1.1)	1.19 (0.30-4.73)	5 (1.6)	0.95 (0.08-2.43)	13 (3.7)	0.62 (0.22-1.71)	2 (0.6)	0.32 (0.09-1.08)
Highest	3 (0.9)	1.00 (0.21-4.69)	2 (0.6)	0.17 (0.05-0.57)	21 (6.4)	1.38 (0.26-3.67)	1 (0.3)	0.16 (0.05-2.52)†

Note: Persistent marker found at both baseline and follow-up. ARIA++ score 0 to 1.1 indicates least isolation; ARIA++ score 1.2 to 2.4, low-mid isolation; ARIA++ score 2.5 to 4.9; high-mid isolation; ARIA++ score 5.0 to 14.0, highest isolation. SEIFA score 989 to 1,103 indicates least disadvantage; SEIFA score 960 to 988, low-mid disadvantage; SEIFA score 836 to 959, high-mid disadvantage; SEIFA score 680 to 835, highest disadvantage.

Abbreviations: ACR, albumin-creatinine ratio; AOR, adjusted odds ratio; ARIA, Accessibility and Remoteness Index of Australia; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; HPF, high-power field; RBC, red blood cell; SBP, systolic blood pressure; SEIFA, Socio-Economic Indexes For Areas.

*Adjusted when appropriate for ethnicity, age, sex, birth weight, BMI SD, systolic blood pressure, diastolic blood pressure, isolation category, and disadvantage category.

†Referent group.

‡Trend $P < 0.05$.

§To allow analysis, 0.5 added to cells.

single estimations of urinary blood and protein in children vary according to posture, illness, exercise, and time of day.[22] A 2 times greater rate of transient hematuria may reflect the greater incidence of transient disease seen in indigenous children, such as postinfectious glomerulonephritis.[8] Persistence of these markers is infrequent in our cohort and does not occur more frequently in Aboriginal children.

Obesity is a frequent predictor of CKD in these children, although no more so in Aboriginal children. Rates of persistent obesity of 5.3% found in our study are similar to national rates of obesity in Australian elementary school–aged children of 6%.[23] Increasing BMI was predictive of persistent systolic hypertension, and these children are at risk of early-onset diabetes, cardiovascular disease,[24,25] and most likely CKD. They will be closely followed up during the final 2 years of the study.

There was a decreasing risk of persistent systolic hypertension and persistent albuminuria in the most disadvantaged children. These associations seem contradictory to other studies.[5,26,27] Our study sampled children in areas where Aboriginal children reside, in areas of greatest disadvantage for the state of New South Wales.[28] Therefore, the highest socioeconomic quartile in our cohort (indicating lesser disadvantage) correlates with mid-range socioeconomic categories in other comparative studies.[29,30] Our findings are consistent with these studies, showing risk factors for chronic disease with a bell-shaped curve across different socioeconomic environments; lowest risk occurs at either extreme of socioeconomic status, with highest risk occurring in mid-range socioeconomic categories.

A potential limitation of our study was the 37% lost to follow-up, but we have shown that this group was not significantly different from children who were followed up, except for age and geographic location. There were proportionally more children followed up in remote areas compared with urban areas. This reflects the close relationships originally established between area health workers in remote communities and shows a greater degree of disengagement in urban children. The greater proportion of older children lost to follow-up results from older children absent or no longer at school, and we accept that they are likely to be the children most at risk of chronic disease. We are attempting to address these differences at our final 4-year follow-up. Although these issues are a concern in terms of sampling bias, regression analyses for risk of CKD markers in Aboriginal children were adjusted for age and location in an attempt to account for these imbalances.

The study was adequately powered to find relatively small differences in risk of persistent markers of CKD if they existed between Aboriginal and non-Aboriginal children. However, persistent markers were much less frequent than anticipated, which may have affected the study power. Measurement of the main predictor of risk, Aboriginal status, was performed using best practice recommendations.[9] Measurement of social disadvantage and geographic isolation was made by using standardized systems that have been applied reliably in geographically and ethnically similar population-based samples.[3,31] We accept that unmeasured confounding from individual-level socioeconomic factors remains as a study bias.[30] With further data collection, multilevel analyses could be used to identify, measure, and correct for ecological bias when spatially aggregated measures are applied to individual data, an approach we will use for future follow-up.[32] Parentally recalled birth weight has been shown as a reliable proxy for recorded birth weight in population-based research.[33]

Albuminuria is the strongest predictor of death, cardiovascular disease, and ESRD in Aboriginal adults, which is why it was used in our study.[34,35] Spot albumin-creatinine ratio at the cut-off value used in this study has good receiver operator curve characteristics for detecting pathological albuminuria.[36] Blood pressure was measured using appropriate cuff sizes, with repeated measurements performed in hypertensive children. A 90th percentile cutoff was used to classify hypertension because we anticipated insufficient outcomes to perform analyses at a 95th percentile cutoff. Obesity was determined using BMI SDs, which has been validated for use in this age group of children,[37] and our prevalence of obesity is similar to national surveys.[23] Measurement of such outcomes as central obesity and blood lipid, glucose, and insulin levels would have been desirable for evidence of prediabetes and metabolic syndrome[25]; however, measuring all possible risk factors was beyond the practicali-

ties of such a large school-based screening study. Painful and embarrassing procedures would have been counterproductive to the current success of our follow-up recruitment rates.

Within New South Wales, there is no increased risk of persistent markers of CKD in Aboriginal children compared with non-Aboriginal children, and the 3-fold increased risk of CKD experienced by Aboriginal adults in New South Wales and 9-fold increased risk of all indigenous Australians is not yet established in this age group. This suggests that adolescence and young adulthood are likely to be critical times for preventative strategies. These results also show that a single measurement of markers of CKD in children is misleading because almost 80% of all abnormalities are transient. Increasing BMI is the strongest risk factor for persistent hypertension and persistent hematuria in these children, and obesity remains the most concerning and persistent predictor of CKD in this age group. This suggests that overweight and obesity in children should be addressed from an elementary school age. These results provide useful information for primary health care practitioners, pediatricians, nephrologists, policy makers, and families.

We look forward to reporting the 4-year follow-up of these children and adolescents. This study highlights a need for long-term prospective observational studies of risk of CKD in Aboriginal and non-Aboriginal young adults over a range of sociogeographic areas. We plan to follow up this cohort of children for an additional 8 years into young adulthood.[38]

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