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Original Article – Clinical Science

Association of disease-specific causes of visual impairment and 10-year mortality among Indigenous Australians: the Central Australian Ocular Health Study

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Short running title: Vision impairment, diabetic retinopathy and 10-year mortality in Indigenous Australians

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ABSTRACT

Importance: Visual impairment significantly impairs the length and quality of life but little is known of its impact in Indigenous Australians.

Background: To investigate the association of disease-specific causes of visual impairment with all-cause mortality.

Design: Retrospective cohort analysis.

Participants: 1,347 Indigenous Australians aged over 40 years.

Methods: Participants visiting remote medical clinics underwent clinical examinations including visual acuity, subjective refraction and slit-lamp examination of the anterior and posterior segments. The major ocular cause of visual impairment was determined. Patients were assessed periodically in these remote clinics for the succeeding 10 years after recruitment. Mortality rates were obtained from relevant departments.

Main Outcome Measures: All-cause 10-year mortality and its association with disease-specific causes of visual impairment.

Results: The all-cause mortality rate for the entire cohort was 29.3% at the 10-year completion of follow-up. Of those with visual impairment, the overall mortality rate was 44.9.%. The mortality rates differed for those with visual impairment due to cataract (59.8%), diabetic retinopathy (48.4%), trachoma (46.6%), 'other' (36.2%) and refractive error (33.4%)($P<0.0001$). Only those with visual impairment from diabetic retinopathy were any more likely to die during the 10-years of follow-up when compared to those without visual impairment (HR 1.70; 95 CI, 1.00–2.87; $p=0.049$).

Conclusions and Relevance: Visual impairment was associated with all-cause mortality in a cohort of Indigenous Australians. However, diabetic retinopathy was the only ocular disease that significantly increased the risk of mortality over the 10-

year study period. Visual impairment secondary to diabetic retinopathy may be an important predictor of mortality.

Keywords: Indigenous Australians, Visual impairment, Blindness, Diabetic Retinopathy

INTRODUCTION

Indigenous Australians have mortality rates which are almost twice as high as non-Indigenous and on average have a 10-year shorter life expectancy. For those aged between 35 and 44, the disparities in death rates amongst male and female Indigenous Australians are alarmingly higher at 3.9 and 4.5 times that of same aged non-Indigenous Australians, respectively.[1] Despite the fact there have been some improvements made in the mortality rates and life expectancy over the last decade, there are important health gaps still to address.

Socioeconomic (e.g. income inequality, geospatial location and disadvantage), behavioural (e.g. diet and lifestyle), psychological (e.g. chronic stress and depression) and biochemical factors (e.g. glycameic control) all contribute to health inequities that exist between Indigenous and non-Indigenous Australians.[2] These factors are associated with the development of chronic diseases such as cancer, endocrine disorders and cardiovascular (CVD) disease and it is these chronic diseases that play a major role in the health inequalities.[3]

A well-recognised public health concern that has been linked to increased mortality rates and ocular morbidity in multiple population-based studies is Visual Impairment (VI).[4-7] VI is typically classified as visual acuity worse than 6/12 vision in a person's better seeing eye, and has been shown to be associated with higher mortality even after efforts to control for confounders such as age and sex.[8,9] Some studies also controlled for additional confounders such as socioeconomic status, hypertension, diabetes, smoking, body-mass index and history of CVD and these remained evident.[10] Causes of VI can vary within populations, ages, gender, educational and ethnic groups. Additionally, the reasons for these variations are likely to be multi-factorial and may include genetic predispositions, nutritional and environmental exposures and access to healthcare. Based on previous work in Central Australia, the major causes of VI among Indigenous Australians have been

identified as refractive error (56.7%), cataract (29.3%), diabetic retinopathy (6%) and trachoma (2.2%).[11]

While there is evidence to suggest that VI and mortality are linked, there is currently no available research regarding VI and mortality risk in Indigenous Australians. The overall aim of this study is to investigate the associations between disease-specific VI and all-cause mortality within the Central Australia Ocular Health Study (CAOHS).

METHODS

The CAOHS protocol has been described elsewhere.[11] Briefly, it took place in the 30 largest remote communities within the Statistical Local Area of 'Central Australia'. These remote medical clinics are visited on either a 6 or 12-month basis. This region contained a target population of 2,014 Indigenous persons aged 40 years and over. Those living within and around the city of Alice Springs were excluded. (Figure 1).[12]

Patients were recruited from remote medical clinics at each of the studied communities during the 36-month period of July 2005 and June 2008, where participants were included if they identified themselves as Indigenous Australian. The aims of the study were explained, and written informed consent was obtained. The study followed the tenets of the Declaration of Helsinki and ethical approval from the Central Australian Human Research Ethics Committee was obtained.

A patient's diagnosis of diabetes and/or hypertension was based on a referral from their doctor or health professional, or on self-reporting when evidence was not available. Presenting visual acuity was determined using a tumbling E acuity chart at 3 metres in a well-lit room. If the patient could not read the top letter (6/120 equivalent), they were recorded as either counting fingers at 2 metres or 1 metre, hand movements, light perception or no light perception. Following subjective

refraction performed by an optometrist, best-corrected visual acuity was then determined. A slit-lamp examination of the anterior segment was performed and grading of trachomatous corneal opacification using the World Health Organisation (WHO) simplified grading system was applied[13]. Dilated fundus examination was then performed to grade the crystalline lens using the modified Lens Opacities Classification System III[14] and to clinically examine the optic nerve, posterior pole and peripheral retina as to determine the presence and degree of diabetic retinopathy (DR) using the Early Treatment of Diabetic Retinopathy Study adaptation of the modified Airlie House classification of DR.[15]

VI was defined as a visual acuity worse than 6/12 in the better seeing eye. If this was present, then the examining Ophthalmologist made an assessment regarding the major cause of VI in each eye. In the case of multiple eye pathologies present, it was at the discretion of the visiting Ophthalmologist as to the major cause of VI. This was generally based on the disorder that was less likely to be successfully treatable. Patients were then re-examined in these remote clinics on a 6 or 12-month basis over the ensuing 10 years. A minimum of two time points (recruitment and one other) were necessary to be eligible for analysis and inclusion into the study. Mortality and cause of mortality for those aged 40 years or older at the time of recruitment was established by accessing records from Alice Springs Hospital and the Department of Births, Deaths and Marriages from the Northern Territory and South Australia.

Statistical Analysis System 9.1 (SAS Institute Inc., Cary, NC) was used for statistical investigations including descriptive statistics (median and range of age), Mann-Whitney U test (sex comparison), log-rank tests (overall 10-year mortality rate), Kaplan-Meier survival analysis curves and Cox proportional hazards model (calculation of adjusted hazard ratios). The hazard ration model included adjustment for confounding age, sex, hypertension, visual impairment from refractive error, cataract, diabetes, trachoma and 'other' ocular disorders.

Age was considered as a continuous variable. Patients who were not confirmed to have died during the follow-up period were censored at the last clinic visit that they attended. If they did not attend any clinic visits following recruitment, then they were excluded from the analysis. Sex, VI groups, hypertension, and diabetes were considered as categorical variables. Test statistics, 95% confidence intervals and p-values are presented. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 1,347 (67% of the target population) were assessed and recruited during the 36-month period of the study. Of these, 90 patients were lost to follow-up and were excluded because a second appointment after recruitment was not available, leaving 1,257 patients (93%). The final sample included 476 males (37.9%) and 781 females (62.1%), with a median age of 53 years (range 40 to 93 years) (53 for males and 54 years for females (=0.57)). The minimum follow-up period was 8 years and the remote clinics were visited on a 6 or 12-month basis. The median time for patient follow-up in the remote clinics was 8.7 years (interquartile range: 1.7 years) and 30% (377) were followed for more than 9 years. Those patients who were visually impaired from specific-causes were no more likely to have been censored than those who were not visually impaired (F=1.10, p= 0.36), thus indicating that the process of censoring did not bias our study findings.

At the end of 10 years from study commencement, confirmed all-cause mortality was found to be 29.3% for the entire cohort. Of those with VI, 44.9% had died compared to 17.8% without VI. This differed for those with VI secondary to specific causes such as cataract (59.8%), diabetic retinopathy (48.4%), trachoma (46.6%), 'other' (36.2%) and refractive error (33.4%) (p<0.0001) (Figure 2). Following WHO age-standardisation, these proportions were 17.8% for No VI, and 62.7%, 48.8%, 37.8% and 34.4% for VI due to cataract, DR, trachoma, 'other' and

refractive error, respectively. After adjustment for age, sex, and hypertension, compared with those with no VI, those with VI due to refractive error, cataract, trachoma and 'other' causes, were no more likely to have died in the 10 years after recruitment (Table 1).

However, those who were visually impaired because of diabetic retinopathy were significantly more likely to die during the 10-years of follow-up (HR= 1.70; 95 CI, 1.00 – 2.87; p=0.049).

DISCUSSION

In the current remote Central Australian population of Aboriginal Australians, the 10-year cumulative mortality incidence in those aged 40 years or older at baseline was 29.3%. By comparison, the 10-year all-cause mortality for those aged 40 years or older in the general Australian population as a whole is 13.7%.[16].Of those with VI, the mortality rate was 44.9%. The differences in these mortality rates are one of many key health disparities between Indigenous and non-Indigenous Australians. Of interest, DR was the only disease-specific cause of VI to be associated with all-cause mortality (HR 1.70; 95 CI, 1.00 – 2.87; p=0.049). Although DR has been linked to mortality in other populations, this is the first report in an Aboriginal Australian population.

Prevalent ocular pathologies in non-Indigenous Australians such as cataract, age-related macular degeneration (ARMD), glaucoma and DR have all not only been independently linked to VI, but also to increased risk of mortality, and in some cases be predictive of mortality.[6,17,18] However, these findings have not been consistently shown and the exact reason behind these relationships remains elusive.[5,6,10,18] It is suggested that some eye diseases can be biological markers for cellular ageing.[19] Meanwhile, other eye diseases may share similar aetiologies to systemic cardiovascular diseases and reflect ocular signs of widespread vascular damage.[20] Alternatively, it has been proposed that increased mortality is a consequence of VI itself, which increases the risk of falls,[21] depression,[30] functional disability,[22] loss of

independence, reduced social interaction[23] and an increased need for community support.[24]

In the present study, for disease-specific causes of VI and its relationship with mortality, only those with VI due to DR had a higher risk of mortality. The major causes of VI and blindness in Indigenous Australians; refractive error, cataract and trachoma did not increase the 10-year mortality rate after adjustment for confounders. For cataract in particular, most studies to date have indicated inconsistent findings with the association between cataract and mortality, with some finding a positive association,[5,8,18,25-27] while others finding no association.[22,27-32] Cataract is the second most prevalent cause of VI amongst Indigenous Australians after refractive error, but is strongly associated with increasing age.[11] Our data does not support VI due to cataract being independently associated with increased mortality. The study population has good access to surgical correction of cataract induced visual morbidity and it is interesting to speculate as to whether improving visual acuity could affect mortality.

An important outcome of this study was that DR was the only condition that increased the likelihood of subsequent mortality over the 10-years of follow-up. In fact, our study showed that participants were 70% more likely to die in the following 10-year period after recruitment if they were visually impaired as a result of DR. Diabetes has become a major concern amongst Indigenous populations in Australia and throughout the world. Prevalence data suggests the rates of type 2 diabetes mellitus (T2DM) vary from 3.5 to 33.1%, depending on the study population.[33] Although there is marked variation, the vast majority of studies indicate higher prevalence rates within Indigenous Australian communities when compared to 7.2% in the general Australian population.[34] Meanwhile, the prevalence of DR also appears to be a major concern. In Central Australia, it has been previously reported that 25.4% of Indigenous adults over 40 years old have any DR while 8.4% had vision-threatening DR.[35] In comparison to a non-Indigenous Australian population, the

Australian Diabetes, Obesity and Lifestyle (AusDiab) population-based study found lower rates of any DR (21.9% in known T2DM participants) and vision-threatening DR (approximately 5.4% in known T2DM participants).[36] However, a recent pooling of data from various studies revealed the prevalence of DR to be not significantly different between Indigenous and non-Indigenous Australians, although the author suggested that these findings must be interpreted with caution as at the time of the publication there was no true population-based studies of DR prevalence in Indigenous Australian communities.[37]

With the growing tide of diabetes in Indigenous communities one would expect a simultaneous rise in DR and vision loss. Our results are in agreement with a large population-based study, which showed that the presence of severe DR and consequently VI in the younger age group (mean age of 14.6 years at baseline) was associated with all-cause and ischemic heart disease mortality. Likewise, in the older age group (mean age 54.8 years at baseline) there was an association with all-cause, ischemic heart disease and stroke mortality over a 16-year period.[38] This is not surprising since hyperglycaemia,[39,40] hypertension[39,41] and dyslipidaemia[40,42] are related not only to retinopathy development and progression, but cardiovascular-related mortality in diabetic patients. In addition, a relatively recent meta-analysis of observational studies confirmed such findings, in that the presence of DR was associated with an increased risk of all-cause mortality and cardiovascular events.[43] Other studies have also found a similar association with severity of DR and mortality.[28,44-46] Similar to our study, the Singapore Malay Eye Study (SiMES) found an association between DR and all-cause mortality in subjects with VI, but interestingly no association was found for other eye diseases such as glaucoma, ARMD, and cataract.[10] These results, together with those from the current study, suggest that the co-existence of DR and VI increases the risk of all-cause mortality and is an important risk factor for mortality, particularly for CVD. This is especially

important in Indigenous Australians, since CVD is the number one cause of death[3] and T2DM is extremely prevalent.[33]

It still remains unclear whether or not such an association indicates that VI due to DR is a marker of a direct or an indirect link between VI and mortality. There are a variety of mechanisms by which VI could be associated with mortality. One mechanism is that a condition such as diabetes directly causes VI and increases an individual's risk of death. Secondly, age-related systemic diseases may simply coexist with eye diseases, and these systemic conditions increase the risk of death. Finally, DR related VI may be intrinsically connected by an interplay of risk-conferring genes that have widespread implications not only for the eye but also vital organs elsewhere in the body.[20] Either way, DR should be a substantial sign for clinicians to improve the management of diabetes, with particular emphasis on cardiovascular risk factors.

There are some limitations in the methodology of our study. There is likely a complex interaction between mortality risk factors not controlled for in the current study and VI. Important factors that contribute to overall mortality that were not investigated because of the limited resources and access in these remote communities such as socioeconomic, behavioural, psychological, and biochemical factors (e.g. glyceamic control) means that we can't completely rule out a chance finding. Furthermore, we could not analyse separately those with poor or optimal diabetic control. It is possible that those with poor diabetic control are more likely to have DR and die earlier. Additionally, the results were only just statistically significant ($p= 0.049$), likely due to the relatively small number of those suffering VI secondary to DR. However, it is also possible that correcting for co-variates using standard regression models could underestimate the effect of VI on mortality. Strengths of the study are the long-term follow-up period and the well-documented grading of ocular pathology using well-defined protocols. This is the first study to report on the association of VI attributable to DR and mortality in Indigenous

Australians. Future research should focus on further investigating the overall determinants of health in combination with eye health data in these disadvantaged populations to further understand the mechanisms for the association of DR and mortality. It is clear that early detection and timely treatment of DR is effective at reducing the burden of the disease, and this can be achieved by regular eye examinations or effective retinal photography-based screening.[47] Furthermore, T2DM and DR in Indigenous Australians should be a priority health concern given that it significantly impairs the quality and length of life of those affected and is a common cause of vision loss and blindness.

In conclusion, VI and DR have been strongly linked to mortality in multiple studies, including for the first time in an Aboriginal Australian population. Resources should be directed to Indigenous Australians who suffer disproportionate rates of blindness and VI. Overall, there is an ever-pressing need for prevention, screening and early management of DR as it is sight saving and potentially life-saving.

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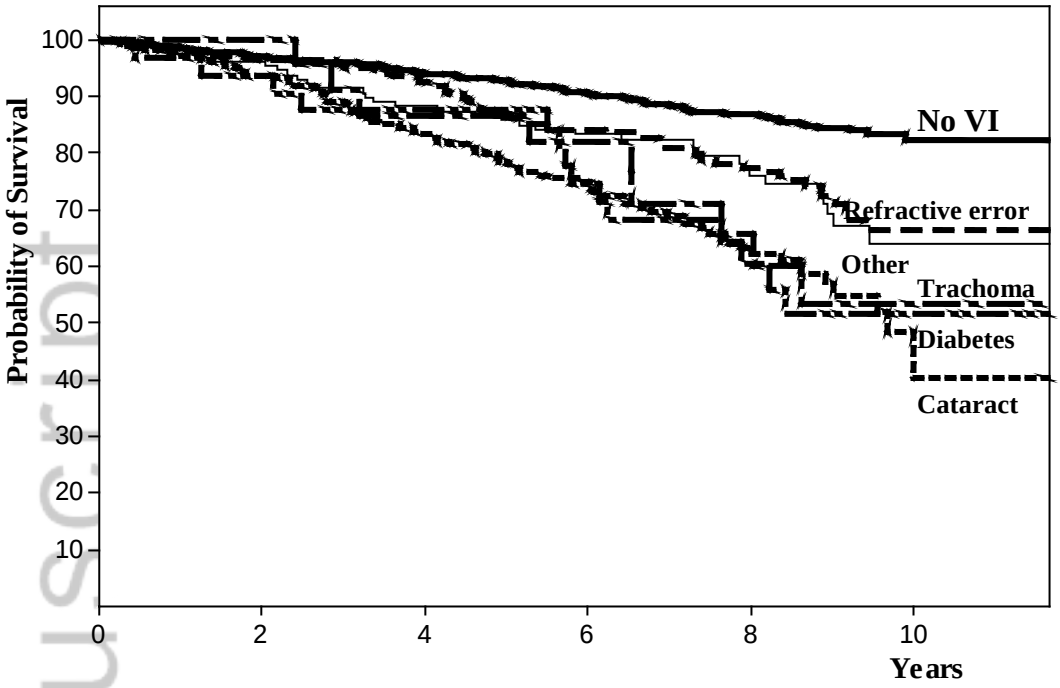
FIGURES

Figure 1: Schematic map of the central Australian statistical local area. (▲) Communities visited during the study.

Figure 2: Survival curve for all-cause mortality after recruitment into the Central Australian Ocular Health Study, stratified for cause of vision impairment at the time of recruitment.



No VI: No vision impairment at the time of recruitment, Refractive error: Vision impairment secondary to refractive error, Trachoma: Vision impairment secondary to trachoma, Diabetes: Vision impairment secondary to diabetic retinopathy, Cataract: Vision impairment secondary to cataract, other: All other causes of vision impairment such as optic neuropathies and trauma

TABLE

Table 1: Showing adjusted hazard ratios of the likelihood that a patient with one of the listed risk factors had died during the 10-year period of follow-up following recruitment into the Central Australian Ocular Health Study versus the reference group.

Risk Factor	**Un-Adjusted Hazard ratio (95% C.I)**	**Age-Adjusted Hazard ratio (95% C.I)**	**Fully-Adjusted Hazard ratio (95% C.I)**
Sex: Male	1.0	1.0	1.0
Sex: Female	0.88 (0.68 – 1.05)	0.87 (0.73 – 1.03)	0.82 (0.69 – 0.98)*
Age (per 10 years)	1.46 (1.35 – 1.58) ****	1.45 (1.33 – 1.57) ****	1.38 (1.26 – 1.50)****
No Vision Impairment:	1.0	1.0	1.0
Vision Impairment secondary to:			
Refractive error	1.20 (0.94 – 1.52)	0.98 (0.79 – 1.22)	1.10 (0.84 – 1.44)
Cataract	1.63 (1.25 – 2.13)****	1.03 (0.81 – 1.33)	1.14 (0.80 – 1.60)
Trachoma	0.76 (0.35 – 1.64)	0.92 (0.57 – 1.49)	1.43 (0.77 – 2.67)
Diabetic Retinopathy	0.69 (0.33 – 1.43)	1.17 (0.73 – 1.90)	1.70 (1.00 – 2.87)*
Other Causes	2.45 (1.60 – 3.74)****	1.51 (1.00 – 2.26)*	1.59 (0.94 – 2.67)

Fully-adjusted data were adjusted for all list risk factors and for age, sex and the presence of systemic hypertension.

'Other Causes' primarily include optic neuropathies and ocular trauma.

(*P<0.05, ****P<0.0001)

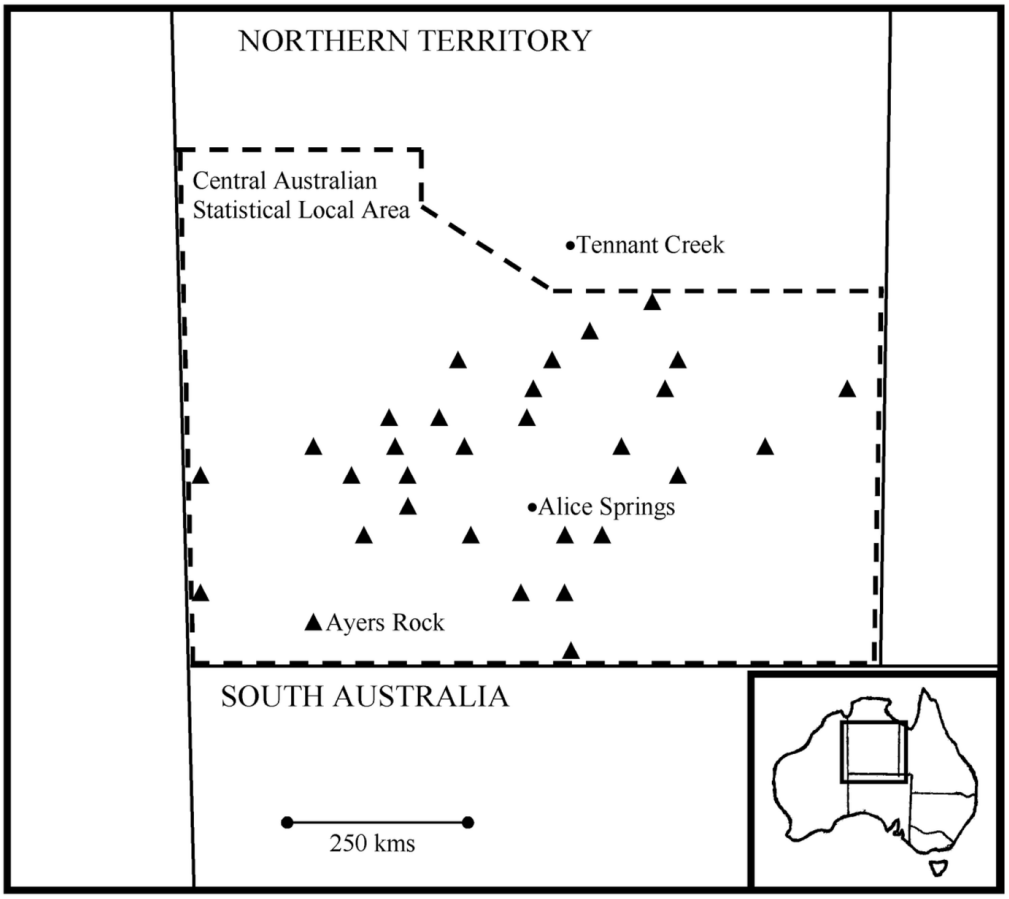


Figure 1.

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