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Vision loss and diabetic retinopathy prevalence and risk among a cohort of Indigenous and non-Indigenous Australians with type 2 diabetes receiving renal haemodialysis treatment: The retinopathy in people currently on renal dialysis (RiPCORD) study

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ABSTRACT

Aims: Diabetic nephropathy, vision loss and diabetic retinopathy (DR) are frequent comorbidities among individuals with type 2 diabetes (T2D). The Retinopathy in People Currently On Renal Dialysis (RiPCORD) study sought to examine the epidemiology and risk of vision impairment (VI) and DR among a cohort of Indigenous and non-Indigenous Australians with T2D currently receiving haemodialysis for end-stage renal failure (ESRF).

Methods: A total of 106 Indigenous and 109 non-Indigenous Australians were recruited in RiPCORD across five haemodialysis centres in urban and remote settings. Clinical assessments, questionnaires and medical record data determined the rates of ocular complications and risk factor profiles.

Results: Prevalence rates include unilateral VI, 23.5 %; bilateral VI, 11.7 %; unilateral blindness, 14.2 %; and bilateral blindness, 3.7 %, with no significant differences between sub-cohorts (p=0.30). DR prevalence rates were 78.0 % among non-Indigenous Australians and 93.1 % among Indigenous Australians (p=<0.001). Non-Indigenous ethnicity (OR: 0.28) and pre-dialysis diastolic blood pressure (OR: 0.84 per 10-mmHg) were protective, while peripheral vascular disease (OR: 2.79) increased DR risk.

Conclusions: Ocular complications among individuals with T2D and ESRF are disproportionately high, especially for Indigenous Australians, and beyond what can be accounted for by risk factor variation. Findings suggest a need to improve screening and preventative efforts within this high-risk population group.

1. Introduction

Diabetic retinopathy (DR) and nephropathy (DN) are key complications of diabetes that, if left untreated, result in significant morbidity and increased risk of mortality.[1–4] Prevalence estimates for DR predict that worldwide 160 million people have some level of DR, and 47 million have the vision-threatening phenotypes proliferative DR (PDR) and diabetic macular oedema (DMO).[5,6] Meanwhile, DN affects 285 million (6.4 %) adults worldwide and is responsible for 30–50 % of all cases of chronic kidney disease (CKD).[4] Given that both

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DR and DN share risk factors such as hyperglycaemia, dyslipidaemia and hypertension, both can coincide, with up to 49 % of individuals with nephropathy also having co-existing retinopathy.[7–9] Furthermore, epidemiological eye health surveys have found associations between vision loss, such as vision impairment and blindness, and CKD.[10] While DR and DN have parallels in that they are both microangiopathies; there is much still to be understood about the associations between the two. Some evidence suggests that DR can predict future DN development,[11,12] differentiate between DN and other causes of CKD and that the presence of DR is one of the most significant predictors of DN, with an estimated pooled diagnostic odds ratio of 5.7.[13]

The Aboriginal and Torres Strait Islander population (respectfully referred to as Indigenous Australians herein) have high rates of T2D-associated complications, with approximately 39 % and 50 % of Indigenous Australian adults with T2D having some level of DR and DN, respectively.[14,15] T2D is the single most critical contributor to end-stage renal failure (ESRF) among Indigenous Australians, accounting for two-thirds of incident ESRF requiring dialysis and treated on average 30 years earlier (55 vs 85 years) compared to the non-Indigenous population.[16] DR accounts for 5–12 % of vision loss in Indigenous Australians, yet only 1.7 % among non-Indigenous Australians. A population-based survey including Indigenous and non-Indigenous Australian adults found an association between DR and CKD.[17] The study analysed data from 335 individuals from South Australia and the Northern Territory who had undergone vitrectomy surgery for end-stage DR and found that Indigenous Australians were more likely to have CKD or be currently undergoing haemodialysis for ESRF. The differences were significant, with 79 % of Indigenous people with end-stage DR who had undergone vitrectomy having CKD and 35 % currently receiving haemodialysis treatment for ESRF. Comparatively, in the non-Indigenous group rates were 51 % and 7 %, respectively.[17] Additionally, mortality rates after vitrectomy surgery, despite being similar between Indigenous and non-Indigenous people, were heavily influenced by the presence of CKD and ESRF.[18] More recent evidence from primary health care data showed that markers of renal impairment, including an abnormal estimated glomerular filtration rate, severe macroalbuminuria and CKD, were more prevalent in those with sight-threatening maculopathy.[19]

Collectively, these findings highlight an important association between DR and DN among Indigenous Australian people. However, research has yet to focus on comparing the profiles of DR and vision loss among Indigenous and non-Indigenous Australians receiving haemodialysis (and indicator of end-stage kidney disease in the same way vitrectomy is for DR), and further investigations are warranted into the severity and prevalence estimates of DR and vision loss within these settings. Within a clinic-based study of Indigenous and non-Indigenous Australians who are currently receiving haemodialysis care for ESRF, we sought to determine the prevalence of vision impairment, blindness and DR utilising established methods of vision and retinal photography screening. The comorbidities and clinical risk factors associated with the presence of DR are also explored, as are the associated causes leading to end-stage CKD.

2. Materials and methods

2.1. Study context and ethical approvals

The Retinopathy in People Currently On Renal Dialysis (RiPCORD) study aimed to determine the epidemiology of vision loss and DR among a cohort of Indigenous and non-Indigenous Australian patients with laboratory-confirmed T2D currently receiving haemodialysis. The cross-sectional study was conducted between 2017 and 2021, involving adults aged over 18 years with diagnosed T2D and undergoing renal haemodialysis treatment at the time of recruitment. The study region included two distinct geographic regions; Central Australia and South Australia. The Central Australia region included the Alice Springs township with haemodialysis centres servicing patients across an area of approximately 548,400 km^2 and includes the largest dialysis centre in the Southern Hemisphere. Two separate clinical centres for haemodialysis treatment exist in Alice Springs, one government-owned organisation and the other privately owned. The second region is Southern Metropolitan Adelaide, which includes three dialysis units comprising two major tertiary hospitals and a single privately-owned haemodialysis centre.

Letters of support were obtained following community consultations between the ophthalmology departments at Flinders University and Alice Springs Hospital, along with key stakeholders involved in the care of dialysis patients, including unit managers and staff. In Central Australia, the research team consulted with the patient representatives and patients of Western Desert Dialysis (Purple House), an Aboriginal corporation that provides dialysis and social support in remote Indigenous communities, consumer reference groups and patients on dialysis during the early stages of the project and additional letters of support were received. The study was approved by the Southern Adelaide Research Ethics Committee (86.067) and the Central Australian Health and Research Ethics Committee (18–3116).

2.2. Study recruitment

Recruitment was achieved by identifying current patients with diabetes utilising the clinical information medical systems at each site. Patients who were unable to give informed consent were excluded, as were patients without diabetes or those with type 1 diabetes (T1D). The primary cause for renal dialysis was recorded, and those with more than one likely cause were included, as long as T2D was co-occurring. The aims and requirements of the study were explained to each prospective participant. Aboriginal participants were offered an interpreter whenever necessary. A total of 257 individuals across the five dialysis centres participated. Individuals who did not have retinal photography, visual acuity data, DR phenotyping and sufficient documentation of risk factors were excluded (n=18). A further 24 individuals with T1D were excluded, leaving 215 participants for complete analyses (Fig. 1). The final sample included 106 Indigenous Australians recruited primarily from Central Australia (n=102) and 109 non-Indigenous recruited from South Australia across five haemodialysis centres. Participants from Alice Springs were exclusively Indigenous Australians who either resided in Alice Springs or had relocated from remote communities to access clinical haemodialysis facilities. Study participants recruited from the Southern Adelaide regions were primarily of Caucasian ethnicity (>98 %).

2.3. Eye examination protocol

An adapted rapid assessment for avoidable blindness (RAAB) protocol was implemented for this assessment (World Health Organization).[20] Briefly, the protocol is suitable for population-based eye studies and designed to estimate the prevalence and causes of vision impairment (VI), blindness and eye care utilisation, developed for use in low-resource settings. Vision-related questionnaires informing eye health care access, glasses utilisation and previous ocular history were recorded on a standardised form. Any self-reported information was cross-checked with medical records at the haemodialysis clinic. Participants were asked whether they had ever seen an ophthalmologist or optometrist for a specific diabetes-related eye examination, and if so, how long ago (in months). This information was used to determine the proportion of participants with DM who adhered to the Australian National Health and Medical Research Council guidelines.[21]

The eye examination was conducted by trained optometrists, research assistants, ophthalmology trainees or supervising consultants using standardised protocols. Distance visual acuity (VA) using a logMAR chart (Brien Holden Vision Institute, Sydney) at 3 m at the haemodialysis clinic was measured and performed in an area illuminated at a minimum of 500 lux. The tumbling E chart was used for patients who

preferred this to the letter optotypes. Presenting VA was assessed first for the right eye and then for the left eye and whether glasses were used for the measurement. A best-corrected VA (BCVA) surrogate was achieved following the presenting VA, using a pinhole occluder if the presenting VA was worse than 6/12 in the assessed eye. This final pinhole VA is the primary outcome for determining the prevalence of vision impairment and blindness in the current study. Intraocular pressure was measured using a rebound tonometer (iCare, Vantaa, Finland), taking an average of six readings. Subsequently, the pupils were dilated with tropicamide 1 % and phenylephrine 2.5 % to assess the anterior and posterior segments of the eye. The anterior segment was either photographed or viewed with direct ophthalmoscopy using a slit-beam for the cornea and a round beam for lens status. An opacity was deemed not present, probably present, or present based on the retro-illumination technique at 30 cm.

A single 45-degree, macula-centered color retinal photograph of each eye was taken using the Topcon 3D-1 OCT Maestro (Topcon, Japan) for the Southern Adelaide region and the Canon CR32 (Canon Medical Systems, USA) for the Central Australia region to analyse the posterior eye. The retinal images were transferred and stored on a centralised server for disease-specific grading. On average, the clinical examination and eye imaging took 30 minutes and was best achieved before starting haemodialysis or immediately after commencing to allow the patient to settle into their haemodialysis treatment and the side effects of pupillary dilation to subside before exiting the dialysis unit. Care was taken when the patient was on the dialysis chair to not interfere with the haemodialysis equipment, notably the arteriovenous fistula and the dialyser. For the Central Australia cohort, the eye examinations took place before haemodialysis since community feedback suggested this was the ideal approach to not disturb participants during haemodialysis or delay their departure after haemodialysis. The patient utilised the arm without the arteriovenous fistula when holding the pinhole occluder, and the intraocular pressure assessment was carried out from the side opposite the dialyser. Overall, 5 patients (4.7 % of the cohort) were not able to undertake retinal photography (due to frailty) and a head-mounted binocular indirect ophthalmoscope was used to assess the retina and confirmed through a review of existing medical records.

2.4. Study definitions and variables

2.4.1. Vision Loss

All participants were classified into the following severity scaling according to epidemiological eye health surveys from Australia and other high-income countries;[22] with no vision impairment (VA better than 6/12 in both eyes), unilateral vision impairment (VA worse than 6/12 in one eye but no vision impairment in the other), bilateral vision impairment (VA worse than 6/12 in both eyes but not reaching blindness definitions), unilateral blindness (VA worse than 6/60 in one eye) and bilateral blindness (VA worse than 6/60 in both eyes).

2.4.2. Systemic comorbidities and risk factor investigations

Comorbidities related to diabetes-related microvascular and macrovascular complications were recorded using available clinical medical records. Hypertension, hypercholesterolemia, cerebrovascular disease, ischaemic heart disease (angina, myocardial infarction) and peripheral vascular disease were all recorded as absent or present. Risk factor targets for managing T2D, including diabetes duration, glycosylated haemoglobin (HbA_{1c}) percentage and blood pressure (BP) measurements, were also recorded. The HbA_{1c} measurement was based on an average of the most recent three readings (dating back up to three years) because of the paucity of a regular data record in some instances and to provide temporal variability data.[23] The BP was taken as the pre-dialysis recording by the treating nurse during the site visit. Post-dialysis BP was similarly recorded, and the difference was described as the pre-post BP change. The period between the diagnosis of T2D and starting haemodialysis treatment was also recorded as a measure of an aggressive phenotype. The cause of haemodialysis was extracted from available medical records, but where a single a cause could not be identified through this method, type 2 diabetes was assigned as the presumed cause based on clinical judgment as assessed by the medical history, diabetes duration and management.

2.4.3. Classifying diabetic retinopathy

Two ophthalmologists with retinal sub-speciality training independently reviewed all case files, notes, and retinal images of individuals classified as having T2D. Each ophthalmologist graded the severity of DR and the presence or absence of diabetic macular oedema (DMO). Discrepancies were settled through a workshop between the two ophthalmologists, and a third adjudicator was brought in to reach a final consensus-based grading if an agreement could not be reached. If participant images were missing, the binocular indirect ophthalmoscopy grading was used as the best available DR grading after confirmation through medical notes requested from their regular eye care provider. DR was graded based on the simplified Wisconsin scale as; No DR, minimal, mild, moderate, or severe non-proliferative DR, or PDR.[21] The presence or absence of DMO and clinically significant diabetic macula oedema (CSMO) were recorded. DMO grading followed the following criterion: 1) exudates within 1–2 disc diameters of the fovea with intra-retinal haemorrhages, 2) circinate or group of exudates within the macula (the macula is considered the area within the retinal vascular arcade), 3) focal or grid laser scars visible or 4) any combination of the above. Criteria for CSMO were when the DMO as described above was within 500 microns of the foveal centre, exudates within 500 microns of the foveal centre associated with retinal thickening (the thickening itself may be outside the 500-micron radius), retinal thickening one disc area in size (1800 microns or larger) but part of which is within one disc diameter of the macular centre or macular focal/grid photocoagulation scars present. For this report, DMO and CSMO are re-classified as ‘any maculopathy’ when either was present, and a patient-level DR and maculopathy grade was assigned to all participants based on the worse grading of the two eyes.

3. Statistical analysis

Study data were collected and managed using REDCap (Research Electronic Data Capture) and exported for statistical analysis. Response rates were calculated for individuals invited to participate as those who consented, met eligibility criteria, and had ocular outcomes recorded. Participants’ demographic and clinical characteristics were summarised by the mean and standard deviation (SD) for normally distributed continuous data, the medial and interquartile range for skewed data, and counts and percentages for categorical data. Student t-test analysed the differences within continuous variables across groups and chi-squared or Fisher’s exact test for categorical variables and prevalence rates between groups, where appropriate. Any retinopathy (no DR vs any DR) was categorised as a binary outcome variable for the purpose of logistic regression analysis. All potential risk factors were either analysed as binary traits or linear traits with no clinically distinct cut-off points utilised for continuous variables. Univariate logistic regressions were performed to estimate the odds ratio (OR) and 95 % confidence intervals (CI) against DR for each demographic and risk factor without adjustments for the entire cohort to assess variables clinically associated with DR among the cohort of dialysis and T2D participants. The results of the univariate analysis were then used to perform a purposeful multivariate logistic regression analysis, whereby the univariate regression variables that reached 0.25 significance based on Wald chi-square statistics were included as confounders. Risk factors included in the model that did not change (>10 %) the odds ratios were removed. The final multivariate model adjusted for ethnicity, insulin use and peripheral vascular disease before adding other key explanatory variables individually based on purposeful selection. A P-value of less than 0.05 was considered statistically significant, and all analyses were performed

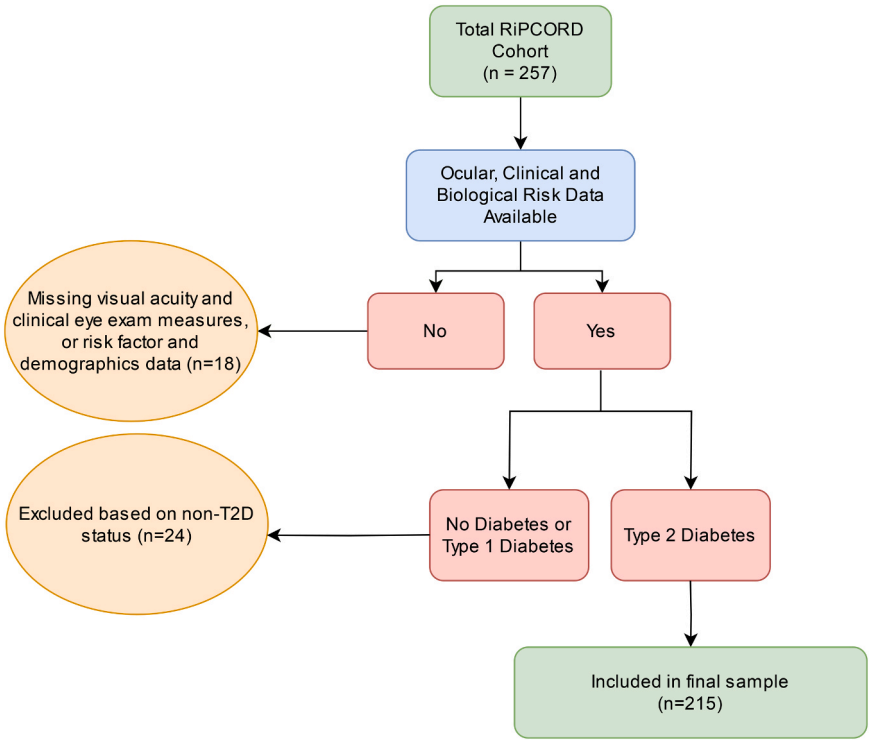

Fig. 1. Flowchart of participants included in the final analysis sample. RiPCORD – Retinopathy in People Currently On Renal Dialysis; T2D – type 2 diabetes.

by STATA software version 17.0 (Stata Corp., College Station, Texas).

4. Results

The demographics and clinical characteristics of the overall study population and among the Indigenous and non-Indigenous Australian sub-populations are shown in Table 1. The response rates across the five sites were between 72 % and 85 %, with the highest participation rate in Alice Springs. Of the total 215 participants, there was an equal distribution of males and females by age, the mean age was 65.1 (SD 13.5) years, but the Indigenous Australian population had a lower percentage of males (30.7 %), and this group on average, were younger (56.3 years, SD 11). Indigenous Australians had a shorter duration of a diabetes diagnosis (15.6 compared to 21.0 years), lower body-mass index, were more likely to be prescribed insulin to manage their diabetes, had a higher pre-dialysis and post-dialysis systolic BP, higher prevalence of neuropathy and smoking, and lower mean intraocular pressure. Overall, RiPCORD study participants had high rates of multi-morbidity, including hypertension (93.0 %), dyslipidaemia (80.5 %), ischaemic heart disease (55.2 %), cerebrovascular disease (17.8 %) and peripheral vascular disease (39.3 %).

The primary cause of ESRF leading to haemodialysis was T2D, being responsible for 89.2 % of all cases within the Indigenous Australian cohort and 89.4 % within the non-Indigenous Australian cohort. The other top causes of ESRF requiring dialysis among Indigenous Australians were hypertension (5.9 %) and glomerulonephritis (2.1 %), both coexisting with T2D. The non-Indigenous Australian population had a larger variety of primary causes for ESRF, such as medication toxicity, reflux nephropathy and renal calculi, amongst others (all causes less than 2.7 %).

The overall prevalence of normal vision in the population was 46.9 % (Table 2), with the remainder having some level of vision impairment or blindness in at least one eye. Within the non-Indigenous and Indigenous cohorts, unilateral vision impairment was most common (23.3 % and 23.6 %, respectively). Unilateral blindness was present among 19.1 % of Indigenous Australians and 8.2 % of non-Indigenous Australians, and bilateral blindness (worse than 6/60 in both eyes) was observed in 2 cases (2.3 %) of Indigenous Australians and 4 cases (5.5 %) among non-Indigenous Australians.

The rates and severity of retinopathy are presented in Table 3. Non-Indigenous participants were more likely to be free of retinopathy (22.0 % vs. 6.9 %, $P<0.001$). There were high proportions of individuals with vision-threatening PDR (27.0 %) and maculopathy (49.2 %). Indigenous Australians are affected at higher proportions primarily by the maculopathy endophenotype of DR (62.7 % versus 36.7 %, $p<0.001$), while non-Indigenous Australians were more likely to reach end-stage PDR (36.3 % versus 16.7 %, $p<0.001$).

Table 4 shows key risk factors associated with DR. In the univariate analysis and among the total cohort, independent risk factors for any retinopathy were insulin use (OR: 2.83, 95 % CI: 1.38–8.16) and the presence of peripheral vascular disease (OR: 2.92, 95 % CI: 1.14–7.44). Meanwhile, increasing age (OR: 0.71 per 10 years, 95 % CI: 0.52–0.98) and non-Indigenous Australian ethnicity (OR: 0.27, 95 % CI: 0.11–0.68) were associated with a reduced odds of any retinopathy. After multivariate logistic regression, non-Indigenous Australian ethnicity remained significant as a protective factor (OR: 0.28, 95 % CI: 0.10–0.73), and peripheral vascular disease associated with an increased risk association of any DR (OR: 2.79, 95 % CI: 1.06–7.33). Of importance, pre-dialysis diastolic BP was associated with a 16 % odds reduction for any DR (OR: 0.84 per 10-mmHg increase, 95 % CI: 0.81–0.89) in the multivariate model, which included multiple risk factors influencing T2D complications.

5. Discussion

In this current cross-sectional clinic-based study of DR prevalence, risk, and burden of vision loss among Indigenous and non-Indigenous Australians who were undergoing dialysis and had T2D, the prevalence rates of any vision loss, DR, and maculopathy were significantly higher than reported in other population-based investigations. Indigenous Australians were disproportionately affected by DR and maculopathy while having similar rates of vision loss compared to the non-

Table 1
Demographic and Clinical Characteristics of the Overall Study Cohort with Type 2 Diabetes and End-Stage Renal Failure by Indigenous and Non-Indigenous Status.

Characteristics	Total Cohort (n = 215)	Non-Indigenous Australians (n = 109)	Indigenous Australians (n = 106)	P – Value*
Demographics				
Age, years (SD)	65.1 (13.5)	73.1 (12.6)	56.3 (11.0)	**<0.001**
Gender, male (n, %)	108 (50.6)	77 (68.1)	32 (30.7)	**<0.001**
Clinical factors				
Body mass index, kg/m2 (SD)	28.8 (6.1)	30.8 (6.7)	27.4 (5.4)	**<0.001**
T2D duration, y (SD)	18.4 (13.4)	21.0 (12.7)	15.6 (13.6)	**<0.01**
Dialysis duration, y (SD)	3.2 (3.1)	3.0 (2.6)	3.4 (3.6)	0.41
Duration from T2D diagnosis and starting dialysis, y (SD)	16.8 (10.0)	20.9 (10.8)	13.0 (7.4)	**<0.001**
Mean HbA_{1c}, % (SD)	7.3 (1.8)	7.5 (1.8)	7.1 (1.7)	0.13
Mean HbA_{1c}, mmol/mol (SD)	56.3 (4.8)	58.5 (4.8)	54.1 (5.9)	0.12
Insulin use, n (%)	97 (46.4)	42 (39.3)	55 (53.9)	0.03
Pre-dialysis SBP (mmHg)	154.0 (25.3)	148.6 (28.1)	157.2 (22.9)	**<0.001**
Pre-dialysis DBP (mmHg)	67.1 (14.5)	70.1 (14.4)	62.4 (13.4)	0.33
Pre-post SBP change (mmHg)	−5.7 (22.5)	−7.9 (21.8)	−4.3 (22.9)	0.21
Co-morbidities				
Hypertension, n (%)	200 (93.0)	101 (89.4)	99 (93.1)	**0.03**
Hypercholesterolaemia, n (%)	169 (80.5)	93 (82.3)	76 (78.4)	0.47
Ischaemic heart disease, n (%)	117 (55.2)	64 (58.2)	53 (51.9)	0.36
Cerebrovascular disease, n (%)	38 (17.8)	27 (24.1)	11 (10.8)	**0.01**
Peripheral vascular disease, n (%)	83 (39.3)	46 (41.1)	37 (37.4)	0.58
Current smoker, n (%)	51 (24.1)	7 (6.2)	46 (44.1)	**<0.001**
Ocular factors				
Intraocular pressure, mmHg (SD)**	11.7 (7.6)	14.4 (7.1)	9.3 (7.2)	**<0.001**
Last eye exam, months (SD)	13.5 (20.3)	11.4 (10.8)	14.6 (23.6)	0.30

SD - standard deviation; n = frequency; T2D – type 2 diabetes mellitus; HbA_{1c} - glycosylated haemoglobin; SBP – systolic blood pressure; DBP – diastolic blood pressure
Data presented are means (standard deviations) or numbers (%) as appropriate for all variables.
**P* value for difference in characteristics by Indigenous Australian status, based on chi-square test or t-test, as appropriate.
**Average intraocular pressure of both eyes

Indigenous sub-cohort. Significant associations with any DR risk among the entire cohort were insulin use (OR: 2.83) and the presence of peripheral vascular disease (OR: 2.92), while non-Indigenous ethnicity (OR: 0.27) was associated with a odds reduction of any retinopathy. In a multivariate model including risk factors of significance, non-Indigenous status remained a protective risk marker (OR: 0.28), as did pre-dialysis diastolic BP (OR: 0.84), while peripheral vascular disease remained a significant risk factor (OR: 2.79) for the presence of any retinopathy.

In the current study, participants receiving haemodialysis care for ESRF, the rates of unilateral vision impairment (23.5 %), unilateral blindness (14.2 %), bilateral vision impairment (11.7 %), and bilateral blindness (3.7 %) were documented, with no significant differences observed within the Indigenous and non-Indigenous Australian subgroups. In large nationwide cohorts of populations from the general community and using random sampling methods for recruitment, the prevalence rates are substantially lower than the current study and highlight the burden of vision disorders within sub-cohorts of populations with T2D and CKD.[24–28] Compared to a nationally representative and population-based sample of community-dwelling Australians, the current study's prevalence rates were approximately 1.8-fold that of the National Eye Health Survey (NEHS) for bilateral vision impairment (6.6 % vs. 11.7 %).[29] The unilateral rates of vision impairment in the current study were also higher among non-Indigenous Australians (14.9 % vs 23.3 %) and Indigenous Australians (12.5 % vs 23.6 %). The greatest discrepancies between this study and the NEHS were in the rates of unilateral blindness, with almost a nine-fold difference in prevalence rates (1.4 % and 2.4 % for non-Indigenous and Indigenous Australians in the NEHS compared to 8.2 % and 19.1 % in the current study, respectively).[29] These findings of greater vision impairment, blindness and retinal pathology among individuals with kidney disease are in keeping with previously reported epidemiological studies of individuals with ESRF and CKD.[10,30,31]

Monocular individuals are at an increased risk of progressing to bilateral vision loss, ultimately affecting their quality of life and independence. Prioritizing this population by providing access to quality eye care that can prevent deteriorating vision in the normal-seeing eye may well be beneficial in preventing incident bilateral vision loss. The exact

Table 2
Prevalence of Unilateral and Bilateral Vision Impairment or Blindness among the Retinopathy in People Currently on Renal Dialysis Study.

Vision Loss Category	Based on the Pinhole Visual Acuity		
	Total Cohort (n=215)	Non-Indigenous Australians (n=109)	Indigenous Australians (n=106)
	n (%, CI)	n (%, CI)	n (%, CI)
No VI	101 (**46.9**, 39–3–55.7)	55 (**50.1**, 39–1–62.1)	47 (**43.8**, 33.8–54.4)
Unilateral VI	50 (**23.5**, 18.1–30.7)	26 (**23.3**, 14.8–34.5)	25 (**23.6**, 15.8–33.7)
Bilateral VI	25 (**11.7**, 8.8–17.8)	13 (**12.3**, 6.4–22.2)	12 (**11.2**, 6.1–19.7)
Unilateral Blindness	31 (**14.2**, 10.1–20.5)	9 (**8.2**, 4.0–17.3)	20 (**19.1**, 12.1–28.7)
Bilateral Blindness	8 (**3.7**, 2.1–8.0)	6 (**5.5**, 2.0–14.0)	2 (**2.3**, 1.0–8.7)

CI: 95 % Confidence Interval
VI: Vision impairment
Unilateral vision loss categories are based on the worse-seeing eye.
Bilateral vision loss categories are based on the better-seeing eye.
*Based on Fisher's exact test
VI = Pinhole visual acuity worse than 6/12 and Blindness = Pinhole visual acuity worse than 6/60

Table 3
Prevalence and Severity of Diabetic Retinopathy and Diabetic Maculopathy for the Cohort and by Indigenous Status.

Diabetic retinopathy severity	Total Cohort	Non-Indigenous Australians	Indigenous Australians	Prevalence Difference[Ω]	P Value[∞]
			Prevalence, % (95 % CI)		
No retinopathy	14.9 (10.7–20.3)	22.0 (15.3–29.2)	6.9 (3.3–13.8)	15.3 (24.4–6.2)	**<0.002**
Retinopathy grades					
Minimal NPDR	7.9 (5.0–12.4)	1.8 (0.4–6.9)	14.7 (9.0–23.1)	12.9 (5.6–20.3)	**0.001**
Mild NPDR	18.7 (13.9–24.4)	15.0 (9.5–23.1)	22.5 (15.3–31.2)	7.5 (−2.9–17.9)	0.16
Moderate NPDR	21.9 (16.9–27.9)	14.2 (8.8–22.1)	30.3 (22.2–40.1)	16.1 (5.2–27.2)	**0.004**
Severe NPDR	9.3 (6.1–14.0)	9.7 (5.4–16.8)	8.8 (4.6–16.2)	0.9 (8.7–6.8)	0.82
PDR	27.0 (21.4–33.3)	36.3 (27.9–45.6)	16.7 (10.6–25.3)	19.6 (31.1–8.2)	**0.001**
Any maculopathy*	49.2 (42.6–56.0)	36.7 (28.1–46.2)	62.7 (53.1–71.7)	26.0 (35.2–16.8)	**<0.001**

CI – confidence interval; NPDR - non-proliferative diabetic retinopathy; PDR – proliferative diabetic retinopathy
*Any maculopathy includes diabetic macular oedema and clinically significant macular oedema combined.
[Ω] Indicates the percentage difference in the prevalence rate between Indigenous and non-Indigenous Australians across the diabetic retinopathy severities.
[∞]P-values indicate the between group difference of Indigenous and non-Indigenous Australians prevalence and corresponding confidence intervals.

Table 4
Univariate and Multivariate Logistic Regression Analysis Investigating Risk Factors for Diabetic Retinopathy for the Total Cohort.

	Any Retinopathy (n=215)			
Characteristic	Unadjusted OR (95 % CI)	P - Value	Adjusted OR** (95 % CI)	P - Value
Age (per 10 years)	0.71 (0.52–0.98)	**0.04**	0.90 (0.67–1.22)	0.78
Gender (male)	0.96 (0.42–2.15)	0.92	1.48 (0.60–3.71)	0.39
Non-Indigenous Australian	0.27 (0.11–0.68)	**0.01**	0.28 (0.10–0.73)	**0.04**
Body mass index (per kg/m^2)	0.92 (0.91–1.01)	0.29	1.01 (0.93–1.11)	0.77
Diabetes duration (per year)	0.98 (0.95–1.01)	0.22	0.98 (0.95–1.01)	0.27
Dialysis duration (per year)	0.90 (0.79–1.03)	0.13	0.90 (0.78–1.04)	0.16
HbA_{1c} (per one per cent)	1.12 (0.85–1.46)	0.40	1.07 (0.79–1.43)	0.66
Insulin use	2.83 (1.38–8.16)	**0.03**	1.47 (0.82–2.64)	0.20
Pre-dialysis SBP (per 10 mmHg)	1.11 (0.90–1.48)	0.16	1.02 (0.99–1.04)	0.19
Pre-dialysis DBP (per 10 mmHg)	0.74 (0.64–1.11)	0.22	0.84 (0.81–0.89)	**0.04**
Pre-post SBP change (per mmHg)	0.98 (0.97–1.01)	0.32	0.98 (0.96–1.02)	0.20
Hypertension	0.88 (0.19–4.01)	0.87	1.08 (0.36–2.61)	0.28
Hypercholesterolaemia	0.68 (0.22–2.09)	0.50	0.68 (0.21–2.20)	0.52
Ischaemic heart disease	0.83 (0.37–1.90)	0.67	0.87 (0.36–2.08)	0.76
Cerebrovascular disease	0.69 (0.26–1.85)	0.46	0.65 (0.22–1.92)	0.44
Peripheral vascular disease	2.92 (1.14–7.44)	**0.03**	2.79 (1.06–7.33)	**0.04**
Current smoker	1.78 (0.53–6.02)	0.35	0.56 (0.14–2.12)	0.39
Intraocular pressure (per mmHg)	0.97 (0.92–1.03)	0.37	1.05 (0.95–1.15)	0.31
Last eye exam (per month)	0.99 (0.97–1.03)	0.94	0.99 (0.95–1.04)	0.89

OR – odds ratio; CI - confidence intervals; HbA_{1c} - glycosylated haemoglobin; SBP – systolic blood pressure; DBP – diastolic blood pressure
**Adjusted for age, gender, ethnicity, insulin use and peripheral vascular disease
The logistic regression model is statistically significant overall (p-value = 0.001).
The pseudo R-squared value of 0.11 indicates a moderate fit.
The Hosmer-Lemeshow test suggests a good fit (p-value = 0.6331).

reason underpinning the association between high rates of vision loss and CKD is not entirely understood, but since CKD and eye diseases are both microvascular complications of T2D and share several risk factors such as increasing age, diabetes, hypertension, smoking, and obesity, this may in part explain the association. Additionally, underlying molecular pathways of atherosclerosis, endothelial dysfunction, and inflammation are associated with significant eye diseases such as cataracts, age-related macular degeneration, retinal vascular changes, DR and CKD.[32–34] People living with CKD who require dialysis or kidney transplantation, especially from rural regions, face many difficulties in accessing healthcare. Barriers such as limited availability of primary care facilities and specialist services such as ophthalmology, transport options and socioeconomic disadvantages and increasing costs associated with relocating for treatment could not only increase the risk of mortality but could be associated with higher rates of ocular complications.[35–37]

In the current analysis, findings indicate that Indigenous Australians on dialysis experience significantly higher rates of any DR (93.1 % vs 78.0 %) and maculopathy (62.7 % vs 36.7 %) compared to their non-Indigenous counterparts. Conversely, PDR (36.3 % vs 16.7 %) was more commonly seen among non-Indigenous Australians. The prevalence of DR among the non-Indigenous cohort (78.0 %) is very similar to that of a large cohort from Europe with T2D receiving haemodialysis treatment. [38] That cohort was established to examine the effects of atorvastatin compared to placebo on adverse cardiovascular events, but also had retinal photography on 1255 individuals available for post hoc analyses and found a DR prevalence of 71 %.[38] However, the reported rate of 93.1 % among our Indigenous Australian sample is, to the best of our knowledge, the highest reported rate in any epidemiological investigation into DR prevalence. For example, one study of consecutive haemodialysis patients from Qatar who underwent eye examinations for DR detection in a similar method to the current study found that 45.0 % (n = 252) had DR, while a study in Western Samoa, had a DR prevalence of 43.2 %.[39] Landmark studies of DR prevalence that do not specifically recruit patients currently receiving haemodialysis treatment, such as The Blue Mountains Eye Study and Singapore Malay Eye Study, all report lower DR prevalence rates.[14,40] The reasons for these disparities might not simply be explained by sub-optimal levels of established risk factors associated with DR among this Indigenous Australian cohort; in fact, they were younger (indicating an aggressive phenotype), had a shorter duration of diabetes, a lower body-mass index and a similar HbA_{1c} per cent. However, these risk profiles could be counterbalanced by a longer dialysis duration, more frequent use of insulin, a higher systolic BP, shorter duration from T2D diagnosis and starting dialysis treatment and high rates of smoking. Further research should aim to understand why the disparities in DR prevalence exist beyond T2D risk factor control, but as previously mentioned, social determinants and structural barriers to care are likely contributing.

Indigenous Australians often must relocate away from family and Country for treatment, adjust to life with a chronic condition, lose valuable time to dialysis, and incur additional financial costs - all at the expense of their social and emotional well-being as well as treatment

adherence.[41,42] In reference to the finding that PDR was more common among the non-Indigenous cohort, this may reflect that the non-Indigenous cohort had an average duration of diabetes greater than twenty years, both of which are well-known risk factors for developing PDR.[43] The maculopathy rates, however, were higher in the Indigenous cohort (62.7 % vs 36.7 %; $p<0.001$), reflecting different patterns of disease among Indigenous Australians. This substantiates data from primary health care of an association of kidney markers and sight-threatening maculopathy but also highlights that while PDR and maculopathy share risk factors, there may be differences in their genetic and molecular pathways. It is possible that the high rates of DR amongst Indigenous Australians reflect that a large majority have DN as opposed to other causes of ESRF and others have suggested that a clinical diagnosis of true diabetes-related nephropathy can be made when PDR exists in a patient with macroalbuminuria.[44] However, one small-scale study with renal biopsies found that DN was present in 50 % of patients without DR, and 40 % of patients with DR had non-diabetic nephropathy either alone or in combination with DN.[45] Nevertheless, the presence of retinopathy is related to both prevalent and incident ESRF.[46]

This study demonstrated important associations between DR and clinical factors. Firstly, non-Indigenous ethnicity was a protective factor for DR in both univariate and multivariate models, which further highlights the disparities in DR rates between Indigenous and non-Indigenous Australians. Secondly, insulin use and the presence of peripheral vascular disease were associated with a 2.83 and 2.92 increase in the odds of retinopathy, respectively. Time since diagnosis, insulin therapy, cardiovascular profile, and renal dysfunction are associated with DR in patients with T2D.[47] Lastly, peripheral vascular disease is an independent risk factor for DR, with studies reporting that several measures of retinopathy were strongly associated with peripheral vascular disease, especially with chronic limb ischemia and in the context of diabetes.[38,48] Paradoxically, for every 10 mmHg increase in pre-dialysis diastolic BP, there was a 16 % odds reduction of DR, possibly driven by the non-Indigenous cohort having a lower rate of retinopathy but a higher average diastolic BP (70.1 mmHg vs 62.4 mmHg).

The current study has several strengths and limitations for consideration. The standardised eye examination alongside comprehensive clinical risk factor data collection provides valuable insights and information on confounders, yet we cannot exclude the possible effects of residual confounding factors on our results. For example, we did not consider dialysis-related factors other than pre-post BP changes, like an increase in body weight during dialysis, episodes of hypotension, or dialysis adequacy, as well as the specific amount of smoking and the important social determinants. Similarly, the cross-sectional design and relatively small sample size limit the ability to explore bidirectional associations of DR and the confidence intervals remain large. Concerning the association between DR and DN, it's important to note that both conditions are more prevalent among Indigenous populations, which may influence this observed link. Moreover, hospital-based studies can inadvertently highlight associations due to patients' elevated risk profiles, even when no true link exists. Some data relied on self-reported measures but was cross-checked with existing medical records wherever possible, and some individuals could not have retinal photography taken. These outcomes were similarly derived from medical records or a clinical eye exam using a head-mounted binocular indirect ophthalmoscope, both of which could impact prevalence rates and render them imprecise - although it occurred infrequently (n=5). Finally, we did not have sufficient data to accurately determine the disease-specific causes of vision impairment within our study population. Therefore, the proportion that DR and maculopathy contribute to the rate of vision loss in the current study is unknown, with other common eye diseases such as uncorrected refractive error and cataracts likely also important.

6. Conclusions

The prevalence of T2D globally and among Indigenous and non-Indigenous Australians is increasing, and with it, microvascular complications leading to vision loss and the need for renal therapy. Both complications can increase morbidity and mortality, impacting an individual's quality of life. Among Indigenous Australians who experience disproportionate rates of both complications, insights into the epidemiology and risk factors are essential in preventing multi-morbidity within an already disadvantaged population. Our findings add to the evidence that individuals with CKD are at significant risk for developing vision complications, including vision impairment, blindness, retinopathy, and maculopathy. The rates of DR and maculopathy are more prevalent among Indigenous Australians and require increased resources to tackle this inequity. Screening for vision and retinal changes within haemodialysis centres is warranted, given the high rates of eye disease for Indigenous and non-Indigenous Australians.

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Declaration of competing interest

The authors have no conflict of interest to declare.

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Research data statement

Due to the sensitive nature of the questions asked in this study, survey respondents were assured raw data would remain confidential and would not be shared. Therefore, the data is not available and the data that has been used is confidential.

Submission declaration

This work has not been published previously, is not under consideration for publication elsewhere and all authors approve the submission.

Author contributions

Conceptualization; JE, TH and JEC, Data curation; JE, TR, EL and CP, Formal analysis; JE and CP, Funding acquisition; TH and JEC, Investigation; JE, JEC, TR and TH, Methodology; JE and CP, Project administration; JE, CP, TR and TH Resources; JEC and TH, Software; Not

Applicable, Supervision; JEC and TH, Validation; JE and TH, Visualization; JE and TH, Roles/Writing - original draft; JE and CP and Writing – All authors. JJE, EL, CP, TR, and TH collected the data. JE and CP wrote the first draft of the manuscript and researched the data. NH, EL, TR and CP edited the manuscript and provided suggestions. TH, SL, JG, AB, LMB, JG and JEC edited the manuscript, contributed to the discussions and provided overall direction for the study. JJE finalised the submission.

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