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Original Article – Clinical Science

## **Prevalence and characteristics of choroidal nevi: the Australian National Eye Health Survey**

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## ABSTRACT

**Importance:** Choroidal nevi are a common incidental finding on fundus examination. The National Eye Health Survey (NEHS, 2015-16) provides an up-to-date estimate of the prevalence of choroidal nevi in non-Indigenous and Indigenous Australian adults.

**Background:** To describe the prevalence and characteristics of choroidal nevi amongst non-Indigenous and Indigenous Australian adults.

**Design:** Population-based cross-sectional study

**Participants:** This study included 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:** Choroidal nevi were graded from retinal photographs using standard protocols.

**Main outcome measure:** Prevalence of choroidal nevi

**Results:** In the non-Indigenous population aged 50 years and over, the weighted prevalence of choroidal nevi was 2.1% (95% CI: 1.4, 3.3). Among Indigenous Australians aged 40 years and over, the weighted prevalence of choroidal nevi was 0.68% (95% CI: 0.4, 1.3). The average maximum diameter, surface area and distance from the disc of the choroidal nevi was 1730 $\mu\text{m}$ , 2,766,800 $\mu\text{m}^2$  and 3400 $\mu\text{m}$ , respectively. After multivariate adjustments, Indigenous participants (OR = 0.28,  $p = 0.01$ ) and those of older age (OR = 0.79 per 10 years,  $p = 0.02$ ) were less

likely to have choroidal nevi. Choroidal nevus was not the primary cause of vision loss in any participant.

**Conclusions and relevance:** Choroidal nevi were relatively infrequent amongst NEHS participants, however non-Indigenous Australians had a significantly higher prevalence than Indigenous Australians. Choroidal nevi did not affect visual acuity and the majority were small.

**Key words:** Choroidal nevi, epidemiology

## INTRODUCTION

Choroidal nevi are a common incidental finding on fundus examination, most frequently appearing as discrete oval or round lesions of increased choroidal pigment.<sup>1,2</sup> While the majority of cases are benign, the clinical significance of choroidal nevi relates to their association with reduced vision when foveal in location and the rare potential for malignant transformation in approximately 1 in 4300-8845 cases.<sup>3-6</sup>

The majority of data on the prevalence of choroidal nevi comes from clinical-based studies, with a wide variation in reported rates (0.2% to 30%) that is likely attributable to differences in study populations and grading methods employed.<sup>1,4,7-9</sup> Internationally, there have been few previous population-based estimates of the prevalence of choroidal nevi,<sup>10-12</sup> with rates ranging from 1.4% in the Singapore Malay Eye Study<sup>12</sup> to 4.1% in Caucasians in the Multi-Ethnic Study of Atherosclerosis (MESA).<sup>10</sup> In Australia, a population-based study conducted in the early 1990's, the Blue Mountains Eye Study (BMES), reported the prevalence of choroidal nevi to be 6.5% in the non-Indigenous population.<sup>2</sup> To our knowledge, no data on the epidemiology of choroidal nevi in Indigenous Australians currently exists. As ethnic variations in the prevalence of choroidal nevi have been reported,<sup>10,12</sup> an understanding of the population-based prevalence in Indigenous Australians is warranted.

The purpose of this report is to describe the prevalence and characteristics of choroidal nevi in non-Indigenous and Indigenous Australian adults recruited from 30 geographic areas across Australia as part of the National Eye Health Survey (NEHS).

## METHODS

### *Study population and general assessments*

The NEHS is a population-based, cross-sectional survey of Indigenous Australians aged 40 years or older and non-Indigenous Australians aged 50 years or older, conducted between March 2015 and April 2016. Details of the NEHS design and methodology have been described in detail elsewhere.<sup>13,14</sup> In brief, multistage random-cluster sampling was used to select thirty Australian sites across five Remoteness Areas (Major City, Inner Regional, Outer Regional, Remote and Very Remote) based on data from the 2011 Australian Census.<sup>15</sup> Participants were recruited door-to-door and an overall examination rate of 71.5% was achieved. The protocol was approved by the Royal Victorian Eye and Ear Hospital Human Research Ethics Committee (HREC-14/1199H) as well as state-based Indigenous organisations. Study procedures adhered to the tenets of the Declaration of Helsinki as revised in 2013 and participants provided written informed consent to participate. Socio-demographic data including age, gender, Indigenous status, ethnicity, years of education, language spoken at home, utilisation of eye health services, as well as medical and ocular histories were collected via an interviewer-administered questionnaire. Presenting distance visual acuity (VA) was measured in each eye using a logMAR chart (Brien Holden Vision Institute, Australia) in well-lit room conditions. Pinhole testing was performed on participants with visual acuity worse than 6/12 in one or both eyes, followed by automated refraction (Nidek ARK-30 Type-R Hand-held auto-refractor/keratometer, Nidek Co., LTD, Japan) if VA improved to 6/12 or better in either eye.

#### *Retinal photography and nevus grading*

Two standard 45 degree colour retinal images were taken of each eye, one of the optic disc and the other of the macula, using a digital retinal camera (Digital Retinography System, CenterVue SpA, Italy). Photography was repeated following pupil dilatation (tropicamide 0.5%) when retinal images were of reduced quality due to small pupil size. Trained retinal graders from the Centre for Eye Research

Australia masked to the identity and clinical characteristics of study participants graded fundus photographs for choroidal nevus and other retinal disease.

A choroidal nevus was defined using the same definition as previous population-based studies.<sup>2,12</sup> That is, an unequivocal pigmented slate blue or green-grey choroidal lesion measuring at least 500 $\mu$ m in diameter. Choroidal lesions resembling nevi that were partially depigmented were graded as patchy hypomelanotic nevi. Once identified, further analysis was conducted to determine; the shape (oval, round, or irregular) and colour (slate blue, green-grey, hypomelanotic, amelanotic or brown) of the nevi, number of nevi, position relative to the fovea (subfoveolar, subfoveal, macular, or extramacular), proximity of posterior margin to the optic disc, quadrant distribution relative to the optic disc and the presence of overlying drusen or other pigment.<sup>2,12</sup> Nevus diameter, surface area and distance to the posterior margin of the optic disc were measured using ImageJ software (developed at the National Institute of Health) after carefully setting the image scale factor.

### **Statistical Analysis**

Participants' demographics and baseline characteristics were summarised by the mean and standard deviation (SD) for normally distributed continuous data, or median and inter-quartile range for skewed data, and counts and percentages for categorical data. Data were weighted by calculating sample weights for all records using the probability of selection at each stage of sampling. Ninety-five percent confidence intervals (CI), taking into account the sampling design, were calculated for the prevalence of choroidal nevi. Univariate and multivariable logistic regression models were used to examine the associations between presence of choroidal nevi and key explanatory variables. Key explanatory variables included age, gender, ethnicity, years of education, language spoken at home and remoteness.

All probabilities quoted are two-sided and all statistical analyses were undertaken using Stata version 14.2 (StataCorp, College Station, TX).

## RESULTS

The study sample of the NEHS consisted of 3098 non-Indigenous and 1738 Indigenous Australians. Of these, 3010 (97%) non-Indigenous and 1682 Indigenous (97%) participants had retinal photographs in at least one eye that were gradable for choroidal nevus (gradable images in only one eye = 4.3%, 202/4692). The mean age of the non-Indigenous and Indigenous study populations were 66.4 years [standard deviation (SD)=9.6] (58.9% female) and 54.8 years (SD=9.9) (53.7% female), respectively.

### *Prevalence and characteristics of choroidal nevus*

In the non-Indigenous population aged 50 years and over, the weighted prevalence of choroidal nevi was 2.1% (95% CI: 1.4, 3.3) (Table 1). Among Indigenous Australians aged 40 years and over, the weighted prevalence of choroidal nevi was 0.68% (95% CI: 0.4, 1.3). Bilateral choroidal nevi were present in two non-Indigenous participants and no Indigenous participant. Two choroidal nevi were present in five eyes of five non-Indigenous participants and one eye of an Indigenous participant. Choroidal nevi were found in 2.8% of males and 1.6% of females in the non-Indigenous population ( $p = 0.09$ ). Among Indigenous Australians aged 40 years and over, the prevalence of choroidal nevi was 0.71% for males and 0.66% for females ( $p = 0.93$ ). Of the 79 eyes with a choroidal nevus, only 2 had vision loss (best-corrected VA of  $<6/12$ ). However, in both cases, the choroidal nevus was not the primary cause of vision loss.

The average maximum diameter, surface area and distance from the disc of the choroidal nevi was  $1730\mu\text{m}$ ,  $2,766,800\mu\text{m}^2$  and  $3400\mu\text{m}$ , respectively. Of the 73 nevi found in 68 non-Indigenous participants, 81.6% were oval or round, 58.9% were green-grey, 52.1% were outside the macular and 9.6% were touching the disc (Table 2). Among the 12 nevi found in 11 Indigenous participants, 83.3% of nevi

were oval or round, 50% were green-grey and none were sub-foveolar in location. Drusen were found on the surface of 17.8% of nevi in the non-Indigenous population and 8.3% of nevi in the Indigenous population.

**Table 1:** Crude and weighted prevalence of choroidal nevus by Indigenous status, age and gender

	<b>n</b>	<b>Crude % (95% CI)</b>	<b>Weighted % (95% CI)</b>
<b>Non-Indigenous</b>			
Female	23	1.4 (0.09, 2.1)	1.6 (0.7, 0.3)
Male	43	3.1 (2.2, 4.1)	2.8 (1.4, 3.3)
<b>Age</b>			
50-59	27	3.4 (2.2, 4.9)	3.3 (2.0, 5.4)
60-69	21	1.8 (1.1, 2.8)	1.7 (0.92, 2.9)
70-79	16	2.2 (1.3, 3.5)	2.1 (1.1, 3.9)
80+	2	0.61 (0.07, 2.2)	0.98 (0.23, 4.1)
Total	66	2.2 (1.7, 2.8)	2.1 (1.4, 3.3)
<b>Indigenous</b>			
Female	4	0.5 (1.6, 1.2)	0.66 (0.28, 1.5)
Male	7	0.9 (0.3, 1.9)	0.71 (0.20, 2.5)
<b>Age</b>			
40-49	1	0.17 (0.04, 0.97)	0.18 (0.02, 1.4)
50-59	4	0.65 (0.18, 1.7)	0.64 (0.23, 1.8)
60-69	4	1.2 (0.32, 3.0)	1.0 (0.32, 3.1)
70+	2	1.3 (1.6, 4.8)	1.9 (0.54, 6.5)
Total	11	0.59 (0.29, 1.1)	0.68 (0.35, 1.3)

**Table 2:** Characteristics of choroidal nevi in non-Indigenous and Indigenous Australians

<b>Characteristic</b>	<b>Choroidal Nevi, No. (%)</b>	
	<b>Non-Indigenous (n = 73)</b>	<b>Indigenous (n = 12)</b>

Diameter (mm)		
0-1	13 (17.8)	2 (16.7)
1-2	40 (54.8)	8 (66.6)
>2	20 (27.4)	2 (16.7)
Shape		
Oval	32 (43.8)	4 (33.3)
Round	28 (38.4)	6 (50.0)
Irregular	13 (17.8)	2 (16.7)
Color		
Slate blue	24 (32.9)	2 (16.7)
Green-gray	43 (58.9)	8 (66.6)
Hypomelanotic	2 (2.7)	1 (8.3)
Brown	4 (5.5)	1 (8.3)
Position		
Subfoveal	1 (1.4)	0 (0.0)
Subfoveal	7 (9.6)	1 (8.3)
Macular	27 (36.9)	4 (33.3)
Extramacular	38 (52.1)	7 (58.3)
Posterior margin touching disc	7 (9.6)	2 (16.6)
Quadrant relative to optic disc		
Upper temporal	21 (28.8)	2 (16.7)
Upper nasal	8 (10.9)	5 (41.7)
Lower temporal	34 (46.6)	5 (41.7)
Lower nasal	10 (13.7)	0 (0.0)
Drusen present	13 (17.8)	1 (8.3)
Other pigment present	1 (1.4)	0 (0.0)

Due to the low frequency of choroidal nevi in Indigenous Australians, Indigenous and non-Indigenous data were combined in logistic regression analysis examining associations between choroidal nevi and selected characteristics (Table 3). After controlling for all variables in the model (model 1), Indigenous participants (OR = 0.25,  $p = 0.005$ ) were less likely to have choroidal nevi. When adjusting for only variables identified as  $p < 0.10$  in the univariate analysis (model 2), Indigenous participants (OR = 0.28,  $p = 0.01$ ) and those of older age (OR = 0.79 per 10 years,  $p = 0.02$ ) were less likely to have choroidal nevi.

**Table 3:** Relationship between choroidal nevus and selected characteristics in Australians (n=4692)

	Univariate		Multivariable <sup>1</sup>		Multivariable <sup>2</sup>	
	OR [ 95% (CI)]	p	OR [ 95% (CI)]	p*	OR [ 95% (CI)]	p*
Indigenous	0.31 (0.14, 0.71)	0.01	0.25 (0.10, 0.63)	0.01	0.28 (0.11, 0.73)	0.01
Age (per 10 years)	0.80 (0.67, 0.96)	0.02	0.81 (0.63, 1.05)	0.11	0.79 (0.66, 0.96)	0.02
Gender (male)	1.84 (0.89, 3.80)	0.10	1.93 (0.88, 4.26)	0.10	1.99 (0.92, 4.29)	0.08
Education (year)	1.04 (0.99, 1.10)	0.12	1.03 (0.97, 1.10)	0.31		
English spoken at home	2.84 (0.34, 23.62)	0.32	1.18 (0.09, 15.33)	0.89		
<i>Ethnicity</i>						
Oceanian	1		1			
European	0.45 (0.18, 1.17)	0.10	0.48 (0.19, 1.19)	0.11		
Others	0.22 (0.03, 1.64)	0.13	0.24 (0.02, 2.62)	0.23		
<i>Remoteness</i>						
Major City	1		1			
Inner Regional	1.46 (0.49, 4.31)	0.48	1.38 (0.47, 4.03)	0.54		
Outer Regional	0.89 (0.38, 2.10)	0.78	0.86 (0.37, 1.99)	0.71		
Remote	1.63 (0.79, 3.34)	0.18	1.54 (0.75, 3.17)	0.23		
Very Remote	0.59 (0.20, 1.76)	0.33	0.55 (0.24, 1.27)	0.16		
Self-reported diabetes	0.45 (0.18, 1.12)	0.08	0.49 (0.18, 1.31)	0.15	0.45 (0.05, 1.21)	0.13
Self-reported stroke	0.23 (0.05, 1.08)	0.06	0.25 (0.05, 1.17)	0.08	0.26 (0.05, 1.21)	0.08

OR = Odds ratio; CI = Confidence interval; \*Statistical significance was set as a p value of  $\leq 0.05$  (two tailed) <sup>1</sup>full model; <sup>2</sup>reduced model, which included only  $p < 0.10$  in the univariate logistic regression model.

## DISCUSSION

This paper presents the prevalence of choroidal nevi in a population-based, national sample of non-Indigenous and Indigenous Australian adults. The weighted prevalence of choroidal nevi was 2.1% in non-Indigenous Australians aged 50 years and over and 0.68% in Indigenous Australians aged 40 years and over. In line with previous population-based reports,<sup>2,10,12</sup> there was a trend towards a decreasing prevalence of choroidal nevi with increasing age.

The clinical relevance of choroidal nevus relates to the rare transformation to melanoma. Nevi of diameter  $>6\text{mm}$ , 1-3 mm in elevation<sup>1,16,17</sup> and/or with the posterior margin bordering the optic disc<sup>18</sup> have been identified as particularly suspicious in previous literature. Furthermore, while overlying drusen is often suggestive of lesion chronicity,<sup>16,19</sup> there is some evidence that it may be associated with nevus growth.<sup>2</sup> In the present study, the majority of nevi were small (mean diameter = 1.75mm) and the largest lesion measured 5.77mm in diameter. A total of 9.6% (7/73) and 16.6% (2/12) of nevi were touching the optic disc in the non-Indigenous and Indigenous population, respectively. This is higher than that reported in the BMES (6.1%),<sup>2</sup> the Singapore Malay Eye Study (0%)<sup>12</sup> and the MESA (4.3%).<sup>10</sup> In the non-Indigenous population, we found that 17.8% (13/73) of nevi had overlying drusen, similar to the Singapore Malay Eye Study (20%)<sup>12</sup> and the MESA (24.8%)<sup>10</sup> but substantially lower than the BMES (98%).<sup>2</sup> The BMES employed stereoscopic fundus photography and therefore it is possible that their finer grading system may have contributed to this finding.

When compared to previous international studies, the prevalence of choroidal nevi in non-Indigenous Australians (2.1%) in the NEHS was lower than that reported in Beijing Eye Study (2.9%),<sup>11</sup> similar to the MESA (2.1%)<sup>10</sup> and higher than the Singapore Malay Eye Study (1.4%).<sup>12</sup> Of note, we report a markedly lower prevalence than that found in non-Indigenous Australians in the BMES (6.5%).<sup>2</sup> Differences in the retinal photography methods employed in the present study and the BMES are likely to be contributory as the latter study employed 6-field, 30-degree stereoscopic fundus photography. Previous research estimates that 25% of nevi would likely be missed on 2-field photography,<sup>12,20</sup> and as such we acknowledge that by not employing a wider photographic field, it is likely that the present study underestimated the prevalence of choroidal nevi. Interestingly, while the mean nevus diameter in the NEHS was larger than that found in the BMES (NEHS=1.75mm vs. BMES=1.25mm), other characteristics of nevi were similar including shape (round or oval; NEHS=82% vs. BMES=75%), position (lower temporal; NEHS=47% vs. BMES=45%) and colour (blue-grey; NEHS=92% vs. BMES=87%).

To our knowledge, this is the first population-based study to examine the prevalence and characteristics of choroidal nevi in Indigenous Australians. After adjusting for age and other potential confounders, we report that Indigenous Australian adults were approximately 75% less likely to display a choroidal nevi compared to non-Indigenous Australians. Previous research has suggested a difference in the prevalence of choroidal nevi between Caucasian populations and those of other ethnicities.<sup>10,12</sup> For example, the MESA<sup>10</sup> reported very low frequencies of choroidal nevi among African American (0.7%) and Hispanics (1.2%) compared to Caucasians (4.1%) in the same cohort. These findings are in line with previous studies that have reported nevi of the skin and iris are more common in Caucasians.<sup>21-24</sup> Furthermore, differences in fundus pigmentation between Indigenous and non-Indigenous Australians should also be taken into account, where it is easier to detect a choroidal

nevus in the more pale, non-Indigenous fundi. Of interest, anatomic features of choroidal nevi including size, colour and position were similar amongst Indigenous and non-Indigenous Australians.

Similarly to the BMES,<sup>2</sup> MESA<sup>10</sup> and the Singapore Malay Eye Study,<sup>12</sup> there was a trend towards a decreasing prevalence of choroidal nevi with increasing age in non-Indigenous participants in the NEHS. That is, the prevalence was over 3-fold higher in those 50-59 years old (3.3%) compared to those aged 80+ years (0.98%). As with previous studies, there is no obvious explanation for the age differences in the prevalence of choroidal nevi, however this finding may be partly explained by the established relationship between age and image gradability,<sup>25</sup> where a decreasing media clarity in the older age groups may have led to a detection bias. Furthermore, a relatively small representation of the oldest age group in the sample may have resulted in an unstable estimate of choroidal nevi in this group.

The strengths of this study include the national population-based design, stratification by Indigenous status and the use of a standardised protocol to grade for choroidal nevi. The principal limitation includes the use of non-stereoscopic images in only two fields of view which is likely to have led to an underestimation of the prevalence of choroidal nevi. However, this is unlikely to have influenced comparisons of prevalence amongst non-Indigenous and Indigenous participants in this study. Furthermore, a small proportion of participants had gradable images for only one eye (4.3%, 202/4692) which may have also led to an underestimation in the prevalence.

In summary, we report the prevalence of choroidal nevi to be 2.1% in non-Indigenous Australian adults, and even more infrequent amongst Indigenous Australian adults (0.68%). Choroidal nevi did not affect visual acuity and nevus

characteristics were largely comparable to the few previous population-based reports in Caucasian, Asian and multi-ethnic cohorts.

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