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Original Article – Clinical Science

Prevalence of retinal vein occlusion in the Australian National Eye Health Survey

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Key words: retinal vein occlusion, epidemiology, vision loss

ABSTRACT

Importance: In Australia, knowledge of the epidemiology of retinal vein occlusion (RVO) remains scarce due to a paucity of recent population-based data. The National Eye Health Survey (NEHS, 2015-16) provides an up-to-date estimate of the prevalence of RVO in non-Indigenous and Indigenous Australian adults.

Background: To determine the prevalence and associations of retinal vein occlusion (RVO) in a national sample of Indigenous and non-Indigenous Australian adults.

Design: Population-based cross-sectional study

Participants: A total of 3098 non-Indigenous Australians (aged 50-98 years) and 1738 Indigenous Australians (aged 40-92 years) living in 30 randomly selected sites, stratified by remoteness.

Methods: RVOs were graded from retinal photographs using standardised protocols and recorded as central retinal vein occlusion (CRVO) or branch retinal vein occlusion (BRVO).

Main outcome measure: Prevalence of RVO

Results: In the non-Indigenous population, the sampling weight adjusted prevalence of any RVO was 0.96% (95% CI: 0.59, 1.6), with BRVO observed in 0.72% (95% CI: 0.41, 1.2) and CRVO in 0.24% (95% CI: 0.13, 0.47). Any RVO was found in 0.91% (95% CI: 0.47, 1.7) of Indigenous Australians aged 40 years and over, with BRVO observed in 0.83% (95% CI: 0.40, 1.7) and CRVO in 0.07% (95% CI: 0.02, 0.32). Older age (OR = 1.64 per 10 years, p = 0.006) and the presence of self-reported diabetes (OR = 3.24, p = 0.006) were associated with any RVO after multivariable adjustments. RVO was attributed as the cause of monocular vision loss (<6/12) in seven (0.25%) non-Indigenous and six (0.36%) Indigenous participants.

Conclusions: These data suggest that RVO is relatively uncommon in the non-Indigenous Australians aged 50 years and over and Indigenous Australians aged 40 years and over. Similar to previous Australian and international reports, the prevalence of RVO rose sharply with age.

INTRODUCTION

Retinal vein occlusion (RVO) is the second most common retinal vascular disorder behind diabetic retinopathy[1] and a common cause of vision loss among older adults in Australia[2,3] and worldwide.[4] Both age[5-8] and vascular risk factors (e.g. systemic hypertension)[6,8,9] have been identified as the most consistent risk factors for RVO. Previous reports have suggested that RVO has a detrimental effect on vision-related quality of life.[10] Despite this, little is known about the epidemiology of RVO in Australia. With substantial demographic changes, including the ageing of our population, up-to-date national population based-data is warranted.

Epidemiological data of the prevalence of RVO have been documented in several countries, with rates ranging from 0.3% in the Atherosclerosis Risk in Communities & Cardiovascular Health study (ARIC)[11] in the United States to 2.1% in the Hisayama study in Japan.[12] In Australia, a landmark population-based study conducted in the early 1990's, the Blue Mountains Eye Study (BMES),[8] reported the prevalence of RVO to be 1.6% in the non-Indigenous population. Furthermore, state-level data derived from the blind pension registration of Western Australia,[3] although not specific to RVO, reported that retinal vascular occlusions (venous and arteriolar) were attributed as the main cause of blindness in 3.4% of all cases. While these studies provide insights into the burden of RVO in Australia, there has been substantial ageing of the Australian population since their completion[13] and Indigenous Australians have been inadequately

represented. To the best of our knowledge, no data on the epidemiology of RVO in Indigenous Australians currently exists. As Indigenous Australians display a higher rates of vascular risk factors, such as hypertension and hypercholesterolaemia,[14] compared to the non-Indigenous population, a better understanding of the burden of RVO in Indigenous communities is needed.

The objective of this study is to describe the prevalence and associations of RVO in a national sample of the Indigenous and non-Indigenous Australian adults recruited in the National Eye Health Survey (NEHS).

METHODS

Study population

The NEHS was a cross-sectional, population-based study of non-Indigenous Australians (aged 50 years or older) and Indigenous Australians (aged 40 years or older), conducted between March 2015 and April 2016. Details of the sampling, recruitment and clinical examination methodologies have been described in detail elsewhere.[15,16] In brief, the study aimed to investigate the prevalence of vision impairment (VI), blindness and common eye diseases in a nationally representative sample of the Australian population. A multi-stage, random-cluster sampling methodology was utilised to select thirty sites across five Australian States and one Territory, stratified by remoteness. Trained recruiters went door-to-door to recruit approximately 100 non-Indigenous Australians and 50 Indigenous Australians from each site. The overall positive response and examination rates were 85.3% (5764/6760) and 71.5% (4836/6760), respectively. Ethics approval was obtained from the Royal Victorian Eye and Ear Hospital (RVEEH) Human Research Ethics Committee (HREC-14/1199H) and additional ethical approvals were obtained at the state level to conduct research within Indigenous communities.

The NEHS was conducted in accordance with the tenets of the Declaration of Helsinki as revised in 2013 and all participants provided written informed consent.

Examination procedures

Socio-demographic data, ocular and medical histories and previous utilisation of eye health services were obtained from all participants using an interviewer-administered questionnaire. Presenting distance visual acuity (VA) was assessed using the logMAR chart (Brien Holden Vision Institute, Australia) and automated refraction was performed (Nidek ARK-30 Type-R Hand-held auto-refractor/keratometer, Nidek Co., LTD, Japan) on participants who improved to ≥6/12 with pinhole. Vision impairment (VI) was defined as a visual acuity of <6/12 to ≥6/60 in the better eye and blindness was defined as worse than 6/60 in the better eye. Anterior segment assessment was conducted using a Keeler PSL One hand-held slit lamp (Keeler Ophthalmic Instruments, UK) and intraocular pressure (IOP) was measured in both eyes using the iCare tonometer (iCare, Finland). Two non-stereoscopic, 45-degree, retinal photographs were taken of each eye, one centred on the optic disc and the other centred on the macula using a Diabetic Retinopathy Screening (DRS) non-mydriatic fundus camera (CenterVue SpA, Italy). Pupillary dilatation was conducted when retinal images were of reduced quality due to small pupil size.

Trained retinal graders from the Centre for Eye Research Australia (CERA), masked to the clinical characteristics of study participants, graded all images for the presence or absence of branch or central RVO. Similar to previous population-based studies,[6-8] recent central RVO was characterised by the presence of retinal or optic disc edema, scattered superficial or deep hemorrhages, and venous dilation. Old RVO was characterised by collateral vessels at the optic disc, occluded and sheathed retinal veins and evidence of scatter retinal photocoagulation. Branch RVO was identified according to similar signs, but limited to the retinal sector drained by the obstructed venule.

Statistical Analysis

Participant demographic characteristics were summarized by mean and standard deviation (SD) for normally distributed continuous data, or the median and inter-quartile range for skewed distributed data, and counts and percentages for categorical data. Normality was examined using boxplots, Kolmogorov-Smirnov and Shapiro-Wilks tests. Ninety-five percent confidence intervals (CI), taking into account the sampling design, were calculated for prevalence of RVO.

Univariate and multivariable logistic regression analysis was used to assess the effects of a set of key explanatory variables on RVO. Key explanatory variables included age, gender, ethnicity, years of education, language spoken at home, remoteness, history of diabetes and history of stroke. Lack of multicollinearity between the independent variables in the model was verified. Statistical interaction was tested for all predictors of RVO. A plot of the residuals compared with estimates was examined to determine if the assumptions of linearity and homoscedasticity were met.

All analyses were performed by incorporating the sampling weights to obtain unbiased estimates from the complex NEHS sampling design. Analyses were conducted with Stata version 14.2.0 (Stata Corp, College Station, TX). A two-tailed p-value <0.05 was considered statistically significant.

RESULTS

A total of 4836 individuals were recruited and examined in the NEHS, including 3098 non-Indigenous and 1738 Indigenous Australians. Of these, 4692 (97%, 3010 non-Indigenous and 1682 Indigenous) participants had retinal photographs in at least one eye that were gradable for RVO (gradable images in only one eye = 4.3%, 202/4692).

Among the 144 excluded participants were 85 (59%) individuals who had missing retinal images for both eyes and 59 (41%) individuals who had retinal images that were deemed ungradable in both eyes. The mean age of non-Indigenous and Indigenous participants was 66.4 years [standard deviation (SD)=9.6] (58.9% female) and 54.8 years (SD=9.9) (53.7% female), respectively.

Prevalence of retinal vein occlusion

In the non-Indigenous population aged 50 years and over, the weighted prevalence of any RVO was 0.96% (95% CI: 0.59, 1.6), with BRVO observed in 0.72% (95% CI: 0.41, 1.2) and CRVO in 0.24% (95% CI: 0.13, 0.47). Any RVO was found in 0.91% (95% CI: 0.47, 1.7) of Indigenous Australians aged 40 years and over, with BRVO observed in 0.83% (95% CI: 0.40, 1.7) and CRVO in 0.07% (95% CI: 0.02, 0.32) (Table 1). Bilateral RVO was only present in one Indigenous participant. The weighted prevalence of any RVO increased with age in non-Indigenous participants, with the following age-specific prevalence's; 0.37% in those <60 years, 0.92% in those aged 60-69 years, 1.5% in 70-79 year olds and 1.6% in those ≥80 years (p = 0.12). In the Indigenous population, the prevalence of RVO for the age groups <60 years, 60-69 years, ≥70 years were 0.54%, 1.5% and 2.2%, respectively (Figure 1, p = 0.06). Among non-Indigenous Australians aged 50 years and over, the prevalence of RVO was 1.2% for males and 0.78% for females (p = 0.13). Any RVO was found in 1.2% of males and 0.72% of females in the Indigenous population (p = 0.43). Extrapolating these findings to the Australian population, we estimate that approximately 56,559 non-Indigenous Australians aged 50 years and over and 1,175 Indigenous Australians aged 40 years and over have RVO.

Table 1: Prevalence [(% (95% CI)] of branch retinal vein occlusion, central retinal vein occlusion and any retinal vein occlusion, stratified by Indigenous status

	Non-Indigenous (n = 3010)			Indigenous (n = 1682)		
		Crude	Weighted		Crude	Weighted
	n	% (95% CI)	% (95% CI)	n	% (95% CI)	% (95% CI)
Branch RVO	22	0.73 (0.46 (1.1)	0.79 (0.45, 1.4)	12	0.71 (0.37, 1.3)	0.83 (0.40, 1.7)
Central RVO	5	0.17 (0.05, 0.39)	0.19 (0.08, 0.49)	2	0.12 (0.01, 0.43)	0.07 (0.02, 0.32)
Any RVO	27	0.90 (0.59, 1.3)	0.96 (0.60, 1.6)	14	0.83 (0.46, 1.4)	0.91 (0.47, 1.7)

CI = Confidence Interval; RVO = Retinal vein occlusion

Vision loss and RVO

In the non-Indigenous population, RVO was attributed as the cause of monocular vision impairment in 7 participants (CRVO = 4; BRVO = 3; n = 2 also had vision loss in the fellow eye), representing 0.25% of the total non-Indigenous sample. RVO was not the main cause of blindness in any non-Indigenous participant. Among the Indigenous population, RVO was attributed as the cause of monocular vision impairment and blindness in 5 cases (CRVO = 1; BRVO = 4; n = 1 also had vision loss in the fellow eye) and 1 case, respectively. This represented 0.36% of the total Indigenous sample.

Associations between RVO and selected characteristics

Adjusted logistic regression analysis revealed that there was no significant difference in the prevalence of RVO between Indigenous and non-Indigenous Australians (OR = 1.19, p = 0.72). Therefore, due to the low frequency of RVO found in the NEHS, Indigenous and non-Indigenous data were combined in logistic regression analysis examining associations between RVO and selected characteristics (Table 2).

After adjusting for covariates, older age (OR = 1.64 per 10 years, p = 0.006) and the presence of self-reported diabetes (OR = 3.24, p = 0.006) were associated with any RVO. Furthermore, geographic remoteness was associated with RVO, with participants residing in Inner Regional areas being less likely to have RVO than those in Major City areas (OR = 0.11, p = 0.01).

Table 2: Relationship between retinal vein occlusion and selected characteristics in Australians (n=4692)

Associated factors	**Univariate logistic regression OR [95% (CI)]**	**p**	**Multivariable logistic regression OR [95% (CI)]**	**p***
Indigenous	0.92 (0.40, 2.14)	0.84	1.19 (0.46, 3.08)	0.72
Age (per 10 years)	1.56 (1.16, 2.09)	0.005	1.64 (1.17, 2.31)	0.006
Gender (male)	1.57 (0.88, 2.83)	0.12	1.34 (0.68, 2.68)	0.39
Education (year)	0.98 (0.85, 1.14)	0.83	1.02 (0.89, 1.16)	0.78
English spoken at home	1.44 (0.20, 10.25)	0.71	0.67 (0.08, 5.45)	0.70
Ethnicity				
Oceanian	1		1	
European	0.69 (0.19, 2.46)	0.55	0.49 (0.14, 1.76)	0.26
Others	1		1	
Remoteness				
Major City	1		1	
Inner Regional	0.48 (0.14, 1.58)	0.22	0.38 (0.13, 1.09)	0.07
Outer Regional	0.14 (0.03, 0.74)	0.02	0.11 (0.02, 0.56)	0.01
Remote	0.67 (0.16, 2.90)	0.58	0.57 (0.14, 2.38)	0.43
Very Remote	0.70 (0.08, 5.98)	0.74	0.35 (0.05, 2.42)	0.28
Self-reported diabetes	3.24 (1.56, 6.74)	0.003	3.24 (1.43, 7.25)	0.006
Self-reported stroke	2.00 (0.49, 8.24)	0.32	1.30 (0.24, 6.97)	0.75
Mean IOP	0.97 (0.87, 1.08)	0.54	0.98 (0.88, 1.10)	0.76

OR = Odds ratio; CI = Confidence interval; IOP = Intra-ocular pressure

*Statistical significance was set as a p value of ≤0.05 (two tailed)

DISCUSSION

This paper presents the prevalence of RVO in a population-based, national sample of non-Indigenous and Indigenous Australian adults. The weighted prevalence of any RVO was 0.96% in non-Indigenous Australians aged 50 years and over and 0.91% in Indigenous Australians aged 40 years and over. Similar to previous studies,[5-8] the prevalence of RVO rose sharply with age, with non-Indigenous persons aged 80 or older approximately 4 times more likely to have RVO than persons aged under 60 years of age.

The prevalence of RVO in non-Indigenous Australians in the NEHS is similar to that reported in the Beaver Dam Eye Study (0.8%),[5] the Multiethnic Study of Atherosclerosis (1.1%)[17] and only marginally higher than the Singapore Malay Eye Study (0.7%)[6] and the Beijing eye study (0.7%).[7] In contrast, we report a lower prevalence than that found in the BMES (1.6%).[8] A further comparison of age-specific rates revealed the prevalence of RVO in non-Indigenous participants in the NEHS was not significantly lower than that of the BMES in the age categories <60 years ($\chi^2 = 1.75$, $p = 0.19$), 60-69 years ($\chi 2 = 1.75$, $p = 0.69$) and 70-79 years ($\chi 2 = 1.75$, $p = 0.19$). However, the prevalence of RVO was significantly lower in NEHS participants aged 80 years and older (NEHS = 1.6% vs. BMES = 4.6%, $\chi 2 = 1.75$, $p = 0.01$). This finding is somewhat surprising, given the relatively stable prevalence of vascular risk factors, including hypertension,[18] in Australia over the past two decades. It must be noted that differences in the grading methods employed in the BMES and the NEHS may also be contributory, as the former study employed ophthalmologist clinical examinations coupled with stereoscopic fundus photography. Therefore, it is possible that the present study underestimated the prevalence of RVO.

To the best of our knowledge, the present study is the first to describe the prevalence of RVO in a population-based sample of Indigenous Australian adults. We report that the weighted prevalence of RVO amongst Indigenous Australians to be 0.91%.

Although it has been well established that Indigenous Australians display higher rates of vascular risk factors than non-Indigenous Australians,[14] a considerably lower life-expectancy (approximately 10 years lower than non-Indigenous Australians)[19] – may have contributed to this relatively low prevalence of RVO. Despite this, RVO remains an important cause of unilateral vision loss, with our data showing that approximately 2.5 per 1000 non-Indigenous and 3.6 per 1000 Indigenous Australian adults have vision loss due to RVO.

Consistent with the findings of previous studies,[5-8] increasing age was significantly associated with RVO, with non-Indigenous persons aged 80 years and older and Indigenous Australians aged 70 years or older, being 4 times more likely to have RVO than persons aged under 60 years of age. This is likely to reflect the higher rates of arteriosclerosis and vascular risk factors in the aging population.[20] Similarly to previous population based[5] and case control studies,[21,22] a significant association was observed between RVO and self-reported diabetes in the NEHS. While the etiology remains largely unclear, this finding may reflect the commonly shared cardiovascular risk factors (e.g. hypertension and hyperlipidemia) that exist between diabetes and RVO.[21] Unlike previous studies, we did not find associations of RVO with ethnicity,[20] however it must be noted that this study was unlikely to be sufficiently powered to detect meaningful differences between ethnic groups.

Strengths of the current study include its national scope, population-based sample and masked grading of retinal images. There are also some notable limitations. First, the small number of cases of RVO and the failure to capture several known and potential risk factors (arterial hypertension, atherosclerosis, lipid profiles, smoking), limited our ability to conduct a more meaningful risk factor analysis. Second, the use of non-stereoscopic images in only two-fields of view may have led to an underestimation of prevalence of RVO. Third, 4.3% (202/4692) of participants had gradable images for

only one eye. Accordingly, this may have also led to an underestimation of the prevalence of RVO.

In conclusion, this study demonstrated that RVO is relatively uncommon in the non-Indigenous Australians aged 50 years and older (0.96%) and Indigenous Australians aged 40 years and older (0.91%). With the limitation of current treatment options for RVO, a clearer understanding of systemic and ocular RVO risk factors may be important for the development of preventative strategies.

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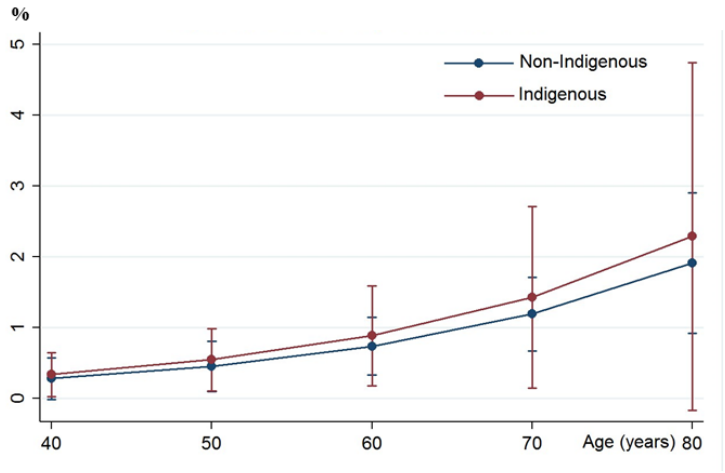

Figure 1: Adjusted prevalence of any retinal vein occlusion for Indigenous and non-Indigenous participants, by age