Title Page

Title

The Association between Retinal Nerve Fibre Layer Thickness and Myopia in a Black South African Population.

This document represents an MMED dissertation structured as a submissible article. The article shall be submitted to the African Vision and Eye Health Journal in strict accordance with the guidelines outlined in Appendix D.

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Abstract

Background: Myopia is a prominent cause of visual impairment worldwide. While optical coherence tomography (OCT) consistently measures the thickness of the retinal nerve fibre layer (RNFL), recognising irregularities in RNFL for eyes with high myopia is complicated by a high rate of false positive diagnoses for optic nerve diseases, primarily glaucoma.

Aim: This study compared the RNFL thickness in African myopic eyes to non-myopic eyes and compared the RNFL thickness in different degrees of myopia in the same demographic group.

Setting: The outpatient department of St John Eye Hospital is the ophthalmology department of Chris Hani Baragwanath Academic Hospital in Johannesburg, South Africa.

Methods: A cross-sectional study of a black ethnical South African population comparing retinal nerve fibre layer thickness between a myopic group and their healthy non-myopic counterparts. One hundred and thirty-nine eyes of 139 patients were enrolled in the study.

Results: Participants were separated into a control group (n=68) and a myopic group (n=71). The participants in this study had a mean age (SD) of 48.1(16.2) years. The average RNFL thickness in the non-myopic group (107.1µm) was substantially thicker compared to the myopic group (98.1µm) (p=0.003). The average RFNL thickness in the high myopic group was 16.0µm lower compared to the low myopic group (p<0.001). The findings from the multivariate regression analysis in this study indicate that average RNFL thickness is significantly affected by both axial length (p <0.001) and age (p=0.017).

Conclusion: This study's findings indicate that non-temporal RNFL thickness is reduced in a myopic South African population of black ethnicity compared to the non-myopic control group from the same demographic. Additionally, it demonstrates that the high myopic group has thinner RNFL than the low myopic group.

Contribution:

Developing a population-specific normative database that can be adjusted for refractive error would make the analysis of RNFL thickness in myopia more accurate. Subsequently, this could play a pivotal role in reducing false positives and misdiagnoses of glaucoma in individuals with high myopia.

Introduction

Myopia is one of the leading causes of impaired vision worldwide.[1–5]. The prevalence of myopia exhibits regional variations but has been increasing globally over the past few decades. By extrapolating current data, Holden et al.[1] have estimated that the global prevalence of myopia will be 50% by 2050.[1] The prevalence of myopia in African countries currently ranges from 1.7% to 17%, with an anticipated increase attributed to the ongoing urbanisation of these countries. [1,4,6] Myopia presents a significant economic and social burden. It increases the risk of developing several pathological ocular conditions, including a 50% higher risk of developing open-angle glaucoma. [1,2,7] Primary open-angle glaucoma (POAG) accounts for 15% of blindness cases annually in Sub-Saharan Africa, highlighting the significant impact of POAG on visual health in this region.[8]

Optical Coherence Tomography (OCT) facilitates the reproducible acquisition of the retinal nerve fibre layer (RNFL) thickness around the optic disc and is essential in diagnosing and monitoring glaucoma progression. Changes in the optic disc due to myopia pose challenges in diagnosing and managing diseases like glaucoma.[2,9,10] Unfortunately, normative databases typically exclude or contain too few myopic individuals, so identifying 'true' or 'non-myopia-related' RNFL irregularities in eyes with high myopia is complicated by false-positive errors.[2,3,10–13] Various studies (summarised in Tables 1 and 2)[4,14–24]have demonstrated a negative correlation between myopia and RNFL thickness and a similar distribution of RNFL thickness among different severity groups of myopia. A study in Turkey discovered that incorporating a myopic database into OCT software yielded more reliable data for assessing glaucoma in myopic eyes.[25]

A further complicating factor is that retinal nerve fibre layer thickness differs among ethnic groups, leading to inaccurate categorisation compared to default European normative databases.[26] Studies done in Ghana[8], Nigeria[27], and South Africa demonstrated an increased average RNFL thickness in Sub-Saharan African black populations compared to studies on individuals of European descent.[6,8,28,29] The variations in the average RNFL of the non-myopic groups (of different ethnicities) are readily apparent in the studies summarised in Tables 1 and 2.

To our knowledge, no studies have evaluated the relationship between RNFL thickness and myopia in a Black South African population. This study aims to compare the RNFL thickness between black South African myopic and non-myopic eyes and to compare the RNFL thickness in different degrees of myopia in this population group. The study will hopefully serve as a stepping stone in developing a population-specific normative database that can be adjusted for refractive error to make the analysis of RNFL thickness more accurate and prevent false positives and misdiagnoses in individuals with high myopia.

Table 1. Studies comparing RNFL thickness in myopic patients to non-myopic patients

Author	Location	Diagnostic Tool	Myopic Group		Control group		Comment
			Sample size	Average RNFL thickness (µm)	Sample size	Average RNFL thickness(µm)	
Malakar et al [4] 2015	India	FD-OCT	50	87.89±10.37	40	111.64±12.6	Statistically significant thicker RNFL in the emmetropic group. Results correlate with other studies done with SD-OCT
Choi et al.[14] 2006	Korea	SD-OCT Stratus	71	LM 103.85 ± 14.48 HM 100.74 ± 9.15	45	113.29 ± 10.80	A statistically significant difference was found between LM and HM groups (p<0.05) . The study sample comprises a younger population between 23-26 years old. This could account for the increased average RNFL thickness compared to other studies
Schweitzer et al.[15] 2009	Canada	SD-OCT Stratus	10	HM 80.0 ± 18.6	10	108 ± 10.8	Myopic group were all high myopes with a spherical equivalent of ≤ -10D
Singh et al.[16] 2017	India	SD-OCT Cirrus	50	LM 83.76 ± 3.44 HM 78.68 ± 5.67	50	91.26 ± 2.99	Average RNFL thickness was significantly thinner in moderate and high myopes as compared to emmetropes.
Tai et al.[17] 2018	Malaysia	SD-OCT Cirrus	223	LM 97.17±1.86 HM 91.10 ± 4.65	180	99.22 ±2.05	Statistically significant difference observed only between the HM and the EM group.
Jeong et al.[18] 2019	Korea	SD-OCT Cirrus	186	LM 86.9 ± 10.3 HM 82.1 ± 7.6	37	90.2 ± 9.5	The rate of RNFL thinning was the primary objective. No significant difference found between groups. There was however a statistically significant difference in RNFL thickness between the groups.
Kim et al.[19] 2020	Korea	SD-OCT Spectralis	37	HM 81.70 ± 13.07	37	90.84 ± 11.87	In high myopia without pathologic changes, there was a meaningful thinning of the retina and choroid
Cui et al.[20] 2021	China	SD-OCT Spectralis	52	HM 99.04± 8.23	40	103.25 ± 8.32	Myopic group in this study did not include high myopes. The spherical equivalent of patients in this group comprised of refractive errors of -4.71D ±0.89D

Myopic subgroups divided into Low myopia (LM) and high myopia(HM). Criteria for these specific groups varied between studies.

Table 2. Summary of studies comparing RNFL thickness in different degrees of myopia.

Author	Location	Diagnostic Tool	Degrees of myopia						Comment
			Low myopia(LM)		Moderate Myopia(MM)		High myopia(HM)		
			Sample size	Average RNFL thickness (µm)	Sample size	Average RNFL thickness (µm)	Sample size	Average RNFL thickness (µm)	
Zhao et al.[21] 2012	China	Rtvue SD-OCT	17	96.55 ±5.54	31	95.10 ±5.57	59	91.59 ± 4.62	Values provided for average GCIL thickness Negative correlation of GCIL, and peripapillary RNFL thickness against AL
Porwal et al.[22] 2020	India	Cirrus SD-OCT	46	92.17 (±9.84)	34	88.12 (±9.53	20	82.40 (±10.43)	Statistically significant difference in the average RNFL thickness between two groups based on the axial length AL <24mm= 91.40 (±10.17) AL> 24mm =86.06 (±10.09
Ganekal et al.[23] 2021	India	Cirrus SD-OCT	37	97.68±10.84	39	85.10±12.32	24	81.96±5.14	Statistically significant difference in HM group and LM group (P < 0.05)
Miller et al.[24] 2021	USA	Cirrus SD-OCT	27	89.70 ± 4.48	25	85.52 ± 6.40	24	79.33 ± 7.18	Statistically significant difference MM vs. HM P< 0.001 LM vs. HM P< 0.001

Myopic subgroups(SE) into low myopia (LM) (< –3.0D) , moderate myopia (MM) (-3.0D - -6.0D)and high myopia(HM) (> -6.0D). Spherical equivalent(SE); Axial length (AL)

Research methods and design

The study was a prospective, cross-sectional study performed at St John Eye Hospital, the ophthalmology division of Chris Hani Baragwanath Academic Hospital, in the southern part of Johannesburg, South Africa.

Research Participants

The participants were all South African citizens of black ethnicity who had normal intraocular pressure (10-21mmHg) as measured by applanation tonometry with the Perkins or Goldmann applanation tonometer. Myopia was defined by the globe's axial length. Low Myopia (LM) was defined as an axial length of ≥24mm and <26mm. High myopia (HM) was defined as an axial length of ≥26mm. The control group (or no myopia group (NM)) had an axial length of ≥21mm and< 24mm.

Participants were excluded if they had any history of ocular trauma, surgery, or laser procedures; if they had pre-existing ocular diseases, for instance, glaucoma, uveitis, diabetic- and hypertensive retinopathy, and retinal and choroidal diseases; if there was a poor view of the fundus and poor image (OCT) quality secondary to a cataract or other media opacity; or if they had pathological myopic changes as seen on fundoscopy in the macular and peripapillary region (including staphylomas).

Research Data

The data collection occurred between April 2023 and October 2023. The study sample included patients and their healthy family members who presented for routine follow-up visits at the St John Eye Hospital outpatient department. Patients who qualified for the study were provided with an information sheet regarding the study, and after informed written consent was given, all participants underwent a set of tests. The demographic details (age and gender), as well as the medical history of the participants, were diligently documented. An extensive ocular evaluation was performed, which included a best-corrected Snellen visual acuity test at 6 metres, an intraocular pressure measurement, a slit-lamp examination of the anterior segment, and a cycloplegic fundoscopy. This was done to ascertain and document the characteristics of the optic disc (including disc tilt, presence of peripapillary atrophy, and cup-to-disc ratio) and to rule out any other macular diseases or pathological myopia changes. Autorefraction was done using the Charops CRK 7000 (Huvitz Corp., Korea). The axial length measurement was done with the Nidek optical biometer AL-scan (Nidek Co. Ltd, Japan). Peripapillary RNFL thickness and the size of the optic disc (measured as the vertical disc height [VDH]) were obtained with the Heidelberg Spectralis SD-OCT, acquisition software version 6.16.0 (Heidelberg Engineering, Germany). The OCT scan was obtained by first identifying the optic disc. If the system incorrectly identified the disc outline or the patient had a poor fixation on the integrated fixation target, the high-resolution scanning circle was repositioned to ensure centralised placement over the optic disc. The eye length parameter in the OCT Control section was adjusted to correctly align the infrared and OCT section images with high myopic patients. When the image was correctly aligned within the acquisition frame, tracking was engaged, and the images were obtained. Peripapillary RNFL was segmented into average, supero -and-

inferotemporal, supero-and-inferonasal, temporal, and nasal segments, and the thickness of each was obtained separately in micrometres (μm). Disc foveal alignment (FoDi) was manually corrected if the automatic software detection of the fovea failed or if the FoDi angle was outside the range of -7.7° and 7.7° for the non-myopic group. Vertical disc height (VDH) was measured manually on the red-free fundus image obtained during the OCT scan. Images were acceptable if the OCT scan quality was ≥21 dB and the FoDi alignment was within 7.7°. Those with poor-quality scans or a FoDi angle not within an acceptable range were excluded from the study. All the measurements obtained from the OCT, including the scan quality, were documented. The RNFL thickness was documented as an average (overall) value for each patient and each nerve sector, respectively. A second investigator verified all RNFL OCT scans and VDH measurements.

Statistical analysis

The power calculation used a 4μm difference between groups with a standard deviation of 8.3 μm (from Cui et al.[20]) to determine the sample size of 138 patients from a two-sample means test. This sample size was required to yield a statistical power of 80% at a 0.05 significance level.

The data was captured and stored in a REDCap electronic database. [30,31] The one-way ANOVA test was used to compare the mean RNFL thickness measured for each sector of the peripapillary retina across the two groups. A post hoc analysis (Tukey's Honest Significant Difference (HSD)) test was conducted to examine the relationship between the three study groups and RNFL thickness. The dataset for myopes exhibited a non-normal distribution according to the results of the Shapiro-Wilk test. Consequently, we used a non-parametric model (The Wilcoxon rank sum test) as the most appropriate model for analysing these data. The association of age, gender, increased axial length, peripapillary atrophy and optic disc tilt with RNFL thickness were evaluated using linear regression models. Inter-eye correlation was accounted for by randomly selecting one eye for the study.

Ethical considerations

Before conducting this study, the University of the Witwatersrand's Human Research Ethics Committee provided ethical clearance reference number M221035. Adherence to the tenets outlined in the Declaration of Helsinki has been maintained. Written informed consent to participate in the study was obtained from all participants. All collected data were securely anonymised to ensure confidentiality and privacy.

Results

Demographic data

The study enrolled 139 patients aged between 18 and 86, averaging 48 years (Standard deviation (SD) 16.2). The study population was divided into two distinct groups for analysis: the control group (emmetropic group), which comprised 68 patients with a median age of 47.5 years and the myopic group, 71 patients with a median age of 51 years. The myopic group was subdivided into a high myopic group (n=17) and a low myopic group (n=54). Females comprised 66.9% (n=93) of the total patients in this study. The control group had slightly more

female patients, 75%, compared to the myopic group (59.2%). The co-morbidities identified included hypertension, which was the most prevalent among all groups, as well as Diabetes mellitus type 2 and Human Immunodeficiency Virus (HIV) positivity. The distribution of comorbidities was consistent across all study groups. All patients with co-morbidities were receiving treatment tailored to their specific conditions.

Table 3. Demographic features of study subjects

Group	Total	Control	Myope	P-value$^{\Delta}$
	n=139	n=68	n=71	
Age (years)*	48.0 (34.0, 62.0)	47.50 (35.8, 56.3)	51.00 (32.5, 64.0)	0.5
Gender				0.05
Male	46 (33.1%)	17 (25.0%)	29 (40.9%)	
Female	93 (66.9%)	51 (75.0%)	42 (59.2%)	
Comorbidities				
Hypertension	52 (37.4%)	24 (35.3%)	28 (39.4%)	0.6
Diabetes	16 (11.5%)	8 (11.8%)	8 (11.3%)	>0.9
HIV	11 (7.9%)	6 (8.8%)	5 (7.0%)	0.7

HIV, human immunodeficiency virus-positive
* Median (IQR)
Δ Pearson's Chi-squared test/ Wilcoxon rank sum test

Clinical features of study subjects

Table 4 summarises the clinical features of all eyes used in the study. The myopic group's mean BCVA (logMar) was 0.3, was slightly worse than the control group's mean BCVA of 0.2. The myopic cohort exhibited an incidence of cataracts that was approximately 10% higher than that of the control group. This discrepancy could account for the lower visual acuity observed in the myopia group. The intraocular pressure exhibited comparability between the two groups. The mean axial length in the non-myopic group was 23.3 mm, with a standard deviation of 0.6. The myopic group exhibited a mean axial length of 25.5mm with a standard deviation of 1.7. The Spherical equivalent (SE) is significantly lower in the myopic group, with a mean of -5.1DS and -0.9DS in the control group. The outlying minimum SE of -6.5 DS in the control group arises from corneal or lenticular changes; however, the patient remains categorised in the control group since the axial length for this patient is 22.5mm. The vertical disc height and disc size were similar in both study groups. The presence of peripapillary atrophy (PPA) was a relatively equally distributed between the control group with 76.8% and 72.9% in the myopic group. It's important to note that the study did not evaluate the extent or zone of PPA. The myopic group had more than double the amount of disc tilt at 45.1% (n=32) compared to 19.1% in the control group. In both groups, optic discs were tilted more in the vertical meridian (23.0%) when compared to the horizontal meridian (9.4%).

Table 4. Clinical Features of Study Subjects

Group		Control	Myope	P -value*
n		68	71	
BCVA (logMAR)	Range	-0.1- +1.0	-0.1 - +1.0	**<0.001**
	Mean ± SD	0.16±0.25	0.29±0.26	
IOP (mmHg)	Range	08.0 -19.0	07.0- 20.0	0.2
	Mean ± SD	12.5 ± 3.0	13.2 ±3.3	
Axial length(mm)	Range	21.7 – 23.9	24.0 – 29.9	**<0.001**
	Mean ± SD	23.3 ±0.6	25.5 ± 1.7	
SE (diopters)	Range	-6.5 - 2.6	-21.1 – 0.1	**<0.001**
	Mean ± SD	-0.9 ± 1.5	-5.1 ± 5.3	
RNFL(µm)	Range	78.0- 193.0	39- 139	**0.003**
	Mean ± SD	107.1 ±17.2	98.1 ±17.3	
VDH (mm)	Range	1353-2616	1360-2825	0.8
	Mean ± SD	1997.4 ±212.7	1991.0 ±296.9	
CDR	Range	0.2-0.6	0.2-0.7	0.7
	Mean ± SD	0.3 ±0.1	0.3 ±0.1	
Cataracts (%)		32.4	42.3	0.2§
PPA (%)		77.9	71.8	0.4§
Disc tilt (%)	None (%)	80.9	54.9	**0.004**§
	Vertical (%)	16.2	29.6	
	Horizontal (%)	2.9	15.5	

BCVA, Best corrected visual acuity; IOP, intraocular pressure; SE, spherical equivalent; RNFL, average RNFL thickness; VDH, vertical disc height; CDR, cup-to-disc ratio; PPA, peri-papillary atrophy present
* T-test
§ Pearson's chi^2 test

RNFL thickness in the three different study groups

The sectoral RNFL thickness measurements for the different groups in this study are summarised in Table 5. The mean average RNFL thickness of the high myopic group was 86.00µm (SD 21.08), which is statistically significantly thinner than the emmetropic and low myopic groups (p<0.001) (Figure 1). Post Hoc HSD analysis concluded that the high myopic group had an average RNFL thickness of 21.12µm (95% CI: 10.44, 31.8) less than the emmetropic group and 15.89 µm (95% CI 4.94,26.8; p=0.002) less than the low myopic group. There was no statistically significant difference in RNFL thickness between the low myopic and emmetropic groups. (95% CI:-1.94:12.4; p=0.19). This analysis found a significant negative correlation between different levels of

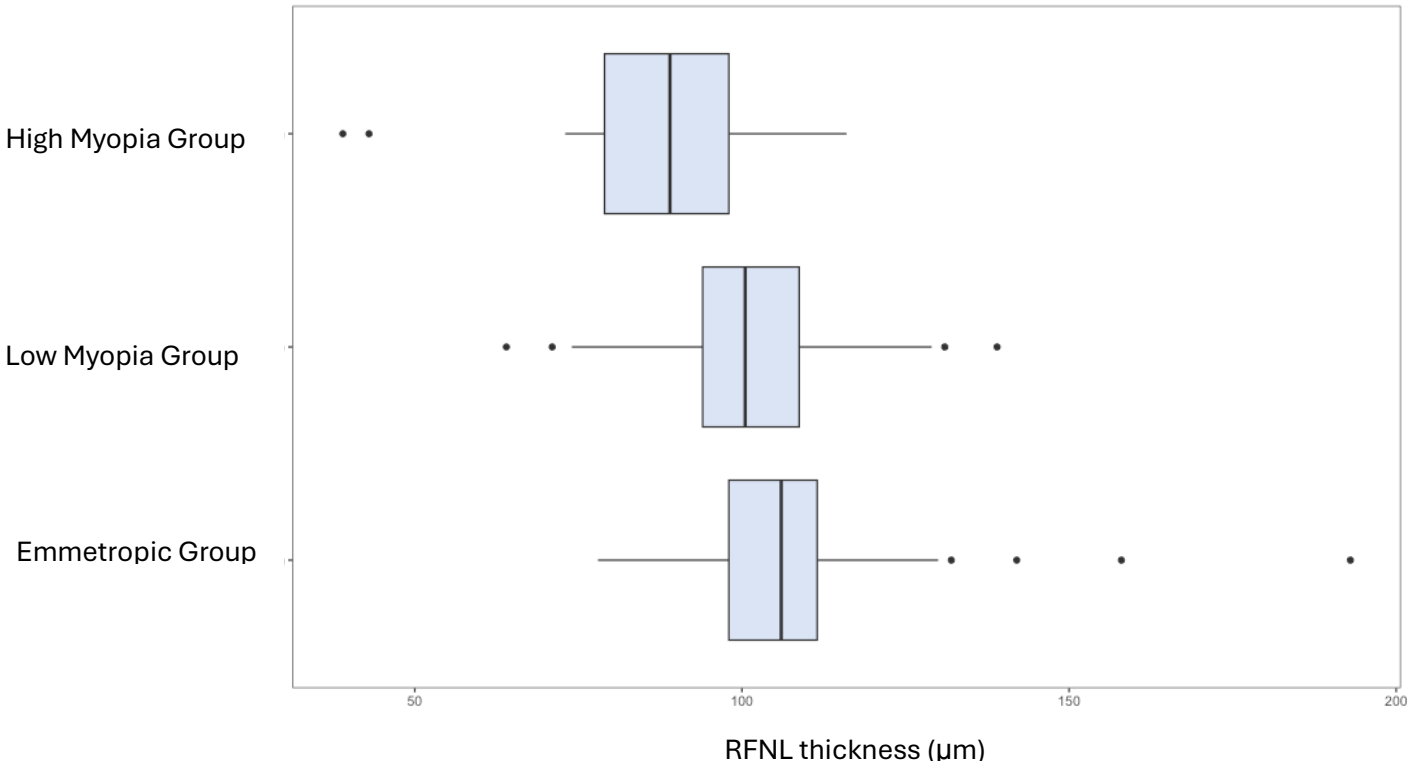
myopia across most sectors, except for the inferotemporal and superotemporal sectors, where the difference was not statistically significant.

Table 5. RNFL thickness sectoral analysis for all three groups. (Emmetrope, Low Myope, High Myope)- mean (Standard deviation)

RNFL Sector (µm)	Emmetrope (Control) N = 68	Low Myope N = 54	High Myope N = 17	p-value*
Average	107.12 (17.22)	101.89 (14.14)	86.00 (21.08)	**<0.001**
Temporal	75.12 (18.32)	75.52 (13.24)	73.47 (15.62)	>0.9
Nasal	82.03 (23.87)	73.61 (18.10)	64.82 (31.15)	**0.011**
Superior nasal	131.28 (33.93)	114.46 (27.50)	91.76 (42.17)	**<0.001**
Superior temporal	145.25 (29.39)	138.35 (30.00)	101.82 (36.23)	**<0.001**
Inferior nasal	134.00 (37.24)	119.61 (26.30)	102.71 (39.99)	**0.002**
Inferior temporal	139.91 (30.98)	145.02 (28.48)	116.29 (35.19)	**0.004**

() Standard Deviation
*One way- ANOVA

Figure 1. Box-plot of average RNFL thickness between 3 groups- Emmetrope, Low Myope, High Myope



Linear regression analysis (Table 6)

Gender was the only variable that did not exert a significant independent effect on RNFL thickness in the univariate analysis. The RNFL thickness showed a decrease averaging 2.1µm (95% CI: -0.4, -0.03; p-value: 0.024) for every decade increase in age (-0.2µm per year). This effect demonstrated stronger statistical significance in the multivariate evaluation (p=0.017). With each unit(mm) increase in axial length, there was a corresponding decrease in RNFL thickness by 4.6µm (95% CI: -6.3, -3.0; p-value < 0.001). Multivariate analysis confirmed axial length as a predictor of RNFL thickness. The average RNFL thickness was reduced by 3.9µm for every 1 mm increase in axial length. (95% CI: 5.7, -2.2; p-value<0.001). Individuals with PPA had an average of 9.7µm thicker RNFL than those without PPA (95% CI: 3.0,16; p-value= 0.005). Patients with vertical tilt had 7.7µm thinner RNFL (95% CI: -15, -0.70; p=0.031) compared to those without tilt, but this was not significant in the multivariate model (95% CI: -12, 2.0µm; p=0.2). Horizontal tilt patients had 13µm thinner RNFL (95% CI: -23, -3.2; p=0.010). After accounting for all variables, only axial length and age retained statistical significance.

Table 6. Linear regression analysis

Characteristic	Simple Models			Multivariate Model		
	β_0	95% CI	p-value	β_0	95% CI	p-value
Age	-0.21	-0.39, -0.03	**0.024**	-0.20	-0.36, -0.04	**0.017**
Gender Female	2.1	-4.2, 8.5	0.5	2.9	-2.8, 8.6	0.3
Axial length	-4.6	-6.3, -3.0	**<0.001**	-3.9	-5.7, -2.2	**<0.001**
PPA	9.7	3.0, 16	**0.005**	4.4	-2.0, 11	0.2
Disc tilt Vertical	-7.7	-15, 0.70	**0.031**	-1.6	-8.6, 5.3	0.6
Horizontal	-13	-23, -3.2	**0.010**	-6.5	-16, -3.1	0.2

CI (Confidence interval), PPA (Peripapillary atrophy)

Discussion

Retinal nerve fibre layer thickness analysis has become one of the most important diagnostic tools in optic nerve disease.[12] Our research findings indicate a significant reduction in RNFL thickness within a myopic black population in South Africa compared to an ethnically matched, non-myopic cohort. This result is consistent with other research showing a negative correlation between RNFL thickness and myopia, as Tables 1 and 2 summarise (pages 6-7). The significance of performing this analysis in a homogeneous population (and having appropriate population-specific databases) is highlighted by comparing our findings to those illustrated in Table 1. Despite the statistical significance of the RNFL thinning in the myopic group in this study, the actual average RNFL thickness in this group is greater than the RNFL in the control groups in Singh et al.'s study [32](91.3µm)

from India and the Korean studies by Jeong et al.[23](90.2µm) and Kim et al.[26](90.8µm). This can be explained by the thicker RNFL in normal black South Africans.[15]

Retinal structural changes associated with myopia are predominantly the result of axial elongation. This causes thinning of the sclera and retina, with changes in retinal vasculature leading to retinal hypoperfusion, microcirculatory alteration in the retina, and choroidal and retinal ischemia. [2,5,7,9,13,26] A further consequence is spreading the retinal nerve fibres across a greater surface area. [2,5,9,11] The measurable effect of these alterations is RNFL thinning, as detected on OCT.[26] Reduced neuronal activity in retinal ganglion cells is another mechanism proposed to cause RNFL thinning in myopia. [9,12] This is evidenced by animal studies demonstrating that myopia could decrease ganglion cell stimulation.[9] Since the change in retinal structure is thought to be the main reason for the link between RNFL thinning and myopia, it follows that the association is more substantial with axial myopia than with refractive myopia (defined by spherical equivalent only). [13] Adjusting for spherical equivalent (SE) in data analysis may cause errors, as the refractive state can fluctuate due to conditions such as cataract development, macular pathology, and corneal refractive surgery.[13] In adherence to this principle, participants in this study were classified into myopia subgroups based on axial length rather than spherical equivalent. This contrasts with most other studies, which primarily use SE for myopia categorisation. This study also demonstrated a significant negative association between RNFL thickness and different degrees of myopia. A study conducted by Malakar et al.[4] revealed findings like the current context, indicating an average RNFL thickness of 87.89 micrometres among individuals categorised within the high myopic group (defined as SE ≥ -6.00DS).[4]

The temporal segment of the optic nerve head is the convergence point for the superotemporal and inferotemporal papillomacular nerve fibre bundles, with macular fibres predominantly situated close to the superior and inferior horizontal sutures near the optic disc. [11]In myopia, stretching of the eye tissue results in the retina being pulled temporally, leading to a rearrangement of nerve fibres. The superior and inferior temporal nerve fibres move closer together, ultimately causing an increase in temporal RNFL thickness. Therefore, it is not surprising that, in this study, a consistent sectoral decrease in non-temporal RNFL thickness was observed. This is in keeping with the literature.[2,7,9,11,14–17,19,23,32–36] Further studies in myopic patients have demonstrated that, despite average RNFL thinning, the temporal RNFL thickness is relatively increased compared to the other optic nerve areas.[7,12,26]

When the retinal nerve fibres converge, they form an essential component of the optic disc; therefore, the RNFL thickness may be correlated with the nerve's size and the implantation angle. [9] Optic nerve features commonly found in myopia include disc tilt, peripapillary atrophy and discrepancy in the demarcation of the disc margin observed on fundoscopy compared to the anatomical disc margin. [3] The failure of the OCT to optimally identify the optic disc margins can be attributed to the underlying structural change in the corresponding outer retinal layers beneath the area of peripapillary atrophy.[3] Temporal stretching during axial lengthening in myopia is

believed to be associated with PPA.[37] Kwon et al.[37] and Ilhan et al.[26] demonstrated thinner RNFL thickness in individuals with PPA. In contrast, our findings indicated an average increase in PPA-related RNFL thickness. In concordance with our research, Zang et al.[38] similarly observed a thicker PPA-related RNFL, which was posited to be concomitant with the relationship between PPA and radial capillary vessel density.[38] Photoreceptor reduction, loss of RPE and choroid capillaries, and displacement or defects in Bruch's membrane are potential factors contributing to PPA. [39] As described by Tang et al.[39] the absence of RNFL change as a contributory factor in the development of PPA may clarify the inconsistency observed in the association between RNFL thickness and PPA across various studies. The correlation between PPA and RNFL thickness must be confirmed through further studies. In this study, 44.3% of the myopic group had tilted discs; this is more than double compared to the 20.3% in the control group. After adjusting for other variables, we found that disc tilt in the horizontal meridian was negatively correlated with RNFL thickness. Peripapillary scleral thinning is associated with the angle at which the optic nerve implants, causing posterior optic disc displacement in the same area.[14] Moghadas et al.[40] and Rauscher et al.[2] found no notable difference in RNFL thickness between the tilted and non-tilted disc groups. In contrast, Hwang et al.[41] reported that the temporal RNFL in temporally tilted optic discs exhibited greater thickness. Ilhan et al.[26] and Lee et al.[13] noted that the RNFL thickness was considerably lower in individuals with tilted optic discs, consistent with the findings in this study. The discrepancies observed in the published results may be ascribed to variations in the methodologies and criteria employed to delineate a tilted optic disc.[40] Thinning of RNFL observed superiorly and inferiorly can be accounted for by tilting of the disc.[26]

Axial length can influence the RNFL thickness obtained on OCT through a magnification effect. [12,16] The projection of the scanning circle in longer eyes appears larger than its true diameter. Theoretically, the RNFL thickness is expected to decrease with an increasing scanning distance to the optic disc. Correction of this magnification effect in non-telecentric OCT instruments can be done using Littman's formula and modified by Bennett's formula. [9,12,34] The Heidelberg Spectral-domain OCT employed in this study incorporates an efficient integrated mechanism that compensates for the magnification effect, thereby rendering the application of the Littman-Bennett formula unnecessary.

The strength of this study lies in the thorough analysis of data to ensure the use of the best-fit model for interpreting the data. To compare our findings with those of other studies, we conducted a parametric t-test, as other studies utilised means rather than medians. The study has a sufficiently large population to establish statistical significance, with an equal number of participants in each study group. This study had limitations. Glaucoma was excluded primarily based on normal intraocular pressure (IOP) and a normal cup-to-disc ratio. It is worth noting that early glaucomatous disease and normotensive glaucoma may have gone undetected, potentially influencing RNFL changes. Although regression analysis has been conducted, it is essential to acknowledge that there may be a lack of statistical significance for confounding variables in this study due to their representation of a small proportion of study subjects.

To the best of our knowledge, no studies have been conducted comparing the RNFL thickness in a myopic black South African population to a non-myopic control group. Our research has established a negative correlation between RNFL thickness and increased axial length, with a more pronounced effect observed in the non-temporal RNFL segment. These findings substantiate the necessity for applying a normative database tailored to the specific population duly adjusted for the axial refractive error. This approach aims to mitigate misdiagnoses related to ethnic variability in optic nerve diseases. We recommend exercising caution when interpreting RNFL findings, particularly in individuals with high myopia. The validation and expansion of these findings necessitate long-term studies within an African population.

Conclusion

The non-temporal RNFL thickness in a black South African myopic group, as assessed using Heidelberg Spectralis SD-OCT, demonstrates significant clinical and statistical thinning compared to a non-myopic black South African population. A comparison between high and low myopia subgroups indicated that the non-temporal RNFL was considerably thinner in individuals with high myopia. When conducting RNFL analysis on myopic individuals, it is imperative to compare them with a population-specific control group that is also adjusted for the axial length of the globe.

Acknowledgements

We thank Dr. F. Nomnqa for her invaluable contribution to developing the study topic. In addition, we extend our appreciation to Dr. H. Alli and Dr. N. Ally for supervising the development of the research method and data collection process. We thank Prof S Williams, who supervised the data analysis and write-up. We wish to extend our sincere gratitude to optometrist Mr T. Phooko (B.Sc.B.Optom) for recruiting patients for enrolment in this study. We thank all patients for participating, which has made this study possible.

Competing interests

The authors affirm that there are no competing financial or personal interests to declare.

Author contributions

Dr Branders drafted the protocol, compiled all the data, and produced the manuscript. Dr Marais offered invaluable insights through astute analysis and interpretation of the data.

Funding

There is no financial disclosure to be made,

Data availability

The data will be available upon request from the corresponding author.

Disclaimer

The opinions of the submitted article belong to the authors and do not reflect the institution's official position.

Adherence to Ethical Standards

Ethical approval

University of the Witwatersrand's Human Research Ethics Committee clearance number = M221035. Compliance with the tenets outlined in the Declaration of Helsinki was maintained.

Participant consent

All patients provided informed written consent to participate in the study. All collected data was securely anonymised to ensure confidentiality and privacy.

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Appendix A :

Ethics clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R49 Dr L Branders

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M221035

NAME: (Principal Investigator)	Dr L Branders
DEPARTMENT:	School of Clinical Medicine Department of Neurosciences Division of Opthalmology Medical School University
PROJECT TITLE:	*The association between retinal nerve fibre layer thickness and myopia in a Black South African population*
DATE CONSIDERED:	2022/10/28
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Drs HD Alli and F Nomnqa
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2023/02/15

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

Addendum B:

Plagiarism declaration

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FACULTY OF HEALTH SCIENCES

SCHOOL OF CLINICAL MEDICINE

DEPARTMENT OF NEUROSCIENCES

Neurology; Neurosurgery; Ophthalmology; Otorhinolaryngology (ENT)

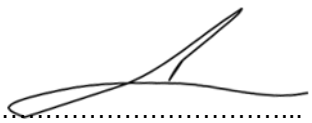
7 York Road, Johannesburg 2193, South Africa *Telephone: 27-11-717 2774*

Plagiarism declaration for written work

I …Lieschen Branders……as a postgraduate student registered for an MMed at

The University of the Witwatersrand declares the following:

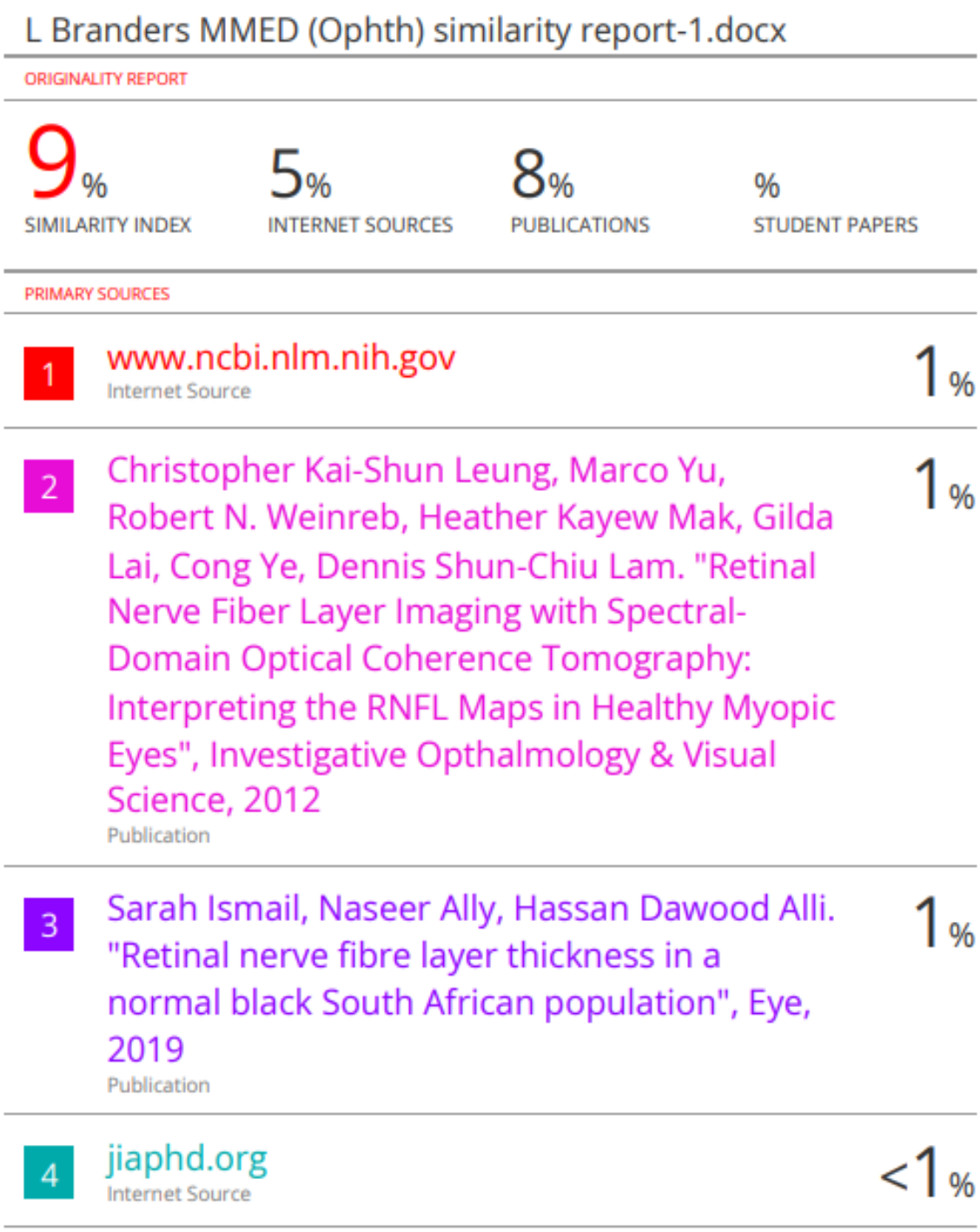
- I am aware that plagiarism is the use of someone else's work without their permission and or without acknowledging the original source.
- I am aware plagiarism is wrong.
- I confirm that this written work is my own work except where I have stated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or if I have failed to acknowledge the ideas or writing of others.

Signature: 

Date: 10/03//2025

Appendix C:

Plagiarism report



L Branders MMED (Ophth) similarity report-1.docx

ORIGINALITY REPORT

9%	5%	8%	%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.ncbi.nlm.nih.gov Internet Source	1%
2	Christopher Kai-Shun Leung, Marco Yu, Robert N. Weinreb, Heather Kayew Mak, Gilda Lai, Cong Ye, Dennis Shun-Chiu Lam. "Retinal Nerve Fiber Layer Imaging with Spectral-Domain Optical Coherence Tomography: Interpreting the RNFL Maps in Healthy Myopic Eyes", Investigative Opthalmology & Visual Science, 2012 Publication	1%
3	Sarah Ismail, Naseer Ally, Hassan Dawood Alli. "Retinal nerve fibre layer thickness in a normal black South African population", Eye, 2019 Publication	1%
4	jiaphd.org Internet Source	<1%

Appendix D:

African Vision and Eye Health Journal article submission Structure guidelines

Original Research Articles

An original article provides an overview of innovative research in a particular field within or related to the focus and scope of the journal, presented according to a clear and well-structured format.

Submission status	open
Word limit	5000-8000 words (excluding the abstract, tables, figures, graphs, and references)
Abstract	maximum: 250 words requires structural headings: Background, Aim, Setting, Methods, Results, Conclusion and Contribution
Main text	requires structural headings, refer to the full structure 'Ethical considerations' is a sub-section in the manuscript and must include: • Name of the ethical review committee • Study approval number • Manner of consent (written, oral) for human participants • Description of measures taken to maintain the confidentiality of data • If the study was not human or animal research or the study was determined to be non-human subjects research or exempt, the authors must provide a statement with those details in this section.
References	60 or less, adhere to the **Vancouver referencing style**
Tables, figures and graphs	7 or less, adhere to the Illustrations requirements found in the AOSIS House style guide
Formatting requirements	apply the guidelines located on the **Formatting requirements page** and the **AOSIS house style guide**
Compulsory supplementary file(s)	the **Authorship, disclosure statements, copyright, and license agreement form**, **Ethical Clearance/Waiver Documentation** and any other relevant form applicable to your submission
Ethical clearance/waiver documentation	evidence of ethical clearance for the study, such as the study approval letter or certificate from the Institutional Review Board (IRB), a waiver from the IRB et cetera

Original Research Article full structure

Title: The article's full title should contain a maximum of 95 characters (including spaces).

Abstract: The abstract, written in English, should be no longer than 250 words and must be written in the past tense. The abstract should give a succinct account of the objectives, methods, results and significance of the matter. The structured abstract for an Original Research article should consist of seven paragraphs labelled Background, Aim, Setting, Methods, Results, Conclusion and Contribution.

- Background: Summarise the social value (importance, relevance) and scientific value (knowledge gap) that your study addresses.
- Aim: State the overall aim of the study.
- Setting: State the setting for the study.
- Methods: Clearly express the basic design of the study, and name or briefly describe the methods used without going into excessive detail.
- Results: State the main findings.
- Conclusion: State your conclusion and any key implications or recommendations.

- Contribution: What key insights into the research results and its future function are revealed? How do these insights link to the focus and scope of the journal? It should be a concise statement of the primary contribution of the manuscript; and how it fits within the scope of the journal.

Do not cite references and do not use abbreviations excessively in the abstract.

Introduction: The introduction must contain your argument for the social and scientific value of the study, as well as the aim and objectives:

- Social value: The first part of the introduction should make a clear and logical argument for the importance or relevance of the study. Your argument should be supported by use of evidence from the literature.
- Scientific value: The second part of the introduction should make a clear and logical argument for the originality of the study. This should include a summary of what is already known about the research question or specific topic, and should clarify the knowledge gap that this study will address. Your argument should be supported by use of evidence from the literature.
- Conceptual framework: In some research articles it will also be important to describe the underlying theoretical basis for the research and how these theories are linked together in a conceptual framework. The theoretical evidence used to construct the conceptual framework should be referenced from the literature.
- Aim and objectives: The introduction should conclude with a clear summary of the aim and objectives of this study.

Research methods and design: This must address the following:

- Study design: An outline of the type of study design.
- Setting: A description of the setting for the study; for example, the type of community from which the participants came or the nature of the health system and services in which the study is conducted.
- Study population and sampling strategy: Describe the study population and any inclusion or exclusion criteria. Describe the intended sample size and your sample size calculation or justification. Describe the sampling strategy used. Describe in practical terms how this was implemented.
- Intervention (if appropriate): If there were intervention and comparison groups, describe the intervention in detail and what happened to the comparison groups.
- Data collection: Define the data collection tools that were used and their validity. Describe in practical terms how data were collected and any key issues involved, e.g. language barriers.
- Data analysis: Describe how data were captured, checked and cleaned. Describe the analysis process, for example, the statistical tests used orsteps followed in qualitative data analysis.
- Ethical considerations: Approval must have been obtained for all studies from the author's institution or other relevant ethics committee and the institution’s name and permit numbers should be stated here.

Results: Present the results of your study in a logical sequence that addresses the aim and objectives of your study. Use tables and figures as required to present your findings. Use quotations as required to establish your interpretation of qualitative data. All units should conform to the **SI convention** and be abbreviated accordingly. Metric units and their international symbols are used throughout, as is the decimal point (not the decimal comma).

Discussion: The discussion section should address the following four elements:

- Key findings: Summarise the key findings without reiterating details of the results.
- Discussion of key findings: Explain how the key findings relate to previous research or to existing knowledge, practice or policy.
- Strengths and limitations: Describe the strengths and limitations of your methods and what the reader should take into account when interpreting your results.
- Implications or recommendations: State the implications of your study or recommendations for future research (questions that remain unanswered), policy or practice. Make sure that the recommendations flow directly from your findings.

Conclusion: Provide a brief conclusion that summarises the results and their meaning or significance in relation to each objective of the study.

Acknowledgements: Those who contributed to the work but do not meet our authorship criteria should be listed in the Acknowledgments with a description of the contribution. Authors are responsible for ensuring that anyone named in the Acknowledgments agrees to be named. Refer to the acknowledgement structure guide on our *Formatting Requirements* page.

Also provide the following, each under their own heading:

- Competing interests: This section should list specific competing interests associated with any of the authors. If authors declare that no competing interests exist, the article will include a statement to this effect: *The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.* Read our **policy on competing interests**.
- Author contributions: All authors must meet the criteria for authorship as outlined in the **authorship** policy and **author contribution** statement policies.
- Funding: Provide information on funding if relevant
- Data availability: All research articles are encouraged to have a data availability statement.
- Disclaimer: A statement that the views expressed in the submitted article are his or her own and not an official position of the institution or funder.

References: Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests. Refer to the journal referencing style downloadable on our *Formatting Requirements* page.

Appendix E:

Approved Research Protocol

The Association between Retinal Nerve Fibre Layer thickness and Myopia in a Black South African Population: A cross-sectional study

Candidate:	Dr. L Branders, Registered for MMed Ophthalmology 2021
Department:	Neurosciences
Division:	Ophthalmology
Student number:	440908
Supervisors:	Dr. H.D Alli, Dr. F. Nomnqa, D.r N. Ally

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DEPARTMENT OF NEUROSCIENCES

Neurology; Neurosurgery; Ophthalmology; Otorhinolaryngology (ENT)

7 York Road, Johannesburg 2193, South Africa *Telephone: 27-11-717 2774*

Plagiarism declaration for written work

I …Lieschen Branders……as a postgraduate student registered for an MMed at
The University of the Witwatersrand declares the following:

- I am aware that plagiarism is the use of someone else's work without their permission and or without acknowledging the original source.
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- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or if I have failed to acknowledge the ideas or writing of others.

Signature: ……

Date: ……2022/07/10……

Table of Contents **Page**

Introduction

Myopia also known as near-sightedness is a common ocular condition and a leading cause of impaired vision worldwide affecting approximately 28% of the world's population. [42–47] The prevalence of myopia varies in different regions of the world but has globally been increasing over the past few decades, [42,43,45–49] Holden et al estimated that up to 50% of the world's population will be myopic by 2050 by extrapolating current data. [42,45,50,51] Currently, the prevalence of myopia in African countries varies widely from 1.7% to 17% and is expected to rise secondary to the urbanization of these countries. [42,46,52]

When light rays enter the eye, they are brought to focus on the retina, and images are formed. In myopia, the light rays entering the eye are brought to a focus in front of the retina. This leads to images being in focus when viewed close by but images further away will be out of focus. This usually results from the eyeball being too long from front to back but can be caused by an overly curved cornea and/or a lens with increased optical power. Myopia can thus be divided into 2 types. Axial myopia- a myopic refractive state primarily resulting from a greater than normal axial length, and refractive myopia- the myopic refractive state that can be attributed to changes in the structure or location of the image forming structures of the eye, i.e., the cornea and lens[53,54] The refractive state of the eye can be expressed as the spherical equivalent (SE) as measured in dioptres.

Myopia presents a large economic and social burden. It increases the risk for several pathological ocular conditions and is a known risk factor for open-angle glaucoma. [42–44,48,49,55–57] Several clinical signs can be seen on fundoscopy in myopic patients including optic disc changes. The optic disc commonly has an oval appearance en-face and is referred to as a tilted disc, it can also be enlarged and have an increased cup-to-disc ratio. Optic disc changes in myopia present challenges in the diagnosis and management of other disease entities like glaucoma that also cause changes in the optic disc. [43–45,49,55,58]

The retina histologically consists of 10 layers. The retinal nerve fibre layer (RNFL) is composed of the axons of retinal ganglion cells and is affected by many different ocular conditions. Optical coherence tomography (OCT) because of its excellent ability to assess peripapillary retinal nerve fibre layer (RNFL) thickness has been extensively used for the diagnosis and follow-up of glaucoma and other optic neuropathies. [43,45,56] It allows non-invasive, contact-free, high-resolution imaging of the RNFL. [45,46,48,58] It has been proven a reliable and reproducible imaging system to measure the thickness of different retinal layers. [43,44,58]The measurement of RNFL thickness on SD-OCT is compared to built-in age and gender-matched European normative databases and this difference is used to assist with glaucoma diagnosis. [44,59]

Retinal nerve fibre layer (RNFL) thinning is now considered one of the more sensitive indicators for predicting early glaucomatous damage. [43,44,58]These structural changes that can be detected by optical coherence tomography have been reported to be evident six years before any detectable visual field defects in up to 60% of patients. [48,56] Although optical coherence tomography (OCT) affords reproducible measurement of the RNFL thickness, detection of RNFL abnormalities in highly myopic eyes is complicated by high rates of false-positive errors. [51] These errors are due to the lack of normative databases for myopic individuals. [44,45,48,55,60]

RNFL thickness varies between different populations which can cause errors when measurements in non-European populations are compared to the built-in European normative database in OCT. [44,59] A study done by Ismail et al demonstrated that RNFL thickness in a healthy black South African population is significantly thicker in comparison with healthy European counterparts. [59] This finding is supported by studies done on black African populations in Ghana[61] and Nigeria.[62]

<u>The Association between Myopia and Retinal Nerve Fibre Layer Thickness</u>

Numerous studies have found a negative correlation between RNFL thickness and the degree of myopia. [44,46,50,57,63–65] Sectoral reductions in the average and nontemporal RNFL thickness have been reported [43,44,50,56–58,63,66–74]. Adjusting for spherical equivalent (SE) might have introduced errors in the analysis of the data considering that refractive SE can vary under certain conditions

(e.g., cataract progression, presence of macula disease, post-refractive surgery). [66]The negative correlation between myopia and RNFL thickness, therefore, has a stronger association in axial myopia compared to refractive myopia (which is defined by spherical equivalent only). [43,45,48]

Thinning of the retinal nerve fibre layer in myopia has been attributed to elongation of the globe, spreading the nerve fibres over a larger surface area. [43,44,47,51,58,66,71] The stronger correlation between axial length and RNFL thinning (compared to spherical equivalent and RNFL thinning) could furthermore indicate that globe elongation (with geometrically concomitant thinning of the globe wall) is an important determinant of RNFL thinning.[43,44,49,58] Currently, there is still no anatomical evidence to support that axial length elongation leads to retinal ganglion axon degeneration However, animal studies demonstrated that myopia could result in decreased stimulation of ganglion cells. It is postulated that reduced neuronal activity in retinal ganglion cells could be an alternative mechanism for RNFL thinning found in myopia. [48,58]

Another mechanism for RNFL thinning could be decreased blood flow in the retinal layers in myopic eyes. A vascular network exists within the RNFL, ganglion cell layer, inner plexiform layer, inner nuclear layer, and the outer plexiform layer of the retina. OCT angiography has demonstrated that the peripapillary flow index and vessel density in the retina were decreased in high myopia. [48,55]The larger retinal vessels play a significant role in peripapillary RNFL thickness since they comprise 13% of the total RNFL thickness. Reduced metabolic demand and arteriolar narrowing could explain thinner RNFL thickness in eyes with increased axial length, but there is still controversy on whether this vascular compromise precedes or follows the RNFL thinning. [48,50]

Multiple studies have demonstrated temporal retinal nerve fibre layer thickness to be significantly increased compared to the other areas of the optic nerve. [43,48,51]The temporal quadrant of the optic nerve head is where superotemporal and inferotemporal papillomacular bundles converge and macular fibres are located mainly near the upper and lower horizontal sutures towards the optic disc. The thicker temporal RNFL has been attributed to RNFL redistribution as the result of eye elongation that drags the retina towards the temporal horizon. [48]

As the convergence of the retinal nerve fibre layer constitutes a part of the optic disc, its thickness may be positively associated with the disc area. [58]In previous studies it was found that the larger optic disc accommodated more retinal nerve fibre axons on histology. [48]. Axial length however can influence the RNFL thickness through a magnification effect. [48,56] The scanning circle is projected to be larger than the actual circle after elongation of the eyeball. Theoretically, the RNFL thickness will become thinner as the distance to the optic disc increases. Correction of this magnification effect can be done by Littmann's formula and modified Bennett'srmula. [48,58]

Various studies have suggested that myopes undergoing RNFL analysis should be compared with a population-specific normative controlled group that is also matched for refractive error. [43,44] Incorporating a normative database for a black South African population for analysis of RNFL thickness would be important to decrease the frequency of erroneous findings in eyes with high myopia. Hence, we will compare the RNFL thickness in myopic eyes to that of normal eyes in the black South African population to answer the question of whether there is a difference in the RNFL thickness between myopic and normal eyes in our setting".

Table 1. Summary of studies comparing RNFL thickness in myopic and emmetropic(EM) control groups.

Author	Location	Diagnostic Tool	Myopic Group		Control group		Comment
			Sample size	Average RNFL thickness (µm)	Sample size	Average RNFL thickness(µm)	
Choi et al.(17) 2006	Korea	SD-OCT Stratus	71	LM 103.85 ± 14.48 HM 100.74 ± 9.15	45	113.29 ± 10.80	A statistically significant difference was found between LM an HM groups ($p<0.05$) .Study sample comprise of a younger population between 23-26 years old. This could account for the increased average RNFL thickness compared to other studies
Schweitzer et al. (27) 2009	Canada	SD-OCT Stratus	10	HM 80.0 ± 18.6	10	108 ± 10.8	Myopic group were all high myopes with a spherical equivalent of ≤ -10D
Malakar et al (05) 2015	India	FD-OCT	50	87.89±10.37	40	111.64±12.6	Statistically significant thicker RNFL in the emmetropic group. Results correlate with other studies done with SD-OCT
Singh et al.(13) 2017	India	SD-OCT Cirrus	50	LM 83.76 ± 3.44 HM 78.68 ± 5.67	50	91.26 ± 2.99	Average RNFL thickness was significantly thinner in moderate and high myopes as compared to emmetropes.
Tai et al.(09) 2018	Malaysia	SD-OCT Cirrus	223	LM 97.17±1.86 HM 91.10 ± 4.65	180	99.22 ±2.05	Statistically significant difference observed only between the HM and the EM group.
Jeong et al.(19) 2019	Korea	SD-OCT Cirrus	186	LM 86.9 ± 10.3 HM 82.1 ± 7.6	37	90.2 ± 9.5	The rate of RNFL thinning was the primary objective. No significant difference found between groups. There was however a statistically significant difference in RNFL thickness between the groups.
Kim et al.(20) 2020	Korea	SD-OCT Spectralis	37	HM 81.70 ± 13.07	37	90.84 ± 11.87	In high myopia without pathologic changes, there was a meaningful thinning of the retina and choroid
Cui et al.(18) 2021	China	SD-OCT Spectralis	52	99.04± 8.23	40	103.25 ± 8.32	Myopic group in this study did not include high myopes. The spherical equivalent of patients in this group comprised of refractive errors of -4.71D ±0.89D

Myopic subgroups divided into Low myopia (LM) and high myopia(HM). Criteria for these specific groups varied between studies.

Table 2. Summary of studies comparing RNFL thickness in >2 different degrees of myopia.

Author	Location	Diagnostic Tool	Degrees of myopia						Comment
			Low myopia(LM)		Moderate Myopia(MM)		High myopia(HM)		
			Sample size	Average RNFL thickness (µm)	Sample size	Average RNFL thickness (µm)	Sample size	Average RNFL thickness (µm)	
Zhao et al.(24) 2012	China	Rtvue SD-OCT	17	96.55 ±5.54	31	95.10 ±5.57	59	91.59 ± 4.62	Values provided for average GCIL thickness Negative correlation of GCIL, and peripapillary RNFL thickness against AL
Porwal et al.(25) 2020	India	Cirrus SD-OCT	46	92.17 (±9.84)	34	88.12 (±9.53	20	82.40 (±10.43)	Statistically significant difference in the average RNFL thickness between two groups based on the axial length AL <24mm= 91.40 (±10.17) AL> 24mm =86.06 (±10.09
Ganekal et al.(14) 2021	India	Cirrus SD-OCT	37	97.68±10.84	39	85.10±12.32	24	81.96±5.14	Statistically significant difference in HM group and LM group (P < 0.05)
Miller et al.(21) 2021	USA	Cirrus SD-OCT	27	89.70 ± 4.48	25	85.52 ± 6.40	24	79.33 ± 7.18	Statistically significant difference MM vs. HM P< 0.001 LM vs. HM P< 0.001

Myopic subgroups divided according to SE into low myopia (LM) (< –3.0D) , moderate myopia (MM) (-3.0D - -6.0D)and high myopia(HM) (> -6.0D).
Spherical equivalent(SE); Axial length (AL)

Study Rationale and Aims

A Cross-sectional study conducted at St John Eye Hospital has shown that African individuals with no ocular pathology have a significantly thicker RNFL than their European counterparts. Studies in non-African patients have shown that the average RNFL thickness in myopic eyes is thinner than in non-myopic eyes (Table 1, Table 2). This study aims to compare the RNFL thickness in African myopic eyes to non-myopic eyes, and the RNFL thickness in different degrees of myopia. Additionally, this study aims to compare the RNFL of myopic eyes to that of the European normative database in the SD-OCT, to determine if there is a significant difference in the RNFL thickness.

Study objectives

Primary Objective

To evaluate the difference in RNFL thickness between myopic eyes (AL ≥24.00mm) and non-myopic eyes (AL ≥21.00mm ≤23.99mm) in a black South African population.
Null hypothesis: There is no difference between the RNFL thickness of non-myopic eyes and myopic eyes.

H_0: $\mu_{RNFL\ myope} = \mu_{RNFL\ non\text{-}myope}$

Secondary objectives

1. To evaluate the difference in RNFL thickness between low (AL ≥24.00mm ≤25.99mm) and high myopic (AL ≥26.00mm) eyes.
   Null hypothesis: There is no difference between the RNFL thickness of low myopes and high myopes.
   H_0: $\mu_{RNFL\ low\ myope} = \mu_{RNFL\ high\ myope}$
2. Evaluate the RNFL thickness with and without the Litmman-Bennett formula applied to adjust for the axial length magnification factor

Null Hypothesis: There is no difference between RNFL measurements when the Littmann-Bennett formula is applied

H_0: $\mu_{\text{RNFL Littmann-Bennet formula applies}} = \mu_{\text{RNFL without Littman Bennet formula}}$

- Littman Bennett formula

  $t = p \times q \times s$

  t - true image size

  p – the camera constant related to the OCT imaging system (magnification factor of the imaging system)

  Heidelberg Spectralis =

  q – The magnification factor of the individual eye

  Estimated by the formula: $q = (AL - 1.82mm) \times 0.01306°/mm^2$

  s – Size of the retinal feature taken from the fundus image (RNFL thickness)

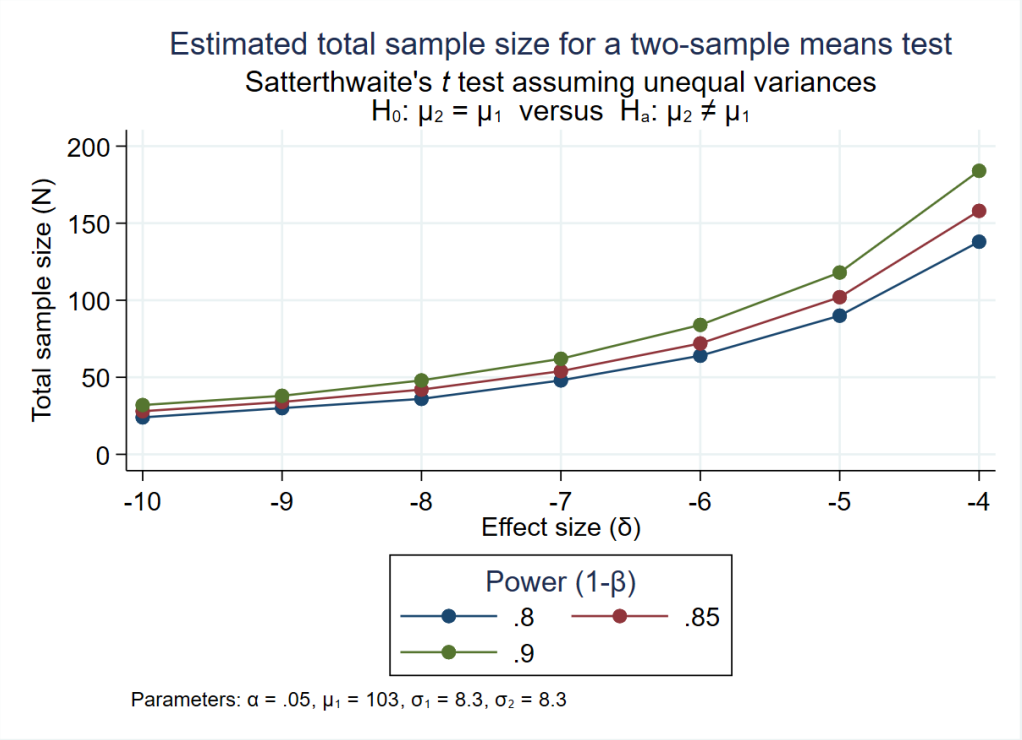
Methodology

Study design

- A cross-sectional comparative study will be done
- A convenient sample will be taken from patients that present to the outpatient department at St John eye hospital in Johannesburg, South Africa.
- Only one eye will be randomly selected and included in the study

Sample Size

Assuming a difference of 4μm and standard deviations of 8.3 μm in both groups as per Cui et al. We calculated a sample size of 138 patients using a two-sample means test with a power of 80% and an alpha level of 005.



Inclusion criteria

- Study group
  - Self-reported identity of black South African ethnicity
  - Myopia as defined by spherical equivalent and axial length
  - Fovea to disc (FoDi) alignment on OCT within 7°[59,75,76]

    The angle between the fovea and the centre of the optic disc as seen on the OCT fundus photo
  - Normal intraocular pressure (10-21mmHg) measured by applanation tonometry with either the Perkins or Goldmann applanation tonometer.
- Control group
  - Self-reported identity of black South African ethnicity
  - Non -Myopic eyes as defined by spherical equivalent and axial length.
  - Fovea to disc (FoDi) alignment on OCT within 7°
  - Normal intraocular pressure (10-21mmHg) measured with either the Perkins or Goldmann applanation tonometer.

Exclusion criteria

- Any history of previous eye trauma, eye surgery, or laser eye procedures.
- Pre-existing ocular diseases such as glaucoma, uveitis, diabetic retinopathy, hypertensive retinopathy, and retinal and choroidal diseases.
- Poor view of the fundus and poor image quality secondary to a cataract.
- Pathological myopic changes as seen on fundoscopy in the macular and peripapillary region. Including staphylomas
- Failure to capture OCT images of acceptable quality ≤21dB. [51,55,59]

Definitions

As defined by the axial length (AL) of the globe.

1. No Myopia (NM) [77]

   Axial length ≥21.00mm ≤ 23.99mm

2. Low myopia (LM) [43,45,46,48,57]

   AL: ≥24mm ≤ 25.99mm

3. High Myopia (HM) [43,45,46,48]

   AL ≥ 26mm

Data collection

- Informed consent will be obtained from each patient (Appendix A)
- Patients will undergo a set of examinations by a single operator

1. Comprehensive eye examination including Snellen visual acuity measurement at 6 meters, slit-lamp biomicroscopy, intraocular pressure measurement and dilated fundus examination.
2. Autorefraction with Charops CRK 7000 (Huvitz Corp. Korea) and axial length measurement with Nidek optical AL scan (Nidek co. Ltd, Japan)

3. Vertical disc height, RNFL thickness, and ganglion cell layer thickness measurement using Spectralis SD-OCT, Heidelberg eye explorer version.1.10.15.0 (Heidelberg Engineering, Germany)

- The following measures will be taken to ensure good quality images:
  - Optic disc will be identified with the built-in eye fixating system
  - The scanning circle will be manually placed centrally over the optic disc head to avoid segmentation errors.
  - FoDi will be manually adjusted if not within 7°
  - Vertical disc height will be measured manually and reviewed by another investigator
- An information collection sheet will be used for each patient to record the data (Appendix B)
- The data will then be captured into the Research Electronic Data Capture (REDCap®) database.

Statistical analysis

- Data collected will be exported to STATA 17.0 (STATACorp, USA) and analysed
- Simple descriptive statistics (mean ±SD, median IQR) will be used to describe the demographic data.
- Data will be checked visually for normality of distribution.
- The primary outcome data will be analysed two-sampled t-test or Wilcoxon rank sum test
- Univariate and multivariate linear regression models will be developed using the following prespecified predictor variables
  - Age
  - Gender
  - Spherical equivalent
  - Optic disc area
  - Vertical disc height

Duration of study

As outlined in the chart below.

	June 2022-July2022	July 2022	Sept. 2022	October 2022	Nov. 2022	December 2022-June 2023	July 2023	Aug. 2023	Sept. 2023	October 2023	November 2023
Literature review and protocol write up											
Protocol submission to supervisors											
Corrections											
Protocol submission											
Ethics application											
Assessors group meeting											
Data collection											
Data analysis											
Report write up											
Report submission to supervisor											
Corrections											
Final report submission											

Ethics Approval

- Ethical approval will be applied for at the Human Research Ethics Committee
- Patient names and hospital numbers will not be included in the research report thus ensuring patient confidentiality
- The information will be captured on a REDCap® database which will be password protected and only accessible by the investigators
- Patients will have informed consent and medical consent in their home language. If necessary, a translator will be used.
- Each patient will be assigned a unique reference number. Their names will not be linked to their records, only their unique reference number.
- The data will be anonymous with no breach of patient confidentiality in published data
- Any abnormalities found during the examination of patients will be treated accordingly and no treatment will be withheld for study purposes.

Funding

Any costs like stationery and printing costs will be covered by Dr. Lieschen Branders the primary investigator This study will therefore not incur any additional cost,-since patients presenting to St John eye hospital for routine eye examination will be recruited.

Reporting plans

• Present at the departmental meeting

• Present at the Ophthalmic Society of Southern Africa (OSSA) annual congress

• Publish in a scientific journal

Authorship

- Principal Investigator – Dr. L Branders

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Appendix A

Medical Consent

Informed Consent Form for the patient who will undergo full ophthalmologic evaluation under slight lamp examination, Heidelberg OCT imaging, and autorefraction at St John Eye Hospital. We are inviting the patient to participate in a research study to determine the association between retinal nerve fibre layer thickness and myopia in a South African population.

This Informed Consent Form consists of two parts:

• Information Sheet (providing detailed information about the study)

• Participant consent sheet (this is where you sign if you agree to participate)

You will be given a copy of the full Informed Consent Form

Part I: Information Sheet

Introduction

My name is Lieschen Branders I am a doctor working at St John eye hospital. I will be doing a study to see if there is a relationship between retinal thickness and near-sighted patients. I will take measurements of near-sighted patients and of patients that are not near-sighted, and I will compare these results.

I am going to give you information and invite you to be part of a research study. You can choose whether or not you want to participate. If you do not wish to be part of this study you are not obligated to and it won't affect your treatment at this hospital.

You may discuss anything in this form with your family and friends. You can decide whether to participate or not after you have talked it over. You do not have to decide immediately. There may be some words you don't understand or things that you want me to explain in more detail because you are interested or concerned. Please ask me to stop at any time and I will take the time to answer any of your questions.

Purpose: Why are we doing this research?

We want to find out if the nerve that enables the eye to see has the same thickness in patients that are near-sighted compared to patients that are not near-sighted. This information can assist us to identify diseases in this nerve in all patients including near-sighted patients.

Choice of participants: Why are you asking me?

We are examining the eyes of patients that have a refractive error and those who don't. You are either a patient with or without near-sightedness and that is why we want to ask you to partake in this study.

Participation is voluntary: Do I have to do this?

You don't have to be in this research if you don't want to be. It's up to you. If you decide not to be in the research, it's okay and nothing changes. This is still your clinic; everything stays the same as before. You will still be treated as a patient in this clinic. Even if you say "yes" now, you can change your mind later and it is still acceptable.

Procedures: What is going to happen to me?

We are going to do a full examination of your eyes. We will also do measurements of the nerve at the back of your eye and test the strength of your eye. You will start by reading letters or numbers. You will then have to sit at 3 different machines.

1. Slit lamp: This is a machine where you sit and rest your chin. While keeping your eyes open I will then shine a light in your eyes and check the condition of your eyes and also look at the back of your eyes through a lens
2. Autorefractor: With this machine, you will also sit down rest your chin, and keep your eyes open. I will shine a light in each of your eyes and the machine will measure the strength of your eyes.
3. OCT: This is another machine where you will sit and rest your chin. A light will again shine in your eye and will measurements of the back of your eye.

None of these procedures cause any pain or discomfort. It only requires you to keep still and keep your eyes open.

You can ask me to stop and explain again at any time and I will explain more about the process. You don't have to remember any of this beforehand we will explain everything as we do it to you again.

Risks: Is this bad or dangerous for me?

These examinations and scans are non-invasive, safe, and have no risk to cause any harm or damage to your eyes.

Discomforts: Will it hurt?

Examining your eyes and doing these measurements and scans don't cause any pain. It does not cause any discomfort. These machines have chin rests where you can rest your chin. You will be sitting on a chair for all of them.

Confidentiality: Is everybody going to know about this?

We will not tell other people that you are in this research study and we won't share information about you with anyone who does not work in the research study. Information about you that will be collected from the research will be put away and no one but the researchers will be able to see it. Any information about you will have a number instead of your name. Only the researchers will know what your number is and we will not share that information.

Sharing the Findings: Will you tell me the results?

When we are done examining you and taking your measurement and scans, we will sit down with you and tell you what we have found. After we collect all the patients' examination information, we will tell more people about the results and whether we found a difference in the nerve thickness of near-sighted patients. We will do this by writing reports and going to meetings with people who are interested in the research that we do. We will not use your names in the reports or the meetings but rather numbers.

Right to Refuse or Withdraw: Can I choose not to be in the research? Can I change my mind?

You do not have to be in this research. It will not be held against you if you say no. It is your choice. You can say “yes” now and change your mind later and it will still be accepted

Who to Contact: Who can I talk to or ask questions to?

You can ask me questions now or later. You can also ask other doctors in the clinic questions. I have provided a telephone number and address where you can reach us or come and see us. If you want to talk to someone else that you know like your family or friends, that’s also okay.

If you need to contact me or my supervisors later, you can use the following contact details:

Dr Lieschen Branders

Telephone no. 0823692082

Email: Lieschenbranders@gmail.com

Dr N Ally

Telephone no. 011 933 8774

Email: Naseer.Ally@ wits.ac.za

Dr H Alli

Telephone no. 0119338774

Email: hdalliyr@gmail.com

Dr F Nomnqa

Telephone no. 011 933 8774

Email: fikiswa.doc@gmail.com

Professor CB Penny

Chairperson of the Human Research Ethics Committee (Medical) at the University of Witwatersrand

Telephone: 011 717 2301

E-mail: Clement.Penny@wits.ac.za.

Ms. Z Ndlovu or Mr Rhulani Mkansi

Committee Secretariat

Telephone no.: 011 717 2700

E-mail at: Zanele.Ndlovu@wits.ac.za or Rhulani.Mkansi@wits.ac.za

If you choose to be part of this research, I will also give you a copy of this paper to keep for yourself.

You are welcome to ask me any questions about any part of the research study. Do you have any questions?

Part 2: Participant consent sheet

Study Title: **The Association between Retinal Nerve Fibre Layer thickness and Myopia in a Black South African Population: A cross-sectional study**

1. I have been given a Participant Information Sheet, which explains what this study is about;

2. The study was explained to me and I understand what will happen if I take part;

3. I was given time to ask any questions I wanted to and was happy with the answers I was given;

   I understand that I will not benefit from the study, should I agree to take part.

4. I also understand that I will not be paid to take part in the study;

   taking part will not cost me anything either

5. I have been given a range of contact details, repeated below, should I require further information at a later stage, or have any cause for concern over anything which is done to me during the study

6. I understand that even if I agree to take part in the study, I can change my mind later and stop being a part of the study at any time

Contact details:

Dr Lieschen Branders

Telephone no. 0823692082

Email: Lieschenbranders@gmail.com

Dr N Ally

Telephone no. 011 933 8774

Email: Naseer.Ally@wits.ac.za

Dr H Alli

Telephone no. 0119338774

Email: hdalliyr@gmail.com

Dr F Nomnqa

Telephone no. 011 933 8774

Email: fikiswa.doc@gmail.com

Professor CB Penny Ms. Z Ndlovu

Chairperson of the Human Research Ethics

Committee (Medical) of Witwatersrand

Telephone no. 011 717 2301

E-mail: Rhulani.Mkansi@wits.ac.za

Mr Rhulani Mkansi

Committee Secretariat

Telephone no.: 011 717 2700

E-mail: Zanele.Ndlovu@wits.ac.za or

Clement.Penny@wits.ac.za.

Participant:

Name of Participant: _____

Date: _____ Place: _____

Signature/mark: _____

Witnessed by:

Name of Witness: _____

Signature: _____ Date: _____

Data collection sheet

Patient Number: _____

History

Age: Gender:

Chronic illness: Hypertension ☐ Diabetes Mellites ☐ RVD status ☐ Other ☐

Treatment:

Previous Ocular History:

Slit lamp examination

Right eye		**Left eye**
	BCVA	
	Lid	
	Conjunctiva /sclera	
	Cornea	
	Anterior Chamber	
	IOP	
	Lens	
	Pupil	
	Fundus	
C/D ratio		C/D ratio
Disc Characteristics		Disc Characteristics
Macula		Macula
Periphery		Periphery

Autorefraction

OD **OS**

Axial Length

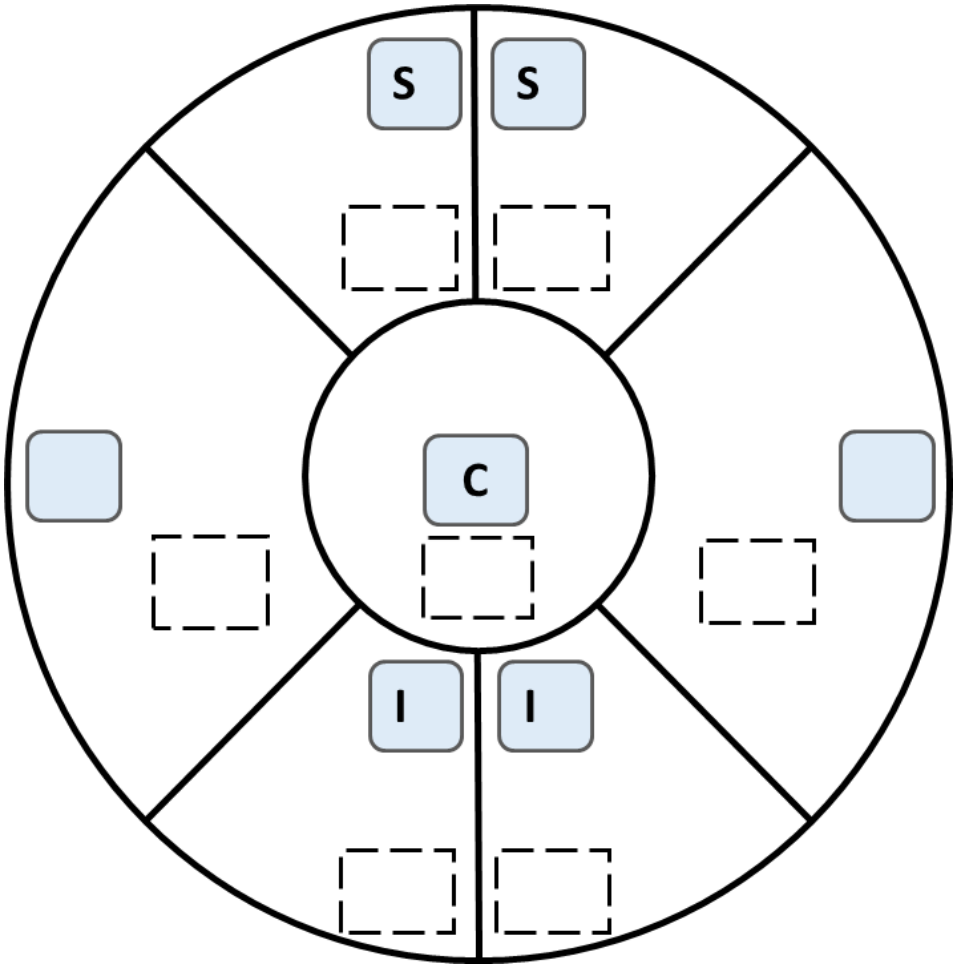
OD **OS**

OCT scan:

Study Eye: **Right** ☐ **Left** ☐ **Quality:** dB

Parameters	Value
Optic disc vertical height	
Fovea to disc alignment (FoDi)	

Retinal nerve fiber layer thickness:



Key:

Abbreviation	Segment
C	Central
ST	Superotemporal
SN	Superonasal
IT	Inferotemporal
IN	Inferonasal

Colour	European database value match
Red	Below normal limits
Yellow	Borderline below normal limits
Green	Within normal limits
Blue	Above normal limits

☐ Littmann Bennet Adjusted