A CLINICAL DESCRIPTION OF ANTERIOR SEGMENT VARIABLES MEASURED USING OPTICAL COHERENCE TOMOGRAPHY IN A HEALTHY SOUTH AFRICAN YOUNG ADULT POPULATION: THE DEVELOPMENT OF NORMAL REFERENCE INTERVALS

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DECLARATION

I, Nishanee Rampersad, hereby declare that

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ABSTRACT

Background: Assessment of anterior segment variables is important to screen, diagnose and monitor ocular anomalies. Previous studies, which have focused exclusively on Caucasian and Asian sub-populations with limited attention to South African sub-populations, suggest that anterior segment variable (corneal and anterior chamber angle) measurements vary with demographic and/or ocular factors. This study investigated anterior segment variables, measured using optical coherence tomography, in a healthy South African young adult population and develop a clinical biometric guideline with normal reference intervals.

Methods: A quantitative cross-sectional research design was used. Multistage random sampling was used to select 700 participants from a university population. Anterior segment variables were measured using the Fourier-domain iVue100 Optical Coherence Tomographer. The Oculus Keratograph, Goldmann applanation tonometer and Nidek US-500 ultrasonographer were used to measure corneal topography, intraocular pressure (IOP) and axial biometry respectively. Data were analysed by descriptive and inferential statistics. The reference intervals were computed using the non-parametric method recommended by the Clinical and Laboratory Standards Institute.

Results: The mean age of the sample, which consisted of 350 males and 350 females, was 20.4 ± 1.8 years. The anterior segment variable measurements of the right and left eyes showed high levels of interocular symmetry with intraclass correlation coefficients greater than 0.933 and marginal mean interocular differences. Accordingly, data from only the right eyes were analysed because of the high levels of interocular symmetry. The mean central corneal thickness (CCT) was 501.91 ± 33.74 µm and significantly thinner than the mean corneal thickness in each quadrant of the paracentral and peripheral cornea ($p < 0.001$). The mean minimum corneal thickness was 495.73 ± 33.89 µm and 1.23% thinner than the

mean CCT measurement ($p < 0.001$). The thinnest point on the cornea was central for 94% of participants ($n = 659$). The anterior chamber angle (ACA) width variables, which included the angle-opening distance taken at 500 µm (AOD500) and trabecular-iris angle (TIA), were ~553 µm and ~37° respectively. The majority of participants showed ACA width variable measurements associated with open non-occludable ACAs. The temporal ACA had slightly higher variable measurements than the nasal ACA. The corneal thickness measurements in the different zones were normally distributed ($p \geq 0.095$) whereas the ACA width variable measurements were asymmetrically distributed ($p < 0.001$).

Black participants had significantly thinner mean corneal thickness measurements than Indian participants (range between 29.10 µm between 36.38 µm) for all zones ($p < 0.001$). For both the nasal and temporal ACAs, Black participants had 10 µm to 22 µm lower median AOD500 measurements ($p \geq 0.031$) and slightly higher (less than 1°) median TIA measurements ($p \geq 0.068$). The mean corneal thickness in males were 0.35 µm to 3.93 µm thicker compared with females ($p \geq 0.137$). Female participants had higher median ACA width variable measurements than male participants for both the nasal and temporal ACAs ($p \geq 0.029$). Emmetropes and hyperopes had the lowest corneal thickness and ACA width variable measurements respectively. The anterior segment variables were inversely correlated with spherical equivalent refraction ($p \leq 0.003$) although the correlation coefficients were relatively weak (range between 0.111 and 0.222).

The CCT was the most important anterior segment variable, with a cut-off value of 527 µm, to influence IOP in the unpruned and pruned regression tree models. The other important variables included the average peripheral corneal thickness, axial anterior chamber depth and average paracentral corneal thickness. The clinical biometric guideline presents the normal reference intervals as well as the associated 95% confidence intervals for the corneal thickness and ACA width variables in a healthy South African young adult population. The normal reference interval for the CCT measurement ranged from 434 µm to

566 µm. In the present study, the mean, range and normal reference interval for the CCT measurement differed when compared with the measurements reported in other studies involving healthy African samples living within the African continent.

Conclusion: This study demonstrated that anterior segment variable measurements in a South African young adult population differ when compared with studies involving Caucasian, Asian and other African sub-populations globally. Consequently, the clinical biometric guideline with normal reference intervals therein should be used by eye care personnel when examining South African individuals. Moreover, the possible influences of demographic and/or ocular factors should be considered when evaluating anterior segment variable measurements.

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LIST OF ACRONYMS AND SYMBOLS

Abbreviation	Meaning
A	Area
ACA	Anterior chamber angle
ACD	Anterior chamber depth
ANOVA	Analysis of variance
AOD	Angle-opening distance
AOD500	AOD measurement taken at 500 μm anterior to the scleral spur
ATR	Against-the-rule
AveAOD500	Average AOD500 measurement
AveParaCT	Average paracentral corneal thickness
AvePeriCT	Average peripheral corneal thickness
AveTIA	Average TIA measurement
CAM	Corneal adaptor module
CART	Classification and regression tree
CCT	Central corneal thickness
CI	Confidence interval
CLEK	Collaborative Longitudinal Evaluation of Keratoconus
CLSI	Clinical and Laboratory Standards Institute
D	Dioptre
d^2	Effect size
DMI	Department of management information
E	Expected effect size
F	Force
ICC	Intraclass correlation coefficient
IFCC-LM	International Federation of Clinical Chemistry and Laboratory Medicine
IOP	Intraocular pressure
K1	Corneal curvature along the flattest meridian
K2	Corneal curvature along the steepest meridian
IQR	Interquartile range
LCD	Liquid crystal display
LE	Left eye
LoA	Limit of agreement
LogMAR	Logarithm of the minimum angle of resolution
MHz	Megahertz

mm	Millimetre
mmHg	Millimetre of mercury
m/s	Metre per second
N	Total sample size
n	Sample size
nm	Nanometre
NR*	Not reported
OCT	Optical coherence tomography
OHTS	Ocular Hypertension Treatment Study
P	Pressure
r	Rank
R	Ratio between the sub-groups standard deviations
RE	Right eye
s	Standard deviation
s^2	Variance
SD	Standard deviation
S-W	Shapiro-Wilk's test
TIA	Trabecular-iris angle
UBM	Ultrasound biomicroscopy
UKZN	University of KwaZulu-Natal
µm	Micrometre
VA	Visual acuity
$\bar{x}$	Mean
WTR	With-the-rule
z	Normal deviate test score
z^*	Critical limit
°	Degree
σ	Pooled standard deviation
α	Significance level or type I error
β	Probability of making a type II error
Δ	Standardised effect size

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CHAPTER 1: INTRODUCTION

1.1 INTRODUCTION TO THE CHAPTER

Knowledge produced in research is integral to addressing health problems that affect individuals and populations particularly in developing countries (Pang et al. 2003). It is well recognised that the prevalence of ocular anomalies and pathologies varies among the different populations of the world (Blake, Lai & Edward 2003; Resnikoff et al. 2008; World Health Organization 2012). Knowledge of the normal ocular biometry variable measurements in the different populations is necessary to understand the mechanisms of ocular anomalies as well as to screen, diagnose and monitor the progression of ocular diseases. This study aimed to investigate anterior segment ocular variables, measured using optical coherence tomography (OCT), in a healthy South African young adult population and to develop a clinical biometric guideline with normal reference intervals. This chapter provides an introduction to the study and includes the background, aim, objectives, research questions and rationale for the study.

1.2 BACKGROUND

The human eye is a complex organ that consists of various layers and structures (Willoughby et al. 2010). The eye is divided into the anterior and posterior segments by the posterior lens capsule (Durand 2015; Addo, Bamiro & Siwale 2016). The anterior segment consists of the cornea, conjunctiva, iris, lens as well as the anterior and posterior chambers whereas the posterior segment consists of the retina, choroid, sclera and vitreous chamber (Addo, Bamiro & Siwale 2016). Ocular biometry refers to the measurement of various variables in the different layers and/or structures within the eye (Wang, Hsieh, & Hung 2007; Millodot 2009). Imaging and quantitative analysis of the ocular biometry variables form an essential part of a clinical eye examination and together with technological advancements

have gained renewed interest in recent years (Konstantopoulos, Hossain & Anderson 2007; Salomão, Esposito & Dupps 2009; Quek et al. 2011; Nadler et al. 2012).

1.2.1 The importance of anterior segment ocular biometry variables

There are several reasons cited in the literature for the importance of performing anterior segment ocular imaging and measuring associated biometry variables. A comprehensive understanding of the ocular anatomical structure and associated biometry measurements is necessary for screening, diagnosing and monitoring ocular anomalies. Ocular imaging and the quantitative analysis of relevant anterior segment biometry variables have enhanced the diagnosis and management of corneal (Li Y et al. 2008; Henriquez et al. 2011; Hong et al. 2011) and anterior chamber angle (ACA) anomalies including glaucoma (Brandt 2004; Dorairaj, Liebmann & Ritch 2007; Dueker et al. 2007; Nolan et al. 2010; Radhakrishnan & Yarovoy 2014).

Anterior segment ocular biometry variables are essential to preoperatively and postoperatively assess ocular surgeries including laser in situ keratomileusis, corneal collagen cross-linking, intracorneal ring segment implants, phototherapeutic keratectomy and phakic intraocular lens implants (Dada et al. 2007; Rohrer et al. 2009; Doors et al. 2010). For these surgical applications, accurate ocular biometry has become more important in light of technological improvements in surgical equipment and procedures together with greater visual expectations of individuals undergoing these ocular surgeries (Rohrer et al. 2009).

In recent years, clinical studies involving ocular biometry have identified certain anterior segment ocular variables as risk factors for the development and progression of ocular diseases. For example Gordon et al. (2002), in the Ocular Hypertension Treatment Study (OHTS), highlighted the importance of central corneal thickness (CCT) measurements as a determinant for the development and progression of primary open-angle glaucoma.

Moreover, there is an association between thinner CCT measurements and glaucoma progression in individuals with higher baseline intraocular pressure (IOP) measurements (Leske et al. 2007). Anterior chamber angle variables have also been used to describe the anatomical relationships within the anterior segment and may therefore be useful for evaluating the risk for developing angle-closure glaucoma (Devereux et al. 2000; Xu et al. 2008; Radhakrishnan & Yarovoy 2014).

As ocular biometry measurements relate to the overall health of the eye, progressive changes in the anterior segment variable measurements may be indicators of ocular changes that are associated with systemic diseases and/or contact lens wear. For example, changes in corneal thickness have been associated with ankylosing spondylitis (Ortak et al. 2014) and diabetes mellitus (Oriowo 2009; Ozdamar et al. 2010; Briggs, Osuagwu & AlHarthi 2016). Moreover, corneal thickness measurements are useful to gauge the endothelial pump and barrier functions of the cornea as disruption of these functions may result in oedema as in the case of contact lens wear (Mohan et al. 2007; Papas 2014).

1.2.2 Studies investigating anterior segment ocular biometry variables

Anterior segment ocular biometry variables have been of interest to researchers across the world. The literature shows that considerable anterior segment ocular biometry data have been reported in several American, Asian and European sub-populations (Wirbelauer et al. 2005; Xu et al. 2008; Amerasinghe et al. 2009; Wylęgała et al. 2009; Leung et al. 2010; Yuen et al. 2010; Ang et al. 2012; Qin et al. 2012; Sihota et al. 2012; Hosseini, Abolbashari & Mohidin 2013). Studies, involving predominantly Asian sub-populations, have also reported on the distribution and normal values for CCT and ACA width variable measurements (Wirbelauer et al. 2005; Rüfer et al. 2007; Zheng et al. 2008; Rüfer et al. 2010; Hashemi et al. 2011; Hwang, Kim & Sohn 2012).

For CCT measurements, studies have shown that Caucasian, Chinese and Hispanic individuals have thicker central corneal measurements than African-American, Aboriginal and Japanese individuals (Brandt et al. 2001; La Rosa, Gross & Orengo-Nania 2001; Shimmyo et al. 2003; Aghaian et al. 2004; Durkin et al. 2007; Torres et al. 2008; Bourne 2011). For ACA width variables, similar measurements were found in Caucasian and Chinese individuals (Leung et al. 2010; Wang et al. 2011). Unlike the plethora of data that exists for sub-populations in developed countries, very few studies have reported on anterior segment ocular biometry variables for African sub-populations living within the African continent. Moreover, the studies involving African sub-populations have only reported on CCT measurements (Mohamed et al. 2009; Ntim-Amponsah et al. 2012; Sardiwalla et al. 2012) with no studies having investigated corneal pachymetry variables beyond the central cornea and/or ACA width variables.

1.3 PROBLEM STATEMENT

The field of anterior segment ocular biometry has gained renewed interest in recent years especially with the development of contemporary non-invasive methods of measurement (Dorairaj, Liebmann & Ritch 2007; Konstantopoulos, Hossain & Anderson 2007; Marschall et al. 2011; Radhakrishnan & Yarovoy 2014; Piñero 2015). Most of the previous research studies investigating normal anterior segment variables have involved American, Asian and European adult sub-populations (Su et al. 2009; Leung et al. 2010; Yuen et al. 2010; Qin et al. 2012; Wang et al. 2012). There is limited information on anterior segment variables in African sub-populations living within the African continent. The few studies conducted in Africa have focused either exclusively on CCT (Mohamed et al. 2009; Ntim-Amponsah et al. 2012) or on the relationship between CCT and IOP (Eballe et al. 2010; Gelaw et al. 2010; Iyamu et al. 2010; Sardiwalla et al. 2012). Moreover, Africa is a large continent and in the absence of extensive data, it is not possible to establish the similarity and/or differences of anterior segment ocular biometry variable measurements among the different African sub-populations. Such information is necessary to inform policy formation and service delivery

across the different countries within the African continent. An enhanced understanding of the normal anterior segment variables in African sub-populations may provide insight into the possible mechanisms of anterior segment ocular anomalies observed in these sub-populations. Consequently, there is a gap in the literature regarding anterior segment variable measurements in African sub-populations.

There is a problem in applying normal anterior segment ocular biometry measurements, obtained in studies involving non-African populations, as reference standards in an African setting. The use of such measurements may negatively influence the clinical interpretation and management of patients presenting to clinical settings across the African continent including in South Africa. This quantitative cross-sectional study will investigate anterior segment variables in a healthy South African young adult population and develop a clinical biometric guideline, with normal reference intervals, that can be used to inform clinical practice within a South African context. Understanding the interocular differences and distribution of anterior segment variables in a South African population, together with the effect of demographic and/or ocular factors on these variables, could aid eye care personnel when examining patients of South African ethnicity.

1.4 AIM AND OBJECTIVES

The study aimed to produce a clinical description of anterior segment variables, measured using OCT, in a healthy South African young adult population. This clinical description facilitated the development of a clinical biometric guideline with normal reference intervals for the anterior segment variables measured using OCT. The study consisted of two phases to achieve the aim of the study. Phase one focuses on the clinical description of anterior segment variables, measured using OCT and consisted of six study objectives (1, 2, 3, 4, 5 and 6). Phase two focuses on developing a clinical biometric guideline, with normal reference intervals, and comparing the values therein to anterior segment variables currently

available for other healthy African sub-populations. Phase two of the study consisted of two study objectives (7 and 8).

The objectives of this study were to:

1. determine the interocular differences in anterior segment variables measured using OCT.
2. determine the distribution of anterior segment variables measured using OCT.
3. investigate racial variations in anterior segment variables measured using OCT.
4. investigate gender variations in anterior segment variables measured using OCT.
5. determine the effect of spherical equivalent refraction on anterior segment variables measured using OCT.
6. develop a regression tree model to determine which anterior segment variables influence IOP.
7. develop a clinical biometric guideline with normal reference intervals for anterior segment variables measured using OCT.
8. compare the clinical biometric guideline to anterior segment variables currently available for other healthy African sub-populations.

1.5 RESEARCH QUESTIONS

1. What are the interocular differences in anterior segment variables measured using OCT?

2. How are the anterior segment variables measured using OCT distributed?

3. What are the racial variations in anterior segment variables measured using OCT?

4. What are the gender variations in anterior segment variables measured using OCT?

5. What is the effect of spherical equivalent refraction on anterior segment variables measured using OCT?

6. Which anterior segment variables influence IOP?

7. What are the normal reference intervals for anterior segment variables measured using OCT in a healthy South African young adult population?

8. How does the clinical biometric guideline compare to anterior segment variables currently available for other African sub-populations?

1.6 SIGNIFICANCE OF THE STUDY

The study sought to clinically describe the anterior segment variables, measured using OCT, in a healthy South African young adult population in order to develop a clinical biometric guideline with normal reference intervals. The significance of this study and its implications for clinical practice, optometry education and research applications are outlined below.

1.6.1 Clinical practice

In South Africa, optometrists function as primary eye care practitioners who perform clinical eye examinations that involve diagnosing ocular anomalies, dispensing visual aids and/or administering vision therapy (Health Professions Council of South Africa 2015). Moreover, clinical eye examinations allow optometrists to screen, diagnose and monitor ocular diseases as well as the ocular manifestations of systemic diseases. Anecdotal reports suggest that ocular biometry measurements obtained in studies involving predominantly Caucasian sub-populations are routinely applied as reference standards to interpret clinical test results in clinical settings within the South African context. However, recent studies involving healthy South African samples have shown that ocular biometry measurements for anterior and posterior segment structures differ from measurements reported in studies involving non-African sub-populations even when devices based on the same operating principles were used (Sardiwalla et al. 2012; Murugan et al. 2015a; Murugan et al. 2015b). Consequently, the application of ocular biometry measurements obtained in studies involving non-African sub-populations may be inappropriate for the clinical interpretation of ocular biometry test results within the South African context.

A clinical biometric guideline with normal reference intervals could be useful for a clinical setting because this will provide a foundation for the interpretation of test results obtained

on South African individuals. Considering the paucity of data concerning normal ocular biometry measurements in South African individuals, the clinical biometric guideline will provide a reference tool and serve as a source of information for eye care personnel in an area that is not well researched within a local context. As evaluation of anterior segment anomalies using OCT depends on comparing the anterior segment ocular variables with normal reference values, this study is relevant as it will provide baseline data obtained on normal healthy South African young adults. Moreover, understanding the normal ocular biometry variable measurements may provide insights into the possible mechanisms of anterior segment ocular anomalies and/or diseases that affect South African individuals. Thus, the results of this study will aid eye care personnel when examining South African patients which makes the study results relevant within a local context (Kamwendo 2016).

1.6.2 Optometry education

In an educational setting, the results of this study may have the potential to contribute towards the review and update of the optometry curriculum concerning anterior segment ocular biometry measurements. The current optometry curriculum makes reference to normal ocular biometry measurements reported in studies involving predominantly Caucasian sub-populations. Kamwendo (2016) asserts that European and other non-African knowledge systems often dominate the curricula of African higher education institutions. The use of Eurocentric knowledge systems as the foundation for the curricula in African higher education institutions as well as the application of measurements reported in studies involving non-African sub-populations as reference standards for an African setting are not exclusive to optometry. These trends have also been observed in other health related disciplines including audiology (Pillay & Kathard 2015), speech language pathology (Panday et al. 2007) and occupational therapy (Joubert 2010) as well as communication studies (Fourie 2005) and education support services (Hay 2003). Consequently there is a strong call, especially for health professions that originated and have their foundations

based in European settings, to develop resources that are relevant to the South African context (Pascoe & Norman 2011).

Africanisation describes the change in paradigm from a European mind-set to an African mind-set (Makgoba 2000; Hay 2003; Kamwendo 2016). The concept of Africanisation, which originated in the 1960s, has been a recurring feature in the literature concerning higher education and knowledge production because it serves as a means of improving the understanding of Africa (Brizuela-García 2006; Kamwendo 2016). As a general concept, Africanisation involves a renewed focus on Africa by highlighting its nuances, emphasising its uniqueness and allowing Africa to take on a greater role (Horsthemke 2004; Louw 2007; Franke & Esmenjaud 2008). Africanisation as a process involves placing renewed interest on problems experienced within the African context and striving to generate knowledge about these problems as well as develop African solutions for them (Maake 1997; Horsthemke 2004; Franke & Esmenjaud 2008).

The results of this study will contribute to the growing body of literature focused on Africa and aid in recognising the validity of knowledge relevant to the communities within Africa (Kamwendo 2016). Consequently, the clinical biometric guideline will provide an African perspective of normal anterior segment ocular biometry measurements that can be added to the knowledge that is available from non-African sub-populations (Horsthemke 2004; Le Grange 2004; Fourie 2005; Msila 2009). Moreover, the clinical biometric guideline may be a useful reference tool, considering the recent inclusion of ocular therapeutics into the South African optometry scope of practice. Thus, the results of this study may be beneficial for enhancing understanding of the possible mechanisms and therapeutic management of anterior segment ocular anomalies and diseases.

1.6.3 Research applications

Health research focuses on identifying and addressing health related problems by developing new knowledge generated using scientific methods (The commission on health research for development 1990). The results of this study will provide a foundation for future research in the field of anterior segment ocular biometry within the South African context. Understanding the normal ocular biometry variations will be useful when characterising ocular changes in other individuals such as the elderly and those with ocular diseases. Moreover, this study will add to future research focused on anterior segment ocular biometry changes and risk factors associated with ocular and/or systemic diseases in South African individuals.

This study may also provide the necessary background to understand differences in the prevalence rates of ocular diseases in race and gender groups within South Africa. Consequently, understanding the effect of demographic and/or ocular factors on normal anterior segment ocular biometry variable measurements can inform research initiatives to address local ocular anomalies within a South African context. As ocular biometry measurements are useful to determine the risk of developing ocular diseases (Gordon et al. 2002), the results of this study may inform research policies and initiatives focused on screening for individuals at risk of developing anterior segment ocular anomalies.

1.7 STUDY OUTCOMES

This study aimed to understand anterior segment variables, measured using OCT, in a healthy South African young adult population and therefore produced a clinical description of these anterior segment variables. From the clinical description, a biometric guideline with normal reference intervals will be developed and compared to anterior segment variables currently available for other healthy African sub-populations living within the African continent. The intention of the study was to develop a clinical biometric guideline that was detailed and relevant in a South African context. The clinical biometric guideline and

information therein will assist eye care personnel when examining South African patients who present to a clinical and/or research setting. The study also examined the interocular differences, distribution and effect of demographic as well as ocular factors on anterior segment variables measured using OCT. Moreover, the study also investigated the influence of anterior segment variables on IOP by developing an automated regression tree model.

1.8 TYPE OF STUDY, METHODS AND DELINEATIONS

This study used a quantitative cross-sectional research design. The cross-sectional study involved administering a structured questionnaire and performing clinical eye examinations on healthy South African young adults. The study involved a well-defined university sample of healthy South African young adults aged between 17 years and 30 years. Consequently, factors known to affect anterior segment ocular biometry variables including age and IOP have been controlled for in the study. An OCT device, which is relatively new within a South African context, was used to measure the anterior segment ocular biometry variables.

1.9 OVERVIEW OF CHAPTERS

This thesis comprises of nine chapters. The description, organisation and information contained in each chapter are outlined in the section below.

i. Chapter 1 – Introduction: presented the introduction and background to the study, problem statement, study aim, objectives as well as research questions, rationale for the study and organisation of the thesis.

ii. Chapter 2 – Theoretical framework: presents the theoretical perspectives that form the background for this study. This includes a brief discussion of the cornea and ACA in terms of its anatomy, physiology, common ocular variables measured and their clinical relevance. The chapter also includes a brief discussion of Darwin's theory of evolution, human variation and an amalgamated theoretical construct that highlights

the influence of environmental and genetic factors on human biological evolution and variation.

iii. Chapter 3 – Literature review - corneal pachymetry: presents a review of previous studies that investigated corneal pachymetry variables.

iv. Chapter 4 – Literature review - ACA width: presents a review of previous studies that investigated ACA width variables.

v. Chapter 5 – Methodology: presents the methodological aspects of the study, which includes a discussion of the study design, population, sampling method, sample, data collection instruments and procedures as well as the data analysis techniques that were used to address the study objectives.

vi. Chapter 6 – Results: presents the results of the study in the form of data tables and figures with supporting text. This chapter begins with the demographic and ocular characteristics of the study sample and thereafter the results are presented with respect to study objectives one to six. Interocular differences and the distribution of anterior segment variables measured using OCT are presented. The results also includes the racial and gender variations in anterior segment variables measured using OCT. The effect of spherical equivalent refraction on the anterior segment variables, measured using OCT, is also presented. The influence of anterior segment variables on IOP is demonstrated with an automated regression tree model.

vii. Chapter 7 – Discussion: focuses on the discussion of the results presented in chapter six for the first six study objectives. This involves discussing the key findings of the study in the context of the literature as well as the theoretical framework and highlighting the implications of these findings.

viii. Chapter 8 – Clinical biometric guideline: addresses study objectives seven and eight, which involve the development of a clinical biometric guideline with normal reference intervals and their comparison to anterior segment variables currently available for other healthy African sub-populations.

ix. Chapter 9 – Conclusions and recommendations: indicates the extent to which the study aim was achieved by summarising the main findings and conclusions of the study. It also outlines the recommendations, strengths and limitations as well as provides suggestions for future research.

1.10 CONCLUSION TO THE CHAPTER

This chapter presented the introduction and rationale to this study by highlighting the importance of anterior segment ocular biometry variable measurements. The background also briefly reviewed previous studies that reported on anterior segment ocular biometry variable measurements. The discussion then proceeded to the problem statement, study aim, objectives and research questions. The chapter ended with the significance of the study in light of clinical practice, optometry education as well as research applications, expected study outcomes and a discussion of the organisation of this thesis.

CHAPTER 2: THEORETICAL FRAMEWORK

2.1 INTRODUCTION TO THE CHAPTER

This chapter presents the theoretical perspectives that form the background for this study. The first section focuses on the anterior segment structures (cornea and ACA) that are relevant to this study. In this section, the anatomy and physiology of the cornea and ACA are reviewed. This is accompanied by a discussion of the corneal thickness and ACA width variables that formed the focus of this study. The second section includes a brief discussion of the two theories (evolution and human variation) that formed the theoretical structure for this study. The chapter ends by presenting an amalgamated theoretical construct which informed this study.

2.2 THE CORNEA

2.2.1 Anatomy and physiology

The cornea is the transparent structure found in the anterior part of the eye and together with the opaque sclera forms the outermost layer of the eye. The anterior and posterior corneal surfaces are in contact with the tear film and aqueous humour respectively. The cornea behaves as a convex optical surface that refracts light to aid in the formation of retinal images. More specifically, the cornea together with the overlying tear film serves as the primary refracting structure and accounts for approximately two-thirds of the total ocular power (Horner, Salmon & Soni 2006; DelMonte & Kim 2011). Other functions of the cornea include serving as a protective barrier against foreign bodies and for stabilising the tear film (Pavan-Langston 2002). The cornea receives its nutrients via the tear film, limbal arcades and aqueous humour as a result of its avascular nature. The peripheral cornea may also be supplied with nutrients from the branches of the anterior ciliary arteries which form the limbal arcades. The cornea is richly innervated by the nasociliary branch of the ophthalmic division

of the trigeminal nerve (DelMonte & Kim 2011). To maintain the metabolism of the cornea, most of the oxygen required is derived from the tear film via diffusion.

Microscopically the cornea consists of five distinct layers although a sixth layer was proposed a few years ago (DelMonte & Kim 2011; Dua et al. 2013). The five corneal layers comprise of three cellular layers and two interfaces. The three cellular layers include the epithelium, stroma and endothelium (Kanski 2008). The epithelium, which is the most anterior layer, is derived from the surface ectoderm (Hassel & Birk 2010). The stroma and endothelium are derived from the neural crest cells (Hassel & Birk 2010). The two interfaces include Bowman's and Descemet's membranes that lie adjacent to the corneal stroma.

A sixth corneal layer, which is thought to lie between the stroma and Descemet's membrane, was recently proposed by Dua and colleagues (Dua et al. 2013). This layer, termed Dua's layer, is described as a thin acellular layer of collagen with a mean thickness of 10.15 µm (Dua et al. 2013). Although Dua's layer is described as an important consideration for corneal diseases and surgeries due to its resilient nature, there has been some controversy about its existence (McKee et al. 2014). Therefore, the rest of this section will focus on the five well recognised corneal layers with limited attention given to Dua's layer.

The epithelium is the outermost corneal layer and accounts for approximately 10% of the total corneal thickness. It consists of five to seven layers of stratified non-keratinised squamous cells on a basement membrane (Kanski 2008). The corneal epithelial cells include flat polygonal cells, suprabasal/wing cells and columnar epithelium cells. The superficial epithelial cells are desquamated into the tear film and replaced by the deeper epithelial cells every seven to ten days (DelMonte & Kim 2011). The compactness of the epithelium is achieved by attachments between the epithelial cells themselves and to the basement membrane. Consequently, the epithelium acts as a fluid barrier and aids in protecting the eye against the entry of microorganisms as well as foreign bodies.

The stroma is the middle corneal layer and accounts for approximately 90% of the total corneal thickness (Kanski 2008; Matthyssen et al. 2018). This layer consists of collagen fibrils, keratocytes, nerve fibres and proteoglycans. The collagen fibrils (Type I, III, V and VI) are regularly arranged to form lamellae (Meek & Leonard 1993). The stroma consists of approximately 200 to 250 lamellae which have a thickness of 1.5 µm to 2 µm and diameter of 25 nm to 30 nm (Hassel & Birk 2010). The lamellae have a uniform arrangement and are parallel to each other and the corneal surface. The transparency of the cornea is dependent on the regular arrangement of the stromal lamella which minimise light scattering (Maurice 1957; Matthyssen et al. 2018). Any alteration in the arrangement of the lamellae will have a negative effect on the transparency of the cornea. Keratocytes are interspersed between the collagen lamellae and are responsible for the synthesis and regulation of collagen fibrils. The proteoglycans, which consist of keratan sulfate and chondroitin sulphate/dermatan sulfate side chains, aid in regulating corneal hydration as well as transparency (Tanihara et al. 2002).

The endothelium, which is the innermost corneal layer, consists of a single layer of non-regenerating hexagonal shaped cells with a thickness of 5 µm and a diameter of 18 µm to 20 µm (Kanski 2008). This layer aids in maintaining the balance of fluid moving between the tear film, cornea and anterior chamber via its active pump which aims to maintain the necessary water level (75% to 80%) in the stroma this being important for corneal hydration and transparency. Moreover, the tight junctions of the endothelial cells aid in preventing the influx of fluid from the anterior chamber into the cornea. Consequently, any loss and/or damage to the endothelial cells will have a negative effect on corneal transparency.

The two corneal interfaces (Bowman's and Descemet's membranes) lie on either side of the stroma. These layers, similar to the stroma, consist of collagen fibrils and serve as anchors to the adjacent corneal layers. As a result, the Bowman's and Descemet's membranes further aid in protecting the eye against injury and/or infections. Bowman's membrane

consists of Type I, III and IV collagen fibrils which are synthesised by the stromal keratocytes and is therefore thought to be continuous with the anterior stroma (Nishida 2005). Bowman's membrane, which has a thickness of 10 µm to 16 µm, does not regenerate after injury (DelMonte & Kim 2011). Descemet's membrane, which has a thickness of 8 µm to 10 µm, acts as a basement membrane for the single layered endothelium cells. It consists of Type IV collagen fibrils as well as fibronectin but unlike Bowman's membrane is discontinuous with the stroma.

2.2.2 Corneal thickness variables and their clinical relevance

The thickness of the cornea is defined as the distance between the anterior and posterior corneal surfaces (Agarwal et al. 2002). Corneal thickness measurements vary across the cornea wherein lower values are usually recorded for the centre than the periphery (Mohan et al. 2007; DelMonte & Kim 2011). The measurement of corneal thickness is termed corneal pachymetry (Kadhim & Farhood 2016) and has diagnostic and therapeutic applications that include diagnosing and monitoring diseases such as keratoconus, pellucid marginal degeneration, corneal dystrophies and oedema (Borboli & Colby 2002; Fontes et al. 2010; Saad & Gatinel 2010). Corneal pachymetry is also an important consideration in assessing the suitability for refractive surgical procedures and contact lens wear (Khurana et al. 2007). Furthermore, the thickness of the cornea is known to influence IOP measurements recorded with applanation tonometry (Whitacre, Stein & Hassanein 1993; Kohlhaas et al. 2006) and is therefore important for screening, diagnosing and monitoring glaucoma disorders (Thomas, Korah & Muliyil 2000; Shih et al. 2004).

There are two types of corneal pachymetry techniques namely spot pachymetry and pachymetry mapping. Spot pachymetry techniques include ultrasound pachymetry, traditional optical pachymetry and confocal microscopy (Mohan et al. 2007). Pachymetry mapping systems include imaging devices based on slit-scanning topography, Scheimpflug photography and OCT (Mohan et al. 2007). Although spot pachymetry techniques are

simple to perform and use relatively cheap equipment, they are limited in terms of how much of the corneal area may be assessed in a single measurement (Wheeler et al. 1992). Moreover spot pachymetry techniques, such as ultrasound pachymetry, are dependent on the manual placement of the probe by the examiner on the cornea and lack fixation targets (Fares et al. 2012). Consequently, spot pachymetry techniques are inadequate for evaluating thickness variations across the cornea in a single measurement and are relatively examiner dependent (Khurana et al. 2007).

Pachymetry mapping techniques are able to simultaneously determine corneal thickness at the centre, the thinnest point and the periphery (Li, Shekhar & Huang 2006; Mohamed et al. 2007). Consequently, the corneal pachymetry maps that are generated in a single measurement with pachymetry mapping techniques extend over a wide area and are more suitable for documenting corneal thickness measurements across the corneal surface. Moreover, studies have shown that corneal pachymetry mapping techniques have comparable (Nam et al. 2010; Huang et al. 2015) or better (Rainer et al. 2002; Leung et al. 2006; Tai et al. 2013) repeatability and reproducibility than spot pachymetry techniques. Nevertheless, researchers caution against comparing corneal thickness measurements across studies as the different corneal pachymetry techniques, which are based on varying principles, are not interchangeable (Wong et al. 2002; Hikoya et al. 2009; Ishibazawa et al. 2011; Chen et al. 2012).

2.2.2.1 Central corneal thickness

Central corneal thickness measurements have been the focus of several studies worldwide (La Rosa, Gross & Orengo-Nania 2001; Nemesure et al. 2003; Shimmyo & Orloff 2005; Su et al. 2009; Nangia et al. 2010). This may be due to the importance of CCT measurements for various surgical and diagnostic applications. Moreover, a thinner CCT measurement has been identified as an independent risk factor for the development of primary open-angle glaucoma (Gordon et al. 2002; Leske et al. 2007). Doughty and Zaman (2000) conducted a

meta-analysis of 300 studies that reported on CCT measurements over a period of 31 years. In this meta-analysis, the mean and range (95% confidence interval) of the CCT measurements for normal eyes were 535 µm and 473 µm to 597 µm respectively (Doughty & Zaman 2000). The mean CCT measurement depends on the measuring device wherein higher values are obtained using ultrasound pachymetry devices (544 µm) than with slit lamp pachymetry devices (530 µm) (Doughty & Zaman 2000).

The central aspect of the cornea, corresponding to its geometric centre, is usually considered to be the thinnest point on the cornea (minimum corneal thickness) (Keech, Simpson & Jones 2010). This assumption may be attributed to the central cornea being the only corneal point that is commonly measured with ultrasound pachymetry (Fam, Lim & Reinstein 2005). However, the thinnest point on the cornea may not always be at the fixed centred position on the corneal surface (Liu, Huang & Pflugfelder 1999). Moreover, with technological advancements in corneal pachymetry techniques, it is being increasingly reported that the thinnest point on the cornea does not lie at the geometric centre. Several studies have reported that the thinnest point on the cornea is inferotemporal to its geometric centre (Khoramnia, Rabsilber & Auffarth 2007; Ashwin et al. 2009; Rüfer et al. 2009; Fares et al. 2012). The clinical relevance of the thinnest point on the cornea relates to the detection and risk of developing keratoconus as well as serves as an important consideration for refractive surgery (Jonsson & Behndig 2005; Li Y et al. 2008; Hashemi et al. 2009; Rüfer et al. 2009).

2.2.2.2 Peripheral corneal thickness

Unlike CCT measurements, peripheral corneal thickness measurements have not attracted much attention in the literature. Despite the limited research interest, peripheral corneal thickness measurements may provide useful information for corneal diseases and surgeries that extend beyond the central cornea (Doughty & Zaman 2000; Fam, Lim & Reinstein 2005). Knowledge of the corneal thickness measurements, beyond the central 2 mm, may

enhance understanding of the mechanisms involved in corneal ectasias that present in the peripheral cornea (Marsich & Bullimore 2000; Fam, Lim & Reinstein 2005). Furthermore, knowledge of peripheral corneal thickness measurements may be useful to achieve a suitable match between the host and donor corneas in penetrating keratoplasty (Rüfer et al. 2007) and may inform the depth of arcuate and limbal relaxing incisions made at the paracentral and peripheral cornea respectively (Loriaut et al. 2014; Read, Vincent & Collins 2014). Peripheral corneal thickness measurements are between 9% and 52% higher than CCT measurements and are known to vary in the different corneal quadrants (Doughty & Zaman 2000). In their meta-analysis, Doughty and Zaman (2000) concluded that the average peripheral corneal thickness measurements for white and non-white individuals were 533 ± 20 µm and 657 ± 71 µm respectively (Doughty & Zaman 2000).

2.3 THE ANTERIOR CHAMBER ANGLE

2.3.1 Anatomy and physiology

The anterior chamber, which is the space between the posterior cornea and anterior iris, contains aqueous humour that is produced by the pars plicata of the ciliary body (Kanski 2008). Even though aqueous humour is produced in the posterior chamber, it drains out of the eye through the anterior chamber via the ACA. The ACA is located at the peripheral part of the anterior chamber and represents the junction between the peripheral cornea, root of the iris and anterior aspect of the ciliary body (Campa et al. 2011). The normal configuration and characteristics of the ACA structures must be known to facilitate screening for ACA anomalies (Kim et al. 2011).

The ACA structures include Schwalbe's line, trabecular meshwork, scleral spur, ciliary body and iris root. Schwalbe's line represents the junction between Descemet's membrane and the sclera and when pigmented is referred to as Sampaolesi's line. The trabecular meshwork lies posterior to Schwalbe's line and consists of porous epithelial tissue being divided into two parts (anterior and posterior), which are differentiated based on their colour

appearances (Cockburn 1991a). The anterior trabecular meshwork is less pigmented and appears whitish whereas the posterior trabecular meshwork is more pigmented and appears greyish-blue to brown. The trabecular meshwork is an important component for draining the aqueous humour. Schlemm's canal lies posterior to the trabecular meshwork and allows for the aqueous humour in the meshwork to drain into the episcleral venous plexus. Schlemm's canal is usually not visible, although if excessive pressure is applied to the episcleral veins, blood in the canal appears as a fine red line beneath the trabecular meshwork (Kanski 2008).

The scleral spur lies posterior to the trabecular meshwork and appears as a whitish band that provides support for the trabecular meshwork and Schlemm's canal (Cockburn 1991a). Within the ACA, the scleral spur is located at the junction of the trabecular meshwork and the interface line formed by the sclera and ciliary body (Ishikawa & Schuman 2004). As a result, the scleral spur represents the anterior projection of the sclera and consists of collagen and elastic tissue (Kanski 2008). The longitudinal muscles of the ciliary body insert into the scleral spur. The most posterior structure in the ACA is the ciliary body which varies between pink and dark brown in colour. The peripheral iris, as it inserts into the ciliary body, is also visible in the ACA. The colour of the iris and different ACA structures mentioned above may vary as their appearances are dependent on ocular pigmentation. Other structures that may be visible in the ACA include iris processes, blood vessels as well as adhesions between the iris and structures therein (peripheral anterior synechia).

2.3.2 Anterior chamber angle width variables and their clinical relevance

The ACA, which is the anatomical angle formed in the anterior segment of the eye, can be described as a triangle with its apex lying in the iris recess and two arms lying on the posterior cornea and anterior iris surfaces (Dawczynski et al. 2007). Evaluating the ACA is important as it can be used to identify normal anatomical variations and/or monitor changes in the ACA structures as well as configuration. Moreover, evaluation of the ACA is necessary

to screen, diagnose, classify and manage glaucoma disorders (Müller et al. 2006). To this extent, visualisation of the ACA can enhance understanding of the pathophysiology and mechanisms involved in glaucoma disorders (Leung & Weinreb 2011). As the configuration of the ACA is the defining feature in primary angle-closure glaucoma, evaluating the ACA allows for early identification of individuals with anatomically narrow angles who may be at risk for developing angle-closure glaucoma (Congdon Wang & Tielsch 1992; Campa et al. 2011; Quek et al. 2011). In addition, the ACA width is routinely assessed in clinical practice to identify patients at risk for angle closure following pupillary dilation.

The ACA can be evaluated qualitatively and/or quantitatively using various techniques (Piñero 2015). Gonioscopy, which uses special contact lenses, enables direct visualisation of the ACA and can qualitatively determine the status (open, closed or occludable) of the ACA (Wirbelauer et al. 2005; Friedman & He 2008). Gonioscopy can also be modified to provide a semi-quantitative evaluation of the ACA when combined with any of the established grading systems (Scheie 1957; Shaffer & Schwartz 1957; Spaeth 1971) or with slit lamp graticules (Congdon et al. 2002). Despite these enhancements, gonioscopy evaluations of the ACA are subjective, depend on the experience of the examiner, require contact with the ocular surface, present with high inter-examiner variations, provide only an estimate of the ACA width and may be inadequate in cases of corneal opacities and/or trauma (Pavlin et al. 1991; Narayanaswamy et al. 2004; Müller et al. 2006; Friedman & He 2008; Nolan 2008).

The van Herick's technique, which is used to subjectively grade the limbal anterior chamber depth, is considered a proxy for evaluating the ACA width in a clinical setting (van Herick, Shaffer & Schwartz 1969; Campa et al. 2011). This may be due to the van Herick's technique allowing for the quick non-invasive evaluation of the ACA as part of a slit lamp biomicroscopy examination. However, this technique only allows for a semi-quantitative evaluation and may be of limited use in cases of limbal anomalies (pterygium and scarring) and when screening

for narrow ACAs (Thomas et al. 1996; Congdon et al. 1997; Larsen, Luraas & Lundmark 2013). As a result of the limitations associated with gonioscopy and van Herick's technique, other methods capable of quantitatively evaluating the ACA have been developed. These methods, which are based on the principles of ultrasonography and OCT, are briefly reviewed below.

High frequency ultrasound biomicroscopy (UBM) allows for visualisation and quantification of the ACA (Pavlin, Sherar & Foster 1990). Even though UBM is one of the first techniques that allowed for quantitative assessment of the ACA, it has a number of limitations (Pavlin, Sherar & Foster 1990). For example, UBM is a contact time-consuming technique that is difficult to perform in the dark and requires topical anaesthetic (Radhakrishnan, Huang & Smith 2005; Dada et al. 2007; Friedman & He 2008). Sometimes UBM is performed with the patient in a supine position which may influence the ACA configuration and resulting measurements (Ishikawa, Liebmann & Ritch 2000). Moreover, the examiner has to subjectively locate the position of the four (superior, inferior, nasal or temporal) ACAs during the scanning process (Ursea & Silverman 2010). Consequently, evaluation of the ACA with UBM may have varying reproducibility due to the lack of predetermined reference points (Urbak, Pedersen & Thorsen 1998; Müller et al. 2006; Li et al. 2007).

Optical coherence tomography also allows for quantitative assessment of the ACA (Radhakrishnan et al. 2001). As the OCT technique is non-contact, it eliminates the influence of mechanical distortion on the ACA variables (Radhakrishnan, Huang & Smith 2005). Moreover, Fourier-domain OCT devices have higher resolutions than UBM devices and provide more detailed images which facilitate better visualisation and identification of the ACA structures (Radhakrishnan et al. 2005). Factors such as changes in pupil size and accommodation, which may influence ACA variables, are better controlled for with OCT devices as they utilise infrared light (Leung et al. 2008). Furthermore, ACA evaluation with OCT devices may be better tolerated by patients because the images are captured rapidly

with the individual in a seated position. Several studies have reported that OCT devices are reliable for repeated measurements of ACA width variable measurements (Müller et al. 2006; Radhakrishnan et al. 2007) which also have good correlations with gonioscopy (Goldsmith et al. 2005; Wirbelauer et al. 2005; See et al. 2007; Wong et al. 2009).

Both UBM and OCT techniques create cross-sectional ACA images that can be analysed to provide quantitative estimates of the ACA width (Pavlin et al. 1991; Pavlin, Harasiewicz & Foster 1992; Pavlin & Foster 1998; Ishikawa et al. 1999; Radhakrishnan et al. 2005). A constant reference point is necessary for reproducible ACA width variable measurements (Hoerauf et al. 2002; Cumba et al. 2012). The scleral spur is used as the reference point in the cross-sectional ACA images as it is a prominent structure that can be consistently identified (Ishikawa Liebmann & Ritch 2000; Ishikawa & Schuman 2004; Patwardhan et al. 2007). Using this reference point, the ACA width is commonly measured in terms of the angle-opening distance (AOD) and trabecular-iris angle (TIA) (Pavlin et al. 1991; Pavlin, Harasiewicz & Foster 1992). Moreover, the AOD and TIA are the most sensitive ACA width variables for differentiating between occuldable and non-occludable ACAs (Henzan et al. 2011). These ACA width variables may be measured at various distances from the scleral spur landmark. As the approximate length of the trabecular meshwork is 500 µm, these ACA width variables are often measured 500 µm anterior to the scleral spur (Campa et al. 2011).

Both the AOD500 (implies the AOD measurement taken at 500 µm anterior to the scleral spur) and TIA variables have been measured in many studies that evaluated ACA width with UBM and OCT devices (Li et al. 2007; Wirbelauer et al. 2005; Wang et al. 2009; Wylęgała et al. 2009). Moreover, studies that have compared ACA width variables obtained using UBM and OCT devices have reported contradictory findings. Some studies have reported similar measurements (Radhakrishnan et al. 2005; Dada et al. 2007) whereas others have reported poor agreement between measurements (Wang et al. 2009; Mansouri,

Sommerhalder & Shaarawy 2010). The two ACA width variables, namely AOD500 and TIA, which formed the focus of this study are briefly outlined below.

2.3.2.1 Angle-opening distance

The AOD500 refers to the linear distance (in µm) measured from the trabecular meshwork to the perpendicular point on the anterior iris surface (Pavlin, Harasiewicz & Foster 1992; Pavlin, Ritch & Foster 1992; Wirbelauer et al. 2005; Cheon et al. 2010; Liu et al. 2011). In an early clinical study, a mean AOD500 of 347 ± 181 µm was reported (Pavlin, Harasiewicz & Foster 1992). More recently, Grewal et al. (2011) reported that the normal AOD500 measurement for the nasal and temporal ACAs were 500 ± 210 µm (range from 120 µm to 830 µm) and 510 ± 220 µm (range from 120 µm to 850 µm) respectively for individuals with open non-occludable ACAs.

2.3.2.2 Trabecular-iris angle

The TIA refers to the angular measurement (in degrees) of the triangle formed by the iris recess, trabecular meshwork and the perpendicular point on the anterior iris surface (Pavlin, Harasiewicz & Foster 1992; Pavlin, Ritch & Foster 1992; Wirbelauer et al. 2005; Mansouri, Sommerhalder & Shaarway 2010; Liu et al. 2011). In normal healthy individuals, the normal TIA measurements is approximately 30° (Pavlin, Harasiewicz & Foster 1992; Wirbelauer et al. 2005; Campa et al. 2011).

2.4 THEORY OF EVOLUTION

The theory of evolution describes the changes that occur over a period of time (Krukonis & Barr 2008). Consequently, the theory of evolution is widespread and may refer to various aspects including language, culture, art, biology, diet and behaviour. Accordingly, evolution is the key theory that makes sense of all aspects in the living world (Dobzhansky 1973; Smith & Davies 2008). Biological evolution, more specifically, entails the process of change that occurs in the characteristics of living species and/or populations over a period of time

(Krukonis & Barr 2008; Smith & Davies 2008). These changes, which occur in the individuals/organisms that constitute the populations that form a species, may be accounted for by genetic drift due to random factors or natural selection (Krukonis & Barr 2008). The theory of evolution was proposed by Charles Darwin in 1859 through his seminal book termed '*on the origin of species by means of natural selection, or the preservation of favoured races in the struggle for life*' (Darwin 1859). The process of evolution is associated with three independent attributes which include:

i. Replication: describes the fact that life forms have offspring.

ii. Variation: refers to each offspring being slightly different from its siblings and/or parents. Consequently, heritable variation is an important component necessary for evolution (Krukonis & Barr 2008).

iii. Natural selection: is a key feature of evolution and relates to the fact that not all offspring will survive. Consequently, natural selection explains that heritable characteristics that contribute to offspring being better suited for a particular environment are passed on to individuals in subsequent generations (Krukonis & Barr 2008). In this way, the heritable characteristics that are favourable are more likely to be present in future generations than unfavourable characteristics (Stanford, Allen & Antón 2008). This makes the process of natural selection the key causative factor for evolution.

The physical characteristics (phenotype) of an individual are influenced by the interaction between its genetic makeup (genotype) and the environment (Krukonis & Barr 2008; Stanford, Allen & Antón 2008). The process of natural selection acts on the physical characteristics of individuals whereby the interaction between the individual and their surrounding environment impacts the physical characteristics of subsequent generations (Krukonis & Barr 2008; Stanford, Allen & Antón 2008). Adaptation is the biological and/or

behavioural process through which an individual increases its chance of survival because of an improvement in function (Smith & Davies 2008; Stanford, Allen & Antón 2008). For example, skin colour in the human species represents a biological adaptation to the environmental conditions (Smith & Davies 2008). Through the process of natural selection, darker coloured skin is favourable in geographic areas that receive greater amounts and intensity of sunlight (Smith & Davies 2008). This relates to the idea of environmentalism which describes the influence the environment has on the anatomy of individuals from a population (Stanford, Allen & Antón 2008). Through the process of evolution, human beings around the world have adapted to their environmental conditions wherein the environment acts like a filter that selects for or against the different physical characteristics (Smith & Davies 2008; Stanford, Allen & Antón 2008). Consequently, the environment is an important consideration in human evolution, natural selection and adaptation (Maslin, Shultz & Trauth 2015). Moreover natural selection, due to the environment, is described as a creative and blind process that influences subsequent generations (Dobzhansky 1973; Stanford, Allen & Antón 2008).

There are geographically related differences in the physical and cultural characteristics of the different populations within the human species (Smith, Terhune & Lockwood 2007; Smith & Davies 2008; Pretty et al. 2009). It is well established that the anatomically modern human species originated and evolved in Africa (Tishkoff & Williams 2002; Manica et al. 2007; Campbell & Tishkoff 2010; Reynolds 2012; Chakravarti 2015; Maslin, Shultz & Trauth 2015). Even though humans moved out of Africa approximately 50 000 years ago and subsequently migrated to other parts of the world, the different human populations throughout the world are genetically similar because there are no major genetic variations between the different populations (Witherspoon et al. 2007; Li JZ et al. 2008; Smith & Davies 2008; Rosenberg 2011; Chakravarti 2015). Moreover, there are higher levels of human variation among individuals within a specific population than between different populations (Goodman 2000; Tishkoff & Williams 2002; Edgar & Hunley 2009; Fujimura et al. 2014). In

addition to differences in the physical characteristics of the various human populations globally, these populations have also culturally adapted to their environmental conditions with behavioural changes and through the use of different artifacts (Smith & Davies 2008). Consequently, human variation is also thought to be related to geographic distance (Templeton 1998; Goodman 2000; Rosenberg 2011).

2.5 THEORY OF HUMAN VARIATION

The theory of human variation, which is a subfield of biological anthropology, refers to differences among individuals throughout the world (Stanford, Allen & Antón 2008). These differences may include anatomical physical characteristics as well as genetics. Human variations and adaptations are thought to be due to the interaction between humans and their environments (Stanford, Allen & Antón 2008; Rosenberg 2011). Human variation is often described in terms of the clinal model which explains that there are gradual changes in the frequency of inherited characteristics across geographical areas (Stanford, Allen & Antón 2008; Fujimura et al. 2014). To this extent, human biological variation is described as a dynamic and continuous process that exists over time and geographic distances (Goodman 2000).

Humans have continuous variation for the various physical characteristics (Stanford, Allen & Antón 2008; Fujimura et al. 2014). Human variation is often described, in terms of race, on the basis of different physical characteristics including skin colour, hair colour and form, eye form as well as head shape (Stanford, Allen & Antón 2008). Of these physical characteristics, skin colour is most commonly used to separate individuals into different groups (Stanford, Allen & Antón 2008). However, despite differences in skin colour that have been observed in individuals from different geographical areas, it was shown that the genes responsible for skin colour are only slightly different among these individuals (Krukonis & Barr 2008). Thus, it is likely that the variation in skin colour observed among these individuals may be accounted for by the environment, natural selection and their adaptation

to their surrounding environments (Krukonis & Barr 2008). Due to the lack of major genetic differences between individuals with different physical characteristics and the wide range of variation that may be observed for any physical characteristic, biological anthropology and the clinal model do not support grouping individuals within the human species into distinct groups (Stanford, Allen & Antón 2008). For this reason, it is proposed that human biological variation is most likely explained by evolution coupled with the migration and expansion of the human species out of Africa (Rosenberg 2011).

2.6 AMALGAMATED THEORETICAL CONSTRUCT

Taken together, the theories of evolution and human variation may account for the variation in physical characteristics observed in individuals from different human populations across the world. Consequently, understanding human biological variation should be approached from the theory of evolution, which foregrounds the gradual changes in physical and cultural characteristics that occur over an extensive period of time and the migration of the anatomically modern humans out of Africa (Goodman 2000; Rosenberg 2011). Figure 2.1 presents the amalgamated theoretical construct, evolution and human variation, which was used to inform this study. Specifically for the anterior segment structures, studies have suggested that corneal and ACA width variable measurements may be affected by environmental factors (Alsbirk 1978; Toh et al. 2005; Zhang et al. 2008; Vijaya et al. 2010). Moreover, researchers have supported the influence of genetics on corneal thickness measurements despite a limited understanding of the specific genes responsible for the variation observed (Toh et al. 2005; Dimasi, Burdon & Craig 2010).

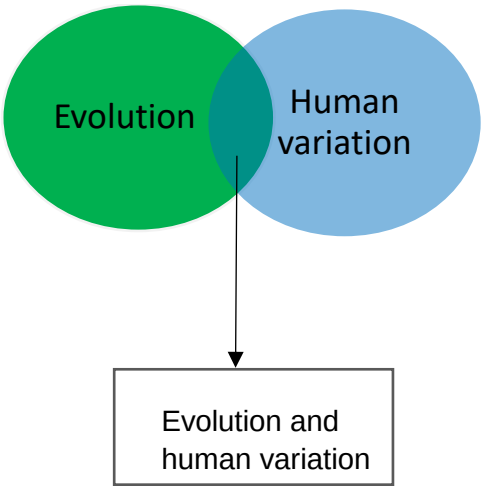


Figure 2.1: An amalgamated theoretical construct

2.7 CONCLUSION TO THE CHAPTER

This chapter presented the theoretical perspectives that informed this study. This included reviewing the cornea and ACA in terms of its anatomy, physiology as well as variables that were the focus of this study. Thereafter the two theories, evolution and human variation, were reviewed. Lastly, the chapter ended with the amalgamated theoretical construct that informed this study. Chapters three and four, which follow, focus on the literature review of corneal pachymetry and ACA width variable measurements respectively.

CHAPTER 3: LITERATURE REVIEW – CORNEAL PACHYMETRY

3.1 INTRODUCTION TO THE CHAPTER

This chapter focuses on the literature regarding corneal pachymetry variables. The discussion begins with a review of previous studies that have reported on corneal pachymetry measurements in normal healthy populations. This is followed by a brief discussion of the factors known to affect corneal pachymetry measurements. The chapter ends with a summary of the state of knowledge regarding corneal pachymetry variables. The review presented in this chapter provides the context for this study particularly for the interpretation of the corneal pachymetry results.

3.2 STUDIES INVESTIGATING CENTRAL CORNEAL THICKNESS

This section presents a summary of previous studies that have reported on CCT measurements in normal healthy populations. This includes studies that have focused on CCT measurements in different countries across the African, European, American and Asian regions as classified by the World Health Organization (World Health Organization 2015). The relevant studies are displayed in tables together with a critical summary of the literature. Table 3.1 shows the various studies that have investigated and reported on CCT measurements in African sub-populations. Table 3.2 shows the various studies that have investigated and reported on CCT measurements in Caucasian sub-populations. Table 3.3 shows the various studies that have investigated and reported on CCT measurements in Asian sub-populations. Thereafter, studies that have investigated and reported on CCT measurements in two or more race groups are displayed in Table 3.4.

3.2.1 Central corneal thickness in African sub-populations

Studies have reported on CCT measurements in normal healthy populations from African countries including Nigeria, Cameroon, Ethiopia, Sudan, South Africa and Ghana. Table 3.1

shows the various studies that have reported on CCT measurements in African sub-populations (Iyamu & Memeh 2007; Mercieca et al. 2007; Mohamed et al. 2009; Eballe et al. 2010; Gelaw et al. 2010; Iyamu et al. 2010; Iyamu & Eze 2011; Rampersad, Mashige & Jhetam 2011; Iyamu & Osuobeni 2012; Ntim-Amponsah et al. 2012; Sardiwalla et al. 2012; Iyamu, Iyamu & Amadasun 2013). Six of the 12 studies were undertaken in West-Africa involving Nigerian samples. In most of the studies, the mean age of participants was more than 40 years with only three reporting mean ages lower than 32 years (Eballe et al. 2010; Rampersad, Mashige & Jhetam 2011; Sardiwalla et al. 2012). This suggests that the studies investigating CCT measurements in African sub-populations have involved predominantly middle-aged adult samples.

As seen in Table 3.1, almost all the studies used ultrasound pachymetry to measure CCT with the only exceptions being the two undertaken in South Africa (Rampersad, Mashige & Jhetam 2011; Sardiwalla et al. 2012). Despite using the same method (ultrasound pachymetry) to measure CCT, differences in the mean CCT measurements are apparent as some studies reported values of ~550 µm (Iyamu et al. 2010; Iyamu & Eze 2011; Iyamu & Osuobeni 2012; Iyamu, Iyamu & Amadasun 2013) whereas other studies reported values of ~530 µm (Mohamed et al. 2009; Eballe et al. 2010; Ntim-Amponsah et al. 2012). In contrast, the two studies that used Scheimpflug photography devices to measure CCT reported lower mean CCT measurements of ~519 µm (Rampersad, Mashige & Jhetam 2011; Sardiwalla et al. 2012).

Overall, there is a wide distribution of mean CCT measurements (range, 518 µm to 550 µm) in the various studies involving African sub-populations. With the exception of Mohamed et al. (2009), all studies reported standard deviations for mean CCT measurements between 30 µm and 39 µm (Table 3.1). The highest mean CCT measurement of 550.1 µm was reported in a Nigerian sample (Iyamu & Eze 2011) and the lowest mean CCT measurements (~519 µm) were reported in the Ethiopian (Gelaw et al. 2010) and South African

(Rampersad, Mashige & Jhetam 2011; Sardiwalla et al. 2012) samples. Even though the difference in mean age of two of these samples is only four years, the variation in mean CCT measurements is ~31 µm (Gelaw et al. 2010; Iyamu & Eze 2011).

The mean CCT measurements reported for West-African sub-populations (Nigeria) are higher than the mean CCT measurements reported for other African sub-populations. The mean CCT in the Nigerian samples is ~19 µm higher than the mean CCT measurements reported in the Sudanese, Ethiopian and Cameroonian samples (Mohamed et al. 2009; Gelaw et al. 2010; Eballe et al. 2010; Iyamu et al. 2010; Iyamu & Osuobeni 2012). A similar pattern is also apparent for the minimum CCT measurements (from the ranges reported) wherein the Nigerian samples (Iyamu et al. 2010; Iyamu & Eze 2011; Iyamu & Osuobeni 2012; Iyamu, Iyamu & Amadasun 2013) had considerably higher values than the other African samples (Mohamed et al. 2009; Eballe et al. 2010; Gelaw et al. 2010; Ntim-Amponsah et al. 2012).

One study involving a Nigerian sample by Mercieca et al. (2007) reported a mean CCT measurement of 535 µm which is lower than the mean CCT values reported in other Nigerian samples (Iyamu & Memeh 2007; Iyamu et al. 2010; Iyamu & Eze 2011; Iyamu & Osuobeni 2012; Iyamu, Iyamu & Amadasun 2013). Possible reasons for this difference could be attributed to the use of a relatively smaller sample (n = 29) that was older (mean age of 63.1 ± 11.2 years) by Mercieca et al. (2007) compared with the other studies involving Nigerian samples (Iyamu & Memeh 2007; Iyamu et al. 2010; Iyamu & Eze 2011; Iyamu & Osuobeni 2012; Iyamu, Iyamu & Amadasun 2013).

Comparable mean CCT measurements of ~530 µm were reported in the studies involving African samples from Cameroon (Eballe et al. 2010), Sudan (Mohamed et al. 2009) and Ghana (Ntim-Amponsah et al. 2012). The studies involving the South African samples consisted of younger participants and reported slightly lower mean CCT measurements

(~519 µm). Apart from the age differences, the use of devices based on Scheimpflug photography to measure CCT may also explain the lower mean CCT measurements observed in the South African samples.

The majority of studies involving African samples reported higher mean CCT measurements in males (Table 3.1). Only two studies (Gelaw et al. 2010; Sardiwalla et al. 2012) reported the opposite trend with slightly higher mean CCT measurements in female than male participants. Moreover in most of the studies (Iyamu & Memeh 2007; Eballe et al. 2010; Gelaw et al. 2010; Iyamu et al. 2010; Iyamu & Osuobeni 2012), these gender differences failed to reach statistical significance with only Mercieca et al. (2007) noting a statistically significant gender difference of 19 µm (541 µm versus 522 µm, $p = 0.035$).

Doughty and Zaman (2000), in their meta-analysis consisting of 300 studies, reported an expected mean CCT measurement of 544 ± 34 µm when using ultrasound pachymetry in normal healthy eyes. Although most of the studies involving African sub-populations have also used ultrasound pachymetry to measure CCT, only the studies involving the Nigerian samples (Iyamu et al. 2010; Iyamu & Eze 2011; Iyamu & Osuobeni 2012; Iyamu, Iyamu & Amadasun 2013) are comparable to the suggested CCT measurement (544 µm). In contrast, the studies (Mohamed et al. 2009; Eballe et al. 2010; Gelaw et al. 2010; Ntim-Amponsah et al. 2012) involving the other African samples have reported considerably lower mean CCT measurements. This observation suggests that, even when ultrasound pachymetry devices are used, there are variations in the mean CCT measurements within the different African sub-populations.

Even though previous studies reporting on CCT measurements in African sub-populations (Table 3.1) have provided useful information, they have some limitations that influence the interpretation of their findings and conclusions. For example, some studies (Mercieca et al. 2007; Iyamu et al. 2010; Iyamu & Osuobeni 2012) have reported on clinic-based samples

that may not be representative of the general population due to their inherent selection bias. Moreover, all studies with the exception of only one (Gelaw et al. 2010) used non-probability convenience sampling to recruit study participants. Other limitations of the studies involving African sub-populations include small sample sizes (Iyamu & Memeh 2007; Mercieca et al. 2007), participants with wide age ranges (Eballe et al. 2010; Gelaw et al. 2010; Ntim-Amponsah et al. 2012), disproportionate number of male and female participants (Mohamed et al. 2009; Eballe et al. 2010; Iyamu & Eze 2011) and contact methods to measure CCT (Iyamu & Memeh 2007; Iyamu et al. 2010). Lastly, none of these studies provided any information related to the sample size estimation except Gelaw et al. (2010) who reported on the power calculation used. Despite these limitations, previous studies that have investigated and reported on CCT measurements in African sub-populations have provided useful information and revealed interesting trends.

Table 3.1: Summary of studies reporting on CCT measurements in African sub-populations

Authors (year)	Country	Sample size (gender allocation)			Age in years		Technique	CCT (µm)		Mean CCT (µm)	
		n	Male	Female	Mean	Range		Mean	Range	Males	Females
Iyamu et al. (2010)	Nigeria	85	49	36	44.65 ± 15.11	20–69	Ultrasound pachymetry	550 ± 36.3	478–662	552.8 ± 38.5	546.3 ± 33.3
Iyamu and Osuobeni (2012)	Nigeria	130	77	53	47.8 ± 16.8	20–79	Ultrasound pachymetry	548.97 ± 34.28	478–662	551.0 ± 37.20	546.06 ± 29.62
Iyamu, Iyamu and Amadasun (2013)	Nigeria	95	56	39	44.9 ± 15.2	20–69	Ultrasound pachymetry	547.0 ± 29.5	487–618	553.2 ± 33.5	542.6 ± 27.8
Iyamu and Memeh (2007)	Nigeria	39	21	18	45.2 ± 15.4	20–75	Ultrasound pachymetry	NR*	NR*	561.8 ± 44.9	541.5 ± 31.1
Iyamu and Eze (2011)	Nigeria	95	56	39	47.1 ± 14.1	20–69	Ultrasound pachymetry	550.1 ± 33.1	478–662	552.0 ± 36.4	544.5 ± 28.8
Mercieca et al. (2007)	Nigeria	29	17	12	63.1 ± 11.2	17–68	Ultrasound pachymetry	535 ± 38	NR*	541 ± 47	522 ± 22
Eballe et al. (2010)	Cameroon	485	163	322	31.4 ± 15.5	5–75	Ultrasound pachymetry	528.74 ± 35.89	440–670	530.27 ± 34.83	527.97 ± 36.41
Gelaw et al. (2010)	Ethiopia	300	184	116	42.57 ± 16.71	18–87	Ultrasound pachymetry	518.68 ± 32.92	430–610	517.96 ± 32.74	519.83 ± 33.31
Sardiwalla et al. (2012)	South Africa	200	100	100	20.1 ± 1.6	18–25	Scheimpflug photography	519.5 ± 38.6	442–642	516.7 ± 40.1	522.3 ± 37.1
Rampersad, Mashige and Jhetam (2011)	South Africa	105	29	76	29.27 ± 14.67	18–82	Scheimpflug photography	518.49 ± 33.01	440–606	NR*	NR*
Mohamed et al. (2009)	Sudan	94	60	34	NR*	NR*	Ultrasound pachymetry	530.15 ± 58.10	420–610	NR*	NR*
Ntim-Amponsah et al. (2012)	Ghana	253	112	141	58 ± 16.1	21–90	Ultrasound pachymetry	530.53 ± 35.64	423–650	NR*	NR*

NR* = not reported
CCT = central corneal thickness

3.2.2 Central corneal thickness in Caucasian sub-populations

Studies have reported on CCT measurements in normal healthy Caucasian populations from countries including Spain, Turkey, Netherlands, Scotland, Iceland, New Zealand and the United States of America. Table 3.2 shows the various studies that have reported on CCT measurements in Caucasian sub-populations (Herse & Yao 1993; Wolfs et al. 1997; Doughty et al. 2002; Eysteinsson et al. 2002; Hahn et al. 2003; Lleó et al. 2003; Sanchis-Gimeno et al. 2004a; Altinok et al. 2007; Gros-Otero, Arruabarrena-Sánchez & Teus 2011). The majority of studies involved Caucasian samples from European sub-populations (Wolfs et al. 1997; Doughty et al. 2002; Eysteinsson et al. 2002; Lleó et al. 2003; Sanchis-Gimeno et al. 2004a; Gros-Otero, Arruabarrena-Sánchez & Teus 2011). These studies included paediatric, young adult, middle-aged adult and elderly adult samples wherein their mean ages ranged between 10.3 years and 72.6 years (Table 3.2).

As seen in Table 3.2, studies involving Caucasian sub-populations have used various methods to measure CCT including ultrasound pachymetry, slit-scanning topography, Scheimpflug photography, specular microscopy and optical pachymetry. Overall, the mean CCT measurements vary from 527 µm to 554 µm with most of the studies reporting standard deviations between 25 µm and 39 µm. The highest and lowest mean CCT measurements were reported in a Spanish and Scottish sample respectively (Doughty et al. 2002; Sanchis-Gimeno et al. 2004a). The mean CCT values (~529 µm) reported for the Northern-European samples (Iceland and Scotland) are lower than the values reported for the Western-European (Netherlands) and Southern-European (Spain) samples of 537.4 µm and 547 µm respectively. This implies that there are variations in mean CCT measurements within the various Caucasian European sub-populations (Table 3.2). Hahn et al. (2003), using ultrasound pachymetry in a sample of 1578 normal healthy participants, reported a mean CCT measurement of 546.5 µm (range, 479.7 µm to 613.4 µm). In an earlier study involving in a paediatric sample, Herse and Yao (1993) measured CCT with an optical pachymeter and reported a mean CCT measurement of 540 ± 25 µm.

In general, higher mean CCT measurements were noted for female participants in all studies involving European Caucasian samples except Sanchis-Gimeno et al. (2004a) and Eysteinsson et al. (2002) where the female participants had 2 µm lower mean CCT measurements than male participants (Table 3.2). Despite using different methods to measure CCT, two studies involving Caucasian sub-populations reported almost identical mean CCT measurements in male and female participants (Herse & Yao 1993; Altinok et al. 2007). In contrast, Hahn et al. (2003) reported a significant gender difference wherein the males had higher mean CCT measurements than females (549.3 µm versus 544.7 µm, p = 0.006). Moreover with the exception of Hahn et al. (2003), the gender differences in mean CCT measurements (range, 2 µm to 15 µm) reported in the other studies involving Caucasian samples failed to reach statistical significance. With the exception of the study by Doughty et al. (2002), all studies that measured CCT with ultrasound pachymetry reported comparable mean CCT values (range from 537.4 µm to 548.21 µm) to the expected CCT measurement (544 µm) when using ultrasound pachymetry (Doughty & Zaman 2000).

The studies involving Caucasian sub-populations have similar limitations to the studies involving African sub-populations. Although the studies involving Caucasian sub-populations have included larger sample sizes than studies involving African sub-populations, the trend of an unequal distribution of male and female participants was observed in almost all studies (Table 3.2). Only one study by Sanchis-Gimeno et al. (2004a) included an equal number of male (n = 500) and female (n = 500) participants. Similar to the studies involving African sub-populations, a wide age range of participants was noted (Eysteinsson et al. 2002; Gros-Otero, Arruabarrena-Sánchez & Teus 2011). However unlike the studies involving African sub-populations which consisted of mainly adult samples, two of the studies involving Caucasian sub-populations included paediatric samples (Herse & Yao 1993; Doughty et al. 2002). Moreover the majority of studies, except three (Herse & Yao 1993; Eysteinsson et al. 2002; Sanchis-Gimeno et al. 2004a), also used ultrasound pachymetry devices to measure CCT. Some studies included clinic-based (Doughty et al.

2002) and hospital-based (Gros-Otero, Arruabarrena-Sánchez & Teus 2011) samples with limited information on the sampling method and sample size estimation techniques used. Nevertheless, the studies reporting on CCT measurements in Caucasian sub-populations have revealed useful information and interesting trends.

Table 3.2: Summary of studies reporting on CCT measurements in Caucasian sub-populations

Authors (year)	Country	Sample size (gender allocation)			Age in years		Technique	CCT (µm)		Mean CCT (µm)	
		n	Male	Female	Mean	Range		Mean	Range	Males	Females
Gros-Otero, Arruabarrena-Sánchez and Teus (2011)	Spain	357	207	150	39.2 ± 13	15–76	Ultrasound pachymetry	548.21 ± 30.7	464–633	546.2 ± 31.8	552.0 ± 29.3
Sanchis-Gimeno et al.(2004a)	Spain	1000	500	500	27.12 ± 2.86	20–30	Slit-scanning topography	554 ± 16	518–589	555 ± 16	553 ± 15
Lleó et al. (2003)	Spain	500	247	253	31 ± 7.94	18–67	Ultrasound pachymetry	546.9 ± 42.42	400–675	542.34 ± 43.84	551.34 ± 40.58
Eysteinsson et al. (2002)	Iceland	925	415	510	NR*	50–85	Scheimpflug photography	529 ± 39	NR*	528 ± 41	526 ± 37
Wolfs et al. (1997)	Nether-Lands	352	199	153	72.0 ± 1.21	55.1–90.2	Ultrasound pachymetry	537.4	427–620	NR*	NR*
Doughty et al. (2002)	Scotland	104	60	44	10.3 ± 3.1	5–15	Ultrasound pachymetry	529 ± 34	441–615	526 ± 36	533 ± 30
		75	75	0	46.1 ± 8.2	32–60	Specular Microscopy	533 ± 33	451–615	533 ± 33	
		91	39	52	72.6 ± 5.1	61–83	Ultrasound pachymetry	527 ± 34	451–625	519 ± 34	534 ± 33
Altinok et al. (2007)	Turkey	625	276	349	NR*	6–88	Ultrasound pachymetry	NR*	NR*	552.2 ± 35.9	552.3 ± 35.4
Hahn et al. (2003)	United States of America	1578	634	944	53.9 ± 10.5	40–70+	Ultrasound pachymetry	546.5 ± 33.5	479.7–613.4	549.3	544.7
Herse and Yao (1993)	New Zealand	1082	515	567	NR*	5–20	Optical pachymetry	540 ± 25	NR*	541 ± 26	540 ± 25

NR* = not reported
CCT = central corneal thickness

3.2.3 Central corneal thickness in Asian sub-populations

Studies have reported on CCT measurements in normal healthy populations from Asian countries including China, Singapore, Japan, Iran, Pakistan, Nepal and India. Moreover, these studies have been conducted in the different Asian regions as classified by the World Health Organization (World Health Organization 2015). The studies undertaken in the different Asian regions including South-Eastern Asia, Eastern-Asia and South-Central Asia are shown in Table 3.3. More than 80% of the studies involved Eastern-Asian and South-Central Asian sub-populations with seven studies each being conducted in these regions.

The distribution of mean CCT measurements among South-Eastern Asian sub-populations ranged between 522 µm and 561 µm (Casson et al. 2008; Ang et al. 2012). This is interesting as the mean age of participants in these three population-based studies are similar yet varying CCT measurements were reported (Casson et al. 2008; Su et al. 2009; Ang et al. 2012). Moreover, two of these studies used ultrasound pachymetry to measure CCT with the difference in mean CCT measurements being ~19.4 µm (Casson et al. 2008, Su et al. 2009). In contrast, Ang et al. (2012) reported a slightly higher mean CCT measurement that may be explained by the use of a different method (OCT) to measure CCT (Table 3.3). The mean CCT measurements were similar for male and female participants in all three studies involving South-Eastern Asian sub-populations (Casson et al. 2008; Su et al. 2009; Ang et al. 2012).

The studies involving Eastern-Asian sub-populations used several methods to measure CCT and included young to elderly aged adult samples (Table 3.3). There appears to be variability in the mean CCT measurements for the Eastern-Asian sub-populations with values ranging between 518 µm and 575 µm (Table 3.3). The two population-based studies involving Japanese samples, which used specular microscopy to measure the CCT, reported the lowest mean CCT measurements (Suzuki et al. 2005; Kawase et al. 2008). Despite using different methods to measure CCT, comparable mean values (range, 549 µm

to 575 µm) were noted in the other Eastern-Asian samples (Cho & Lam 1999; Li et al. 2006). Overall, males had higher mean CCT measurements than females although these gender differences were statistically significant ($p \leq 0.001$) in only three studies (Suzuki et al. 2005; Li et al. 2006; Zhang et al. 2008).

The studies involving South-Central Asian sub-populations included predominantly middle-aged adult samples. With the exception of only two studies (Hashemi et al. 2009; Hashemi et al. 2011), all studies used ultrasound pachymetry to measure CCT. Overall, the mean CCT measurements ranged between 511 µm and 556 µm (Hashemi et al. 2009; Vijaya et al. 2010). The two studies involving the Indian samples (Nangia et al. 2010; Vijaya et al. 2010) reported the lowest mean CCT measurements (511 µm and 514 µm). One study from India (Malik et al. 2010) reported a mean CCT of 545 µm which is higher than the values reported in the other studies involving Indian samples (Nangia et al. 2010; Vijaya et al. 2010). The study by Malik et al. (2010) consisted of a considerably smaller sample ($n = 150$) than the other Indian samples which may explain this discrepancy despite their use of the same method (ultrasound pachymetry) to measure CCT. With the exception of one study (Hashemi et al. 2009), all studies conducted in South-Central Asia reported higher mean CCT measurements in males than females (Table 3.3). However in majority of the studies, these gender differences failed to reach statistical significance with only two studies (Nangia et al. 2010; Vijaya et al. 2010) reporting significantly higher (~7 µm) mean CCT measurements in males ($p < 0.001$).

Although more studies have been conducted in Asian sub-populations, the limitations associated with these studies are similar to the studies involving African and Caucasian sub-populations. These include the use of ultrasound pachymetry to measure CCT (Casson et al. 2008; Malik et al. 2010), focus on mainly middle-aged to elderly adult samples (Suzuki et al. 2005; Yuen et al. 2010; Hashemi et al. 2011), a wide age range of participants (Chen et al. 2009, Thapa et al. 2012) and an unequal number of male and female participants

(Suzuki et al. 2005; Casson et al. 2008). In contrast to the studies involving African and/or Caucasian sub-populations, many of the Asian studies used probability sampling methods such as random (Su et al. 2009; Ang et al. 2012), systematic random (Yuen et al. 2010) and cluster (Thapa et al. 2012) sampling. However, these sampling methods are expected as most of the Asian studies were population-based cross-sectional studies (Yuen et al. 2010; Ang et al. 2012; Thapa et al. 2012). In spite of the limitations associated with the studies that have investigated and reported on CCT measurements in Asian sub-populations, these studies have provided useful information and showed interesting trends.

Table 3.3: Summary of studies reporting on CCT measurements in Asian sub-populations

Authors (year)	Country	Sample size (gender allocation)			Age in years		Technique	CCT (µm)		Mean CCT (µm)	
		n	Male	Female	Mean	Range		Mean	Range	Males	Females
Region: South-Eastern Asia											
Casson et al. (2008)	Myanmar	1909	756	1153	56.2 ± 11.5	40–70+	Ultrasound pachymetry	521.9 ± 33.3	409–640	522.0 ± 32.8	521.9 ± 33.2
Ang et al. (2012)	Singapore	438	222	216	58.5 ± 9.9	40–80	Optical coherence tomography	561.37 ± 34.07	NR*	559.74 ± 35.40	563.05 ± 32.64
Su et al. (2009)	Singapore	3091	1485	1606	58.7 ± 11.0	40–80	Ultrasound pachymetry	541.3 ± 33.4	NR*	540.7 ± 32.9	541.9 ± 33.9
Region: Eastern-Asia											
Suzuki et al. (2005)	Japan	7313	2848	4465	56.7 ± 9.4	40–89	Specular microscopy	517.5 ± 29.8	398–640	521.5 ± 30.3	514.4 ± 29.0
Kawase et al. (2008)	Japan	2597	1154	1443	57.0 ± 11.0	40–92	Specular microscopy	520 ± 32	387–647	525 ± 32	516 ± 32
Cho and Lam (1999)	Hong Kong	151	72	79	28.6 ± 11.3	10–60	Ultrasound pachymetry	575 ± 32	NR*	575 ± 31	574 ± 33
Li et al. (2006)	China	1669	880	789	23.8 ± 5.9	17–48	Ultrasound pachymetry	548.58 ± 34.27	NR*	551.33 ± 34.62	545.52 ± 33.63
Zhang et al. (2008)	China	3100	1342	1758	56.20 ± 10.59	40–101	Optical coherence tomography	556.2 ± 33.1	429–688	560 ± 33.7	554 ± 33.0
Yuen et al. (2010)	China	750	349	401	63.3 ± 7.9	50–90	Optical coherence tomography	562.39 ± 31.85	474–664	563.25 ± 32.97	561.64 ± 30.87
Chen et al. (2009)	Taiwan	500	274	226	60.9 ± 11.2	40–80	Ultrasound pachymetry	554 ± 29	NR*	555 ± 27	553 ± 30

NR* = not reported
CCT = central corneal thickness

Table 3.3: Summary of studies reporting on CCT measurements in Asian sub-populations (continued)

Authors (year)	Country	Sample size (gender allocation)			Age in years		Technique	CCT (µm)		Mean CCT (µm)	
		n	Male	Female	Mean	Range		Mean	Range	Males	Females
Region: South-Central Asia											
Hashemi et al. (2009)	Iran	399	156	243	40.9 ± 16.9	14–81	Slit-scanning topography	555.6 ± 39.9	389–660	555.0 ± 37.1	556.2 ± 42.7
Hashemi et al. (2011)	Iran	3820	1555	2265	50.7 ± 6.2	40–64	Scheimpflug photography	528.5 ± 35.8	NR*	NR*	NR*
ul Hassan et al. (2010)	Pakistan	250	130	120	NR*	40–60	Ultrasound pachymetry	NR*	438–623	529.5 ± 33.6	524.1 ± 33.3
Thapa et al. (2012)	Nepal	2330	1090	1240	51.3 ± 9.56	40–80+	Ultrasound pachymetry	539.10 ± 33.73	NR*	540.54 ± 34.60	537.84 ± 32.91
Malik et al. (2010)	India	150	66	84	42.64 ± 13.63	20–70	Ultrasound pachymetry	544.73 ± 30.46	NR*	547.90 ± 29	542.30 ± 31
Nangia et al. (2010)	India	4711	2191	2520	49.1 ± 13.2	30–100	Ultrasound pachymetry	514 ± 33	290–696	518 ± 34	511 ± 33
Vijaya et al. (2010)	India	6754	3020	3734	NR*	40–70	Ultrasound pachymetry	511.4 ± 33.5	376–826	515.6 ± 33.8	508.0 ± 32.8

NR* = not reported
CCT = central corneal thickness

3.2.4 Central corneal thickness in two or more race groups

Studies have compared CCT measurements in two or more normal healthy populations from countries such as the United States of America, South Africa, Malaysia, Israel, France and Australia. Table 3.4 shows the various studies that have compared CCT measurements in two or more race groups (La Rosa, Gross & Orengo-Nania 2001; Shimmyo et al. 2003; Aghaian et al. 2004; Lifshitz et al. 2006; Durkin et al. 2007; Landers et al. 2007; Torres et al. 2008; Modh-Ali, Ching & Latif 2009; Sardiwalla et al. 2012; Lazreg et al. 2013).

As seen in Table 3.4, there are variations in mean CCT measurements among the different race groups even when the same research methodology, particularly the method used to measure CCT, has been used to conduct the study. Studies that compared the mean CCT measurements among Caucasians, Asians, Hispanics and African-Americans have reported significantly thinner measurements in the latter race group (La Rosa, Gross & Orengo-Nania 2001; Shimmyo et al. 2003; Aghaian et al. 2004; Torres et al. 2008). The mean CCT measurement in African-Americans ranged between 525 µm and 535 µm (Shimmyo et al. 2003; Aghaian et al. 2004) which is lower than the reported mean CCT measurement (range, 541 µm to 563 µm) in Caucasians (Aghaian et al. 2004; Landers et al. 2007).

The same racial trend in mean CCT measurements is also observed when paediatric samples and individuals with glaucoma are considered. Four studies (Hussein et al. 2004; Dai & Gunderson 2006; Muir et al. 2006; Haider et al. 2008) involving paediatric samples, compared CCT measurements between Caucasians and African-Americans and/or Blacks and concluded that Caucasians have thickest mean CCT measurements (Hussein et al. 2004; Dai & Gunderson 2006; Muir et al. 2006; Haider et al. 2008). In the OHTS, Brandt et al. (2001) reported that the mean CCT value in African-American participants was 23 µm thinner than the mean CCT value in Caucasian participants (555.7 µm versus 579.0 µm, $p < 0.0001$). Similarly Nemesure et al. (2003), in the Barbados eye study, also reported

lower mean CCT measurements in Black participants (529.8 µm) than Caucasian participants (545.2 µm).

Differences in mean CCT measurements have also been reported in studies involving two race groups conducted outside the United States of America. Two studies compared CCT measurements between Australian Caucasian and Aboriginal individuals (Durkin et al. 2007; Landers et al. 2007). Both studies (Durkin et al. 2007; Landers et al. 2007) concluded that Caucasian individuals had significantly higher mean CCT measurements (≥ 541 µm) than the Aboriginal individuals (≤ 516 µm). Moreover, the racial differences in mean CCT measurements reported by Durkin et al. (2007) and Landers et al. (2007) were 31 µm and 33 µm respectively (Table 3.4). Differences in CCT measurements are also apparent among the various Asian sub-populations wherein Aghaian et al. (2004) reported significantly thinner mean CCT measurements in Japanese (539 µm) than in Chinese (570 µm) and Filipino (559 µm) participants (Table 3.4). Similar differences in mean CCT measurements, determined with ultrasound pachymetry, were also reported between Malay and Chinese individuals (Mohd-Ali, Ching & Latif 2009).

Three studies have been conducted in Africa wherein CCT measurements were compared between two race groups (Lifshitz et al. 2006; Sardiwalla et al. 2012; Lazreg et al. 2013). In South Africa, Sardiwalla et al. (2012) measured CCT using Scheimpflug photography on 200 young adults. The mean CCT measurement was significantly higher in Indian individuals (527 µm) than in Black individuals (512 µm) ($p = 0.01$). While contributing to the knowledge of CCT measurements in South Africa, the work of Sardiwalla et al. (2012) used non-probability convenience sampling to recruit study participants which limits the generalisability of the study findings and conclusions. The two other African studies (Lifshitz et al. 2006; Lazreg et al. 2013) concluded that the mean CCT measurements in North-African participants were significantly thinner than their European counterparts (French and Russian).

Two studies (Shimmyo et al. 2003; Torres et al. 2008) reported significant gender differences in mean CCT measurements. Shimmyo et al. (2003) reported that male participants showed significantly higher mean CCT measurements than female participants (554 µm versus, 548 µm, $p < 0.001$). Moreover, Torres et al. (2008) reported than American Indian females had significantly higher mean CCT measurements than their male counterparts (558 µm versus 550 µm, $p = 0.03$). The other studies reported inconsistent gender differences in mean CCT measurements. For example, Sardiwalla et al. (2012) reported higher mean CCT measurements in Black males and Indian females than in Black females and Indian males respectively, although these gender differences (range, 2 µm to 13 µm) were insignificant. Despite also reporting insignificant gender differences in mean CCT measurements for Caucasian participants, Aghaian et al. (2004) reported higher measurements in males while Durkin et al. (2007) reported higher measurements in females (Table 3.4).

Overall, there is variation in mean CCT measurements among the different race groups (Table 3.4). Thinner mean CCT measurements have been reported in African-American, Japanese, Aboriginal and Black individuals compared with Caucasian, Chinese, Filipino and Indian individuals (La Rosa, Gross & Orengo-Nania 2001; Shimmyo et al. 2003; Aghaian et al. 2004; Durkin et al. 2007; Landers et al. 2007; Sardiwalla et al. 2012). However, these comparisons and variations should be interpreted with caution as other factors (age, refractive errors, gender distribution and corneal pachymetry devices) may influence the CCT measurements.

Table 3.4: Summary of studies reporting on CCT measurements in two or more race groups

Authors (year)	Country	Technique	Race	Sample size (gender allocation)			Mean age in years	Mean CCT (µm)	Mean CCT (µm)	
				n	Male	Female			Males	Females
Aghaian et al. (2004)	United States of America	Ultrasound pachymetry	Caucasian	36	NR*	NR*	69.1 ± 14.4	562.8 ± 31.1	544.8 ± 37.6*	541.3 ± 37.1*
			Hispanic	27	NR*	NR*	67.5 ± 16.2	563.6 ± 29.1		
			African-American	26	NR*	NR*	62.6 ± 16	524.8 ± 38.4		
			Chinese	41	NR*	NR*	65.9 ± 18.3	569.5 ± 31.8		
			Filipino	33	NR*	NR*	67.6 ± 16	559.0 ± 24.9		
			Japanese	38	NR*	NR*	70.2 ± 13	538.5 ± 29.6		
Shimmyo et al. (2003)	United States of America	Ultrasound pachymetry	Caucasian	1466	NR*	NR*	38.08 ± 9.86	552.59 ± 34.48	553.98 ± 34.37*	547.72 ± 34.48*
			African-American	116	NR*	NR*	37.20 ± 9.78	535.46 ± 33.39		
			Hispanic	203	NR*	NR*	34.21 ± 9.38	551.10 ± 35.54		
			Asian	170	NR*	NR*	34.84 ± 7.29	549.79 ± 32.30		
Torres et al. (2008)	United States of America	Ultrasound pachymetry	Caucasian	46	17	29	54.7 ± 9.6	551.9 ± 28.3	NR*	NR*
			African-American	33	15	18	53.0 ± 9.2	528.5 ± 33.2	NR*	NR*
			American Indian	429	159	270	55.7 ± 11.6	554.8 ± 33.9	550.1 ± 34.5	557.6 ± 33.3
La Rosa, Gross and Orengo-Nania (2001)	United States of America	Ultrasound pachymetry	Caucasian	51	NR*	NR*	65.2 ± 10.3	RE: 555.9 ± 33.2 LE: 555.7 ± 31.6		
			African-American	26	NR*	NR*	63.1 ± 11.8	RE: 533.8 ± 33.9 LE: 534.1 ± 31.8		

NR* = not reported
CCT = central corneal thickness
***** implies for the entire sample
RE = right eye
LE= left eye

Table 3.4: Summary of studies reporting on CCT measurements in two or more race groups (continued)

Authors (year)	Country	Technique	Race	Sample size (gender allocation)			Mean age in years	Mean CCT (µm)	Mean CCT (µm)	
				n	Male	Female			Males	Females
Sardiwalla et al. (2012)	South Africa	Scheimpflug photography	Black	100	50	50	20.2 ± 1.7	512.4 ± 38.9	513.2 ± 41.3	511.6 ± 36.7
			Indian	100	50	50	19.9 ± 1.4	526.5 ± 37.2	520.1 ± 39.0	533.0 ± 34.7
Mohd-Ali, Ching and Latif (2009)	Malaysia	Ultrasound pachymetry	Chinese	43	24	19	20.34 ± 1.14	565.61 ± 34.49	NR*	NR*
			Malay	41	9	32	22.46 ± 0.88	625.04 ± 77.73	NR*	NR*
Lifshitz et al. (2006)	Israel	Ultrasound pachymetry	Mixed	119	52	67	32.4 ± 10.5	545.36 ± 30.44	NR*	NR*
			North African	85	32	53	35.9 ± 11.5	518.87 ± 31.53	NR*	NR*
Lazreg et al. (2013)	France	Scheimpflug photography	French	221	98	123	34.1 ± 9.4	553 ± 38	NR*	NR*
			North African	1662	630	1032	35.6 ± 10.9	518 ± 36	NR*	NR*
Durkin et al. (2007)	Australia	Ultrasound pachymetry	Caucasian	115	51	64	47.2 ± 14.8	RE: 544.6 ± 31.9 LE: 547.1 ± 32.2	542.6 ± 31	546.3 ± 32.7
			Aboriginal	189	80	109	44.8 ± 14.5	RE: 514.9 ± 30.5 LE: 515.6 ± 30.5	515.8 ± 26	514.4 ± 33.6
Landers et al. (2007)	Australia	Ultrasound pachymetry	Caucasian	84	38	46	56 ± 15	RE: 541 ± 31 LE: 543 ± 33	NR*	NR*
			Aboriginal	91	26	65	51 ± 14	RE: 508 ± 33 LE: 510 ± 34	NR*	NR*

NR* = not reported
CCT = central corneal thickness
RE = right eye
LE = left eye

3.3 STUDIES INVESTIGATING PERIPHERAL CORNEAL THICKNESS

This section presents a summary of previous studies that have reported on peripheral corneal thickness measurements in normal healthy populations across the world. Many studies have reported on CCT measurements in different countries (section 3.2), however only a few studies have reported on corneal thickness measurements beyond the central cornea. Table 3.5 shows the previous studies that investigated and reported on peripheral corneal thickness variables (Liu, Huang & Pflugfelder 1999; Módis, Langenbucher & Seitz 2004; Khoramnia, Rabsilber & Auffarth 2007; Rüfer et al. 2007; Zheng et al. 2008; Hashemi et al. 2009; Mohd-Ali, Ching & Latif 2009; Keech, Simpson & Jones 2010; Hashemi et al. 2011; Fares et al. 2012; Huang et al. 2014; Ortiz et al. 2014; Randleman et al. 2015).

As shown in Table 3.5, all studies with the exception of only one (Mohd-Ali, Ching & Latif 2009) measured corneal thickness using non-contact corneal pachymetry methods. Doughty and Zaman (2000), in their meta-analysis, concluded that studies investigating peripheral corneal thickness measurements are inconsistent in their definition and delineation of the area that constitutes the peripheral cornea. All studies presented in Table 3.5, with the exception of only one (Mohd-Ali, Ching & Latif 2009), defined the peripheral cornea as the area corresponding to a 3 mm radius from the central cornea (Liu, Huang & Pflugfelder 1999; Rüfer et al. 2007; Zheng et al. 2008; Ortiz et al. 2014; Randleman et al. 2015). Moreover within this area, four quadrants corresponding to the superior, inferior, nasal and temporal cornea were measured. All except three studies (Mohd-Ali, Ching & Latif 2009; Rüfer et al. 2007; Ortiz et al. 2014) also reported on the mean corneal thickness at the thinnest point (minimum corneal thickness) in addition to the peripheral corneal thickness measurements. Moreover, all studies shown in Table 3.5 also reported on the mean CCT measurements.

As expected, the mean CCT measurement was the thinnest (excluding the minimum corneal thickness) and the corneal thickness measurements increased towards the peripheral

cornea (Table 3.5). In some studies, the CCT measurement was significantly thinner than the four peripheral corneal thickness measurements (Módis, Langenbucher & Seitz 2004; Sanchis-Gimeno et al. 2004a). In all of the studies (n = 13), the temporal quadrant had the thinnest peripheral corneal thickness measurement (Table 3.5). The superior quadrant was identified as the thickest quadrant in more than 75% of the studies with only three studies (Módis, Langenbucher & Seitz 2004; Rüfer et al. 2007; Mohd-Ali, Ching & Latif 2009) noting the nasal quadrant as the thickest. Moreover in nine studies, the superior cornea was thickest followed by the nasal, inferior and temporal cornea (Hashemi et al. 2009; Keech, Simpson & Jones 2010; Hashemi et al. 2011; Fares et al. 2012; Ortiz et al. 2014). This order of the quadrants with decreasing corneal thickness measurements was also observed in a paediatric sample (Zheng et al. 2008).

In all studies (n = 10), the mean minimum corneal thickness was thinner (range, 2.6 µm to 15.7 µm) than the mean CCT measurement (Módis, Langenbucher & Seitz 2004; Zheng et al. 2008). Moreover, the thickness difference between the mean CCT and minimum corneal thickness was statistically significant in some studies (Hashemi et al. 2009; Rüfer et al. 2009; Hashemi et al. 2011; Sanchis-Gimeno, Sanchez-Zuriaga & Martinez-Soriano 2012). Despite using different methods to measure corneal thickness such as Scheimpflug photography (Hashemi et al. 2011; Fares et al. 2012), slit-scanning topography (Liu, Huang & Pflugfelder 1999; Hashemi et al. 2009) and OCT (Keech, Simpson & Jones 2010), the location of the thinnest point on the cornea was most often in the inferotemporal quadrant. The next most common location of the thinnest point on the cornea were the superotemporal and inferonasal quadrants (Liu, Huang & Pflugfelder 1999; Zheng et al. 2008; Mohd-Ali, Ching & Latif 2009).

In the study by Fares et al. (2012), peripheral corneal thickness measurements were also reported at a 7 mm radius from the central cornea. In this study, the nasal quadrant was found to be the thickest (mean 676.78 ± 42.62 µm, range 582 µm to 761 µm) followed by

the superior (mean 671.22 ± 44.28 µm, range 571 µm to 766 µm), inferior (mean 664.21 ± 41.80 µm, range 586 µm to 763 µm) and temporal (mean 639.15 ± 34.59 µm, range 553 µm to 730 µm) quadrants (Fares et al. 2012). Overall, no significant gender differences were noted for either the minimum corneal thickness (Hashemi et al. 2009; Rüfer et al. 2009; Sanchis-Gimeno, Sanchez-Zuriaga & Martinez-Soriano 2012) or the peripheral corneal thickness (Sanchis-Gimeno et al. 2004a) measurements.

Table 3.5: Summary of studies reporting on peripheral corneal thickness measurements

Authors (year)	Sample size (gender allocation)			Age in years		Technique	Mean corneal thickness (µm)					
	n	Male	Female	Mean	Range		CCT	Minimum	Superior	Inferior	Nasal	Temporal
Keech, Simpson and Jones (2010)	25	8	17	32 ± 12	19–58	Optical coherence tomography	537 ± 31.1	526.4 ± 33.1	564 ± 33.7	543 ± 32.4	563 ± 32.5	540 ± 32.3
Randleman et al. (2015)	50	28	22	32 ± 10	18–58	Optical coherence tomography	550.5	542.6	574.8	557.4	567.3	554.3
Huang et al. (2014)	66	33	33	35.4 ± 10.1	18–55	Optical coherence tomography	532.8 ± 26.2	528.1 ± 26.5	542.4 ± 26.6	533.4 ± 26.8	540.0 ± 26.8	533.2 ± 26.3
Hashemi et al. (2011)	3820	NR*	NR*	50.7 ± 6.2	40–64	Scheimpflug photography	528.5 ± 35.8	525.5 ± 35.9	635.5 ± 41.9	608.2 ± 39.8	611.7 ± 43.2	601.0 ± 40.4
Khoramnia, Rabsilber and Auffarth (2007)	67	46	30	46.6 ±16.8	18–77	Scheimpflug photography	538.5 ± 32.3	535.4 ± 33.2	642.1 ± 40.2	608.1 ± 35.0	615.3 ± 34.3	598.5 ± 31.6
Fares et al. (2012)	40	24	16	38.7 ± 14.6	19–76	Scheimpflug photography	550.2 ± 33.8	547.3 ± 34.6	581.6 ± 33.4	576.97 ± 35.3	577.9 ± 31.5	562.7 ± 35.98
Zheng et al. (2008)	926	442	484	11.7 ± 2.6	8–16	Scheimpflug photography	550.7 ± 32.8	548.1 ± 32.8	656.0 ± 38.7	627.9 ± 36.6	642.1 ± 37.3	612.5 ± 36.3
	662	274	388	42.2 ± 5.0	30–68		537.0 ± 29.4	533.2 ± 30	643.6 ± 37.2	613.8 ± 32.4	624.5 ± 35	605.7 ± 33.4

NR* = not reported
CCT = central corneal thickness

Table 3.5: Summary of studies reporting on peripheral corneal thickness measurements (continued)

Authors (year)	Sample size (gender allocation)			Age in years		Technique	Mean corneal thickness (µm)					
	n	Male	Female	Mean	Range		CCT	Minimum	Superior	Inferior	Nasal	Temporal
Mohd-Ali, Ching and Latif (2009)	84	33	51	21.4 ± 1.5	NR*	Ultrasound pachymetry	596.0 ± 45.7	NR	682.3 ± 67.0	691.8 ± 61.6	711.5 ± 51.7	675.2 ± 74.3
Liu, Huang and Pflugfelder (1999)	51	NR*	NR*	47.32 ± 14.1	23–78	Slit-scanning topography	560 ± 30	550 ± 30	640 ± 30	630 ± 30	610 ± 30	590 ± 30
Ortiz et al. (2014)	175	68	107	36.4 ± 9.3	18–67	Slit-scanning topography	544 ± 37	NR*	626 ± 38	608 ± 38	621 ± 38	595 ± 38
Rüfer et al. (2007)	390	242	148	40.7 ± 16.3	10–80	Slit-scanning topography	595 ± 41	NR*	688 ± 42	667 ± 40	689 ± 46	655 ± 42
Hashemi et al. (2009)	399	155	244	40.9 ± 16.9	14–81	Slit-scanning topography	555.6 ± 39.9	550.7 ± 40.6	652.1	634.9	649.8	622.1
Módis, Langenbucher and Seitz (2004)	44	24	20	61.43 ± 16.4	NR*	Slit-scanning topography	593.7 ± 54.2	578 ± 50.5	678 ± 42.3	665.7 ± 40.2	679.5 ± 49.7	655.7 ± 52

NR* = not reported
CCT = central corneal thickness

3.4 FACTORS THAT AFFECT CORNEAL PACHYMETRY MEASUREMENTS

Knowledge of the influence of demographic and ocular factors on corneal pachymetry measurements could assist in understanding the mechanisms of ocular anomalies and diseases. Consequently, research studies that have investigated corneal pachymetry measurements have linked certain demographic and ocular factors with corneal pachymetry measurements. Some of the factors that affect corneal pachymetry variables include age, gender, race and ocular variables such as IOP, refractive error as well as axial length. Other miscellaneous factors include systemic conditions, glaucoma and the method used to measure corneal thickness. A brief discussion of the influence of these factors on corneal pachymetry variables is outlined below.

a. Age

According to Ehlers and Hjortdal (2004), corneal thickness reaches normal adult values during the first two years of life whereas Hussein et al. (2004) suggested that this happens by the age of five years. The influence of age on corneal thickness variables is inconsistent as contradictory results have been reported in the literature. Some studies involving Asian samples have reported that CCT measurements decrease with increasing age (Hashemi et al. 2009; Su et al. 2009; Nangia et al. 2010; Yuen et al. 2010; Hashemi et al. 2011). It is theorised that age-related changes in the corneal stroma including the decrease in keratocyte density and breakdown of collagen fibrils may account for the thinner CCT measurements observed in older individuals (Faragher et al. 1997).

In contrast, other studies have found no relationship between age and CCT measurements (Herse & Yao 1993; Eysteinsson et al. 2002; Khoramnia, Rabsilber & Auffarth 2007; Zheng et al. 2008; Malik et al. 2010) while a few studies have reported an increase in CCT measurements with increasing age (Cosar & Sener 2003; Rüfer et al. 2007). The literature regarding corneal thickness measurements beyond the central cornea is just as inconsistent with some studies (Rüfer et al. 2007; Hashemi et al. 2011) reporting that peripheral corneal

thickness measurements decrease significantly with age while another study suggested that peripheral corneal thickness measurements are not influenced by age (Khoramnia, Rabsilber & Auffarth 2007).

b. Gender

The relationship between gender and corneal thickness measurements has been investigated previously although all possible patterns of gender differences have been reported. Some studies (Hahn et al. 2003; Nemesure et al. 2003; Zhang et al. 2008; Nangia et al. 2010; Vijaya et al. 2010) have found thicker CCT measurements in males, other studies (Torres et al. 2008; Hashemi et al. 2009; Gelaw et al. 2010) have found thicker CCT measurements in females and some studies (Eysteinsson et al. 2002; Nemesure et al. 2003; Altinok et al. 2007; Zheng et al. 2008; Yuen et al. 2010) reported no gender difference. These gender discrepancies may be accounted for by differences in study methodologies particularly the study inclusion criteria as well as the gender and age distributions of the study samples. Moreover, it is likely that unequal sample sizes may also account for some of the differences noted. Limited studies have investigated gender differences in corneal thickness measurements beyond the central cornea with one study (Rüfer et al. 2007) reporting no gender differences for peripheral corneal thickness measurements.

c. Race

A broad range of CCT measurements have been reported in normal healthy individuals of different race groups. Studies have shown that CCT measurements vary in different race groups when measured using the same method and under the same study conditions. Overall, studies have reported statistically significant differences in mean CCT measurements among different race groups ranging from 14 um to 45 um (Shimmyo et al. 2003; Aghaian et al. 2004). Moreover, Caucasian, Chinese and Hispanic individuals have thicker mean CCT measurements than African-American and Japanese individuals (Brandt et al. 2001; La Rosa, Gross & Orengo-Nania 2001; Shimmyo et al. 2003; Aghaian et al.

2004). Differences in the composition of the corneal stroma (collagen fibrils and interfibrillary substance) are thought to be a possible mechanism for the varying corneal thickness measurements (Ehlers & Hjortdal 2004). It is also likely that the differences in mean CCT measurements observed in the different race groups may be partially explained by genetic differences (Dimasi, Burdon & Craig 2010).

d. Ocular variables

Throughout the literature ocular variables including IOP and refractive error have been associated with corneal pachymetry measurements. The relationship between IOP and CCT is well known wherein several studies have reported higher IOP values in eyes with thicker CCT measurements (Zhang et al. 2008; Su et al. 2009; ul Hassan et al. 2010; Nangia et al. 2010; Vijaya et al. 2010). Two studies (Iyamu et al. 2010; Iyamu & Osuobeni 2012) found no relationship between CCT and IOP measurements when the latter was measured with a Keeler Pulsair tonometer.

Contradictory results have been reported for the relationship between refractive error and CCT. The majority of studies have reported that CCT is not associated with refractive error (Fam et al. 2006; Iyamu & Memeh 2007; Zhang et al. 2008; Chen et al. 2009; Hashemi et al. 2009; Su et al. 2009; Nangia et al. 2010). In contrast, other studies have noted that myopes have thinner mean CCT measurements than emmetropes and hyperopes (Nemesure et al. 2003; Mohamed et al. 2009; Mohd-Ali, Ching & Latif 2009; Hashemi et al. 2011; Zha et al. 2013).

Other ocular variables that may influence corneal thickness measurements include axial length and corneal curvature. Some studies have noted longer axial lengths in eyes with thinner CCT measurements (Nangia et al. 2010; Iyamu & Osuobeni 2012). Some researchers have noted flatter corneal curvatures in eyes with thinner CCT measurements (Altinok et al. 2007; Su et al. 2009), although the explanation for this association is unclear.

Other ocular variables such as corneal diameter and lens thickness have also been related to CCT measurements (Henriques et al. 2004; Nangia et al. 2010), but these factors were not within the scope of the present study.

e. Other factors

Thicker CCT measurements have been reported in individuals with diabetes (Goldich et al. 2009; Oriowo 2009). It is well established that corneal thickness measurements vary among the different glaucoma disorders (Wolfs et al. 1997; Gelaw 2012). For example, higher CCT measurements have been reported in individuals with ocular hypertension than in non-glaucomatous individuals (Brandt et al. 2001; Gordon et al. 2002; Brandt 2004) whereas lower CCT measurements have been found in individuals with low-tension and normal tension glaucoma (Gordon et al. 2002; Aghaian et al. 2004). The use of ultrasound pachymetry devices may also influence corneal thickness measurements due to manual placement (by the examiner) and direct contact of the ultrasound probe on the corneal surface (Mohan et al. 2007).

3.5 CONCLUSION TO THE CHAPTER

This chapter reviewed the literature on corneal pachymetry variables which included selected studies that have investigated and reported on corneal pachymetry measurements. Preference was given to studies that included larger sample sizes and used non-contact methods to measure the corneal thickness variables. The review suggests that there is considerable data on corneal pachymetry measurements, particularly in developed countries in Europe, America and Asia. In contrast, only a few studies have investigated corneal pachymetry in African countries and have relied almost exclusively on ultrasound pachymetry to measure corneal thickness. No studies involving African samples have reported on corneal thickness measurements beyond the central cornea. In Africa, ocular diseases and refractive errors are common clinical findings. Consequently, knowledge of the normal anterior segment ocular biometry variables is needed to understand the

mechanisms of ocular anomalies and diseases. In light of this knowledge gap related to corneal pachymetry variables in African populations, the present study aimed to provide a clinical description of central and peripheral corneal thickness measured using OCT in a South African young adult population. This clinical description facilitated the development of a clinical biometric guideline with normal reference intervals for central and peripheral corneal pachymetry variables.

CHAPTER 4: LITERATURE REVIEW – ANTERIOR CHAMBER ANGLE WIDTH

4.1 INTRODUCTION TO THE CHAPTER

This chapter focuses on the literature regarding ACA width variables. This includes a review of previous studies that have reported on ACA width variable measurements and a brief discussion of the factors known to affect these measurements. The chapter ends with a summary of the current knowledge regarding ACA width variables. The review presented in this chapter provides the context for this study particularly for the interpretation of the ACA width variable results.

4.2 STUDIES INVESTIGATING ANTERIOR CHAMBER ANGLE WIDTH

This section presents a summary of previous studies that have investigated and reported on ACA width variables (AOD500 and TIA) in normal healthy populations. The majority of studies have been conducted in Asian countries including Singapore, China, Korea, Japan and India. Some studies have reported on both AOD500 and TIA measurements (Li et al. 2007; Ramani et al. 2007; Leung et al. 2008) whereas other studies have reported only on either AOD500 measurements (Cheon et al. 2010; Sakata et al. 2010; Kim et al. 2011) or TIA measurements (Dada et al. 2007; Xu et al. 2008; Yi et al. 2008). The relevant studies are organised according to the ACA width variables and are displayed in tables that are supplemented with a summary. Tables 4.1 and 4.2 shows the studies that have investigated and reported on AOD500 and TIA measurements respectively. Thereafter, studies that have investigated and reported on ACA width variables in two or more race groups are displayed in Table 4.3.

4.2.1 Angle-opening-distance measurements

As seen in Table 4.1, AOD500 measurements have been investigated using ultrasound biomicroscopy (Ramani et al. 2007; Friedman et al. 2008) and OCT (Leung et al. 2008;

Amerasinghe et al. 2009; Liu et al. 2011) devices. Moreover, both time-domain (Müller et al. 2006; Li et al. 2007; Leung et al. 2008) and Fourier-domain (Grewal et al. 2011) OCT devices have been used to determine AOD500 measurements. With the exception of three (Radhakrishnan et al. 2005; Müller et al. 2006; Wylęgała et al. 2009), all studies in Table 4.1 have involved Asian sub-populations. Moreover, the majority of studies have included elderly adult samples with only three studies reporting mean ages lower than 30 years (Kobayashi et al. 1999; Li et al. 2007; Kim et al. 2011). A recent study by Shimizu et al. (2017) had a sample size of 100 and included an equal number of elderly adult (mean age of 73.7 ± 7.8 years) and paediatric (mean age of 7.1 ± 3.3 years) participants (Table 4.1).

Overall, there is a wide distribution of mean AOD500 measurements for the nasal (range from 267 µm to 651 µm) and temporal (range from 266 µm to 755 µm) ACAs. On average, the mean AOD500 measurements obtained with ultrasound biomicroscopy devices are less than 350 µm and lower than most of the mean AOD500 measurements obtained with OCT devices (Table 4.1). Only four studies using OCT devices have reported mean AOD500 measurements lower than 350 µm (Müller et al. 2006; Amerasinghe et al. 2009; Narayanaswamy et al. 2010; Sakata et al. 2010). This is interesting considering that three of these studies involved Singaporean samples and measured the AOD500 using the same time-domain (Visante) OCT device. Consequently, the lower AOD500 measurements observed in these three studies may be explained by a cohort effect and/or the use of OCT devices with lower resolutions and scanning speeds (Amerasinghe et al. 2009; Narayanaswamy et al. 2010; Sakata et al. 2010). Even though the other study also used a time-domain OCT device in a German sample, the sample consisted of only nine participants which may account for the lower AOD500 measurements (Müller et al. 2006).

The widest mean AOD500 measurements, with values greater than 650 µm, were reported in a Korean sample (Kim et al. 2011). Despite only measuring the nasal ACA, only one other study (Li et al. 2007) which involved a Hong Kong sample reported a mean AOD500

measurement of greater than 600 µm. The narrowest mean AOD500 measurements, with values less than 300 µm, were reported for the Singaporean samples (Amerasinghe et al. 2009; Narayanaswamy et al. 2010; Sakata et al. 2010). This implies that, even when OCT devices are used to measure the AOD500, there are variations in the mean measurements within the different Asian sub-populations wherein higher measurements are reported for Chinese, Korean and Hong Kong samples (Table 4.1).

One study involving a Chinese sample (Friedman et al. 2008) reported gender stratified mean AOD500 measurements for both the nasal and temporal ACAs that were lower than 221 µm making these values two times smaller than the values (454 µm and higher) reported in other studies involving Chinese samples (Leung et al. 2008; Liu et al. 2011). The study by Friedman et al. (2008) measured the AOD500 with an ultrasound biomicroscopy device and used a considerably older sample (mean age 65.1 ± 8.1 years) which may explain this discrepancy. The same pattern is also apparent for the studies involving the Indian samples (Ramani et al. 2007; Grewal et al. 2011). Despite comparable mean ages of the study samples, Ramani et al. (2007) using an ultrasound biomicroscopy device found ~165 µm lower mean AOD500 measurements than Grewal et al. (2011) who used an OCT device. It is likely that the different operating principles associated with these devices (ultrasound biomicroscopy and OCT) and how they measure the AOD500 may account for this difference.

Only three studies have reported on comparative AOD500 measurements in males and females. Ramani et al. (2007) reported no significant gender difference but 10 µm higher AOD500 measurements in females. In contrast, Amerasinghe et al. (2009) and Friedman et al. (2008) noted significantly higher AOD500 measurements in males than females for both the nasal and temporal ACAs (Table 4.1). This is interesting considering that significant gender differences were noted even though the studies by Amerasinghe et al. (2009) and

Friedman et al. (2008) have used OCT and ultrasound biomicroscope devices respectively and involved different Asian sub-populations (Table 4.1).

In majority of the studies, the mean AOD500 measurements for the temporal ACAs were higher than the mean AOD500 measurements for the nasal ACAs (Wylęgała et al. 2009; Cheon et al. 2010; Narayanaswamy et al. 2010). However, only one study (Kim et al. 2011) reported a significant difference between the horizontal ACA measurements wherein the mean AOD500 for the temporal ACA (mean 755 µm, range 222 µm to 1590 µm) was significantly wider than the mean AOD500 for the nasal ACA (mean 651 µm, range 184 µm to 1195 µm) ($p < 0.0001$). The mean AOD500 measurements for the nasal and temporal ACAs were identical in the studies by Radhakrishnan et al. (2005) and Ramani et al. (2007) (Table 4.1).

Table 4.1: Summary of studies reporting on AOD500 measurements

Authors (year)	Country	Sample size (gender allocation)			Mean age in years		Technique	Mean AOD500 (µm)		Mean AOD500 (µm)	
		n	Male	Female	Mean	Range		Nasal	Temporal	Males	Females
Ramani et al. (2007)	India	57	25	32	52.4 ± 10.8	NR*	Ultrasound biomicroscopy	320 ± 110	320 ± 100	Nasal: 310 ± 100 Temporal: 310 ± 80	Nasal: 320 ± 110 Temporal: 320 ± 120
Amerasinghe et al. (2009)	Singapore	239	122	117	56.9 ± 10.34	40-80	Optical coherence tomography	274 ± 131	266 ± 138	Nasal: 293 ± 144 Temporal: 286 ± 141	Nasal: 255 ± 114 Temporal: 245 ± 132
Friedman et al. (2008)	China	268	133	135	65.1 ± 8.1	NR*	Ultrasound biomicroscopy	NR*	NR*	Nasal: 193 Temporal: 220	Nasal: 164 Temporal: 186
Cheon et al. (2010)	Korea	439	176	263	65.7 ± 11.2	30-89	Optical coherence tomography	530 ± 298	581 ± 340	NR*	NR*
Leung et al. (2008)	China	49	NR*	NR*	34.5 ± 11.6	NR*	Optical coherence tomography	527 ± 249	572 ± 275	NR*	NR*
Narayanaswamy et al. (2010)	Singapore	1150	NR*	NR*	62.7 ± 7.7	50-93	Optical coherence tomography	267 ± 130	278 ± 134	NR*	NR*
Sakata et al. (2010)	Singapore	101	44	57	62.4 ± 9.6	41-89	Optical coherence tomography	280 ± 150	270 ± 140	NR*	NR*
Grewal et al. (2011)	India	265	129	136	55.2 ± 5.1	40-82	Optical coherence tomography	480 ± 210	490 ± 220	NR*	NR*

NR* = not reported
AOD500 = angle-opening distance taken at 500 µm

Table 4.1: Summary of studies reporting on AOD500 measurements (continued)

Authors (year)	Country	Sample size (gender allocation)			Mean age in years		Technique	Mean AOD500 (µm)		Mean AOD500 (µm)	
		n	Male	Female	Mean	Range		Nasal	Temporal	Males	Females
Li et al. (2007)	Hong Kong	25	NR*	NR*	27.1 ± 4.5	NR*	Optical coherence tomography	640 ± 272	NR*	NR*	NR*
Liu et al. (2011)	China	30	NR*	NR*	39.5 ± 13.1	24-69	Optical coherence tomography	454 ± 230	507 ± 272	NR*	NR*
Kim et al. (2011)	Korea	40	14	26	29.2 ± 5.44	23-42	Optical coherence tomography	651	755	NR*	NR*
Wylęgała et al. (2009)	Poland	30	13	17	39 ± 7	NR*	Optical coherence tomography	444 ± 98	452 ± 99	NR*	NR*
Radhakrishnan et al. (2005)	United States of America	24	9	15	42.9	NR*	Optical coherence tomography	440 ± 56	440 ± 58	NR*	NR*
Shimizu et al. (2017)	Japan	50 50	11 36	39 14	73.7 ± 7.8 7.1 ± 3.3	50-85 3-16	Optical coherence tomography	370 ± 150 560 ± 150	NR* NR*	NR* NR*	NR* NR*
Müller et al. (2006)	Germany	9	4	5	32.1	26-40	Optical coherence tomography	316 ± 61†		NR*	NR*
Kobayashi et al. (1999)	Japan	46	21	25	1.42 ±1.42	0.08-5	Ultrasound biomicroscopy	349.5 ± 87.1†		NR*	NR*

NR* = not reported
AOD500 = angle-opening distance taken at 500 µm
†average of nasal and temporal angle

4.2.2 Trabecular-iris angle measurements

As seen in Table 4.2, TIA measurements (for the horizontal ACAs) in normal healthy populations have been measured using ultrasound biomicroscopy (Dada et al. 2007; Ramani et al. 2007), Scheimpflug photography (Friedman et al. 2008; Yi et al. 2008) and OCT (Dacosta et al. 2008; Wylęgała et al. 2009) devices. With the exception of only three studies (Müller et al. 2006; Rabsilber, Khoramnia & Auffarth 2006; Wylęgała et al. 2009), all studies in Table 4.2 have involved Asian sub-populations. The majority of studies involved elderly adult samples with only three reporting mean ages lower than 30 years (Li et al. 2007; Yi et al. 2008; Hosseini, Abolbashari & Mohidin 2013) and one involving a paediatric sample (Kobayashi et al. 1999). Moreover, some studies reported on the mean TIA measurement as the average of the nasal and temporal ACAs (Xu et al. 2008; Sihota et al. 2012) while two studies (Rabsilber, Khoramnia & Auffarth 2006; Hosseini, Abolbashari & Mohidin 2013) reported on the mean TIA measurement but failed to describe if these measurements were specific to either the nasal or temporal ACA or the average thereof.

On average, there is a broad distribution of mean TIA measurements for the nasal (range, 22.28° to 44.80°) and temporal (range, 22.82° to 47.32°) ACAs (Table 4.2). The narrowest TIA measurements, with values lower than ~32°, were reported for middle-aged to elderly Indian samples (Dada et al. 2007; Ramani et al. 2007; Dacosta et al. 2008; Sihota et al. 2012). Kobayashi et al. (1999) also reported a mean TIA lower than 32° in a paediatric Japanese sample (mean age 1.42 ± 1.42) which may be accounted for by the anterior chamber not reaching normal adult levels. The widest TIA measurements, with values greater than 43°, were reported for the Hong Kong and Korean samples (Li et al. 2007; Yi et al. 2008). Consequently, there are variations in mean TIA measurements in the different Asian sub-populations (Table 4.2).

One study involving an Indian sample (Hosseini, Abolbashari & Mohidin 2013) reported a mean TIA measurement of 39.36°, which is higher than the values reported in other Indian

studies (Dada et al. 2007; Ramani et al. 2007; Dacosta et al. 2008; Sihota et al. 2012). The study by Hosseini, Abolbashari and Mohidin (2013) included a smaller sample size (n = 60) and used a Scheimpflug photography device to measure the TIA width which may explain this discrepancy. In contrast, similar mean TIA measurements were observed for the two German samples (Müller et al. 2006; Rabsilber, Khoramnia & Auffarth 2006) although they used different devices (Scheimpflug photography and OCT) to determine the TIA measurement and consisted of different sized samples (Table 4.2).

Mean TIA measurements (~35º) were comparable for the studies conducted in Germany (Müller et al. 2006; Rabsilber, Khoramnia & Auffarth 2006) and Poland (Wylęgała et al. 2009) which may be explained by the use of similar optical based devices (OCT and Pentacam) to determine the TIA measurement and the relatively similar mean ages of the study samples. Nevertheless, this similarity in TIA measurements should be interpreted with caution as the sample sizes in these studies were small (n = 9 to 76). In the majority of studies, the mean TIA measurements for the temporal ACAs were wider than the mean TIA measurements for the nasal ACAs (Leung et al. 2008; Yi et al. 2008; Liu et al. 2011) although these differences in the horizontal ACA width variable measurements were not statistically significant ($p > 0.05$) (Dacosta et al. 2008).

Only four studies have reported on comparative mean TIA measurements in males and females. With the exception of one study (Ramani et al. 2007), all studies noted higher measurements in males (Dacosta et al. 2008; Friedman et al. 2008; Hosseini, Abolbashari & Mohidin 2013). However, these gender differences in mean TIA measurements were small (less than 2°) and not statistically significant ($p > 0.05$) (Ramani et al. 2007; Dacosta et al. 2008; Friedman et al. 2008; Hosseini, Abolbashari & Mohidin 2013).

Table 4.2: Summary of studies reporting on TIA measurements

Authors (year)	Country	Sample size (gender allocation)			Mean age in years		Technique	Mean TIA (º)		Mean TIA (º)	
		n	Male	Female	Mean	Range		Nasal	Temporal	Males	Females
Ramani et al. (2007)	India	57	25	32	52.4 ± 10.8	NR*	Ultrasound biomicroscopy	29.56 ± 11.81	32.09 ± 13.34	Nasal: 28.69 ± 10.68 Temporal: 32.07 ± 10.5	Nasal: 30.24 ± 12.82 Temporal: 32.11 ± 15.4
Dacosta et al. (2008)	India	100	50	50	36.78 ± 14.5	19-76	Optical coherence tomography	22.28 ± 7.50	22.82 ± 8.43	Nasal: 22.93 ± 8.19 Temporal: 23.40 ± 8.51	Nasal: 21.64 ± 6.77 Temporal: 22.23 ± 8.39
Friedman et al. (2008)	China	268	133	135	65.1 ± 8.1	NR*	Scheimpflug photography	NR*	NR*	Nasal: 20.3 ± 6.2 Temporal: 18.6 ± 6.5	Nasal: 19.8 ± 5.6 Temporal: 18.0 ± 5.5
Li et al. (2007)	Hong Kong	25	NR*	NR*	27.1 ± 4.5	NR*	Optical coherence tomography	43.1 ± 12.3	NR*	NR*	NR*
Leung et al. (2008)	China	49	NR*	NR*	34.5 ± 11.6	NR*	Optical coherence tomography	38.1 ± 12.3	39.6 ± 13.2	NR*	NR*
Dada et al. (2007)	India	63	43	20	43.5 ± 9.8	NR*	Ultrasound biomicroscopy	28.27 ± 11.3	28.30 ± 13.5	NR*	NR*
Liu et al. (2011)	China	30	NR*	NR*	39.5 ± 13.1	24-69	Optical coherence tomography	32.9 ± 11.1	34.8 ± 11.0	NR*	NR*
Wylęgała et al. (2009)	Poland	30	13	17	39 ± 7	NR*	Optical coherence tomography	35.2 ± 8.9	35.5 ± 9.0	NR*	NR*

NR* = not reported
TIA = trabecular-iris angle

Table 4.2: Summary of studies reporting on TIA measurements (continued)

Authors (year)	Country	Sample size (gender allocation)			Mean age in years		Technique	Mean TIA (º)		Mean TIA (º)	
		n	Male	Female	Mean	Range		Nasal	Temporal	Males	Females
Yi et al. (2008)	Korea	81	51	30	22.3 ± 3.5	18-33	Scheimpflug photography	RE: 43.58 ± 5.04 LE: 44.80 ± 5.38	RE: 45.41 ± 5.30 LE: 47.32 ± 5.66	NR*	NR*
Hosseini, Abolbashari & Mohidin (2013)	India	60	32	28	25.93 ± 6.58	17-39	Scheimpflug photography	39.36 ± 5.42‡		40.23 ± 5.67‡	38.36 ± 5.14‡
Rabsilber, Khoramnia & Auffarth (2006)	Germany	76	NR*	NR*	46.6 ± 16.8	18-77	Scheimpflug photography	34.81 ± 5.05‡		NR*	NR*
Xu et al. (2008)	Beijing	2985	1291	1694	56.20 ± 10.59	40-101	Optical coherence tomography	38.31 ± 16.25†		NR*	NR*
Müller et al. (2006)	Germany	9	4	5	32.1	26-40	Optical coherence tomography	35.9 ± 5.7†		NR	NR
Sihota et al. (2012)	India	398	194	204	51.5 ± 5.41	40-59	Optical coherence tomography	23.24 ± 10.23†		NR	NR
Kobayashi et al. (1999)	Japan	46	21	25	1.42 ± 1.42	0.08-5	Ultrasound biomicroscopy	28.74 ± 7.46†		NR	NR

NR* = not reported
TIA = trabecular-iris angle
RE = right eye
LE = left eye
‡angle not specified
†average of nasal and temporal angle

4.2.3 Anterior chamber angle width in two or more race groups

Only few studies have compared ACA width variables in two or more race groups. Wang et al. (2011) noted similar AOD500 measurements in Chinese participants sampled from different mainland areas in China (northern and southern) and the United States of America. In contrast, the mean AOD500 measurement for the American Caucasian participants was 60 µm to 100 µm higher than the values noted for the Chinese participants (Table 4.3) although it was not specified if these differences were statistically significant (Wang et al. 2011). Leung et al. (2010) noted comparable mean AOD500 measurements in Caucasian and Chinese participants with only a 10 µm insignificant difference between the two groups ($p = 0.769$).

Two earlier studies reported no difference in mean TIA measurements among different race groups (Oh et al. 1994; Congdon et al. 2002). Oh et al. (1994) noted similar TIA measurements among Caucasian, African-American and Asian participants when the ACA width was assessed with gonioscopy together with the Spaeth grading system. Similarly Congdon et al. (2002), using biometric gonioscopy, reported that the mean ACA width was not significantly different in Caucasian (3.72 ± 0.12), Chinese (3.85 ± 0.18) as well as Black (3.83 ± 0.16) participants. This trend of similar TIA measurements in different race groups was more recently verified with the use of an OCT device (Leung et al. 2010). In this study, Leung et al. (2010) reported almost identical mean TIA measurements for Caucasian and Chinese participants ($p = 0.921$).

Despite reporting on gender stratified ACA width variables for the entire sample, Leung et al. (2010) noted significantly wider mean AOD500 and TIA measurements in males than females. On average, the ACA width variables were 80 µm ($p = 0.034$) and 5.6^{o} ($p = 0.026$) higher in male participants (Leung et al. 2010). This is consistent with the results of Oh et al. (1994) wherein males had significantly wider mean TIA measurements than females (33.8^{o} versus 31.7^{o}, $p = 0.002$).

Table 4.3: Summary of studies reporting on AOD500 and TIA measurements in two or more race groups

Authors (year)	Country	Technique	Race	Sample size (gender allocation)			Mean age in years	Mean ACA width (µm/º)	Mean ACA width (µm/º)	
				n	Male	Female			Males	Females
AOD500										
Wang et al. (2011)	United States of America	Optical coherence tomography	Caucasian	121	NR*	NR*	59.8 ± 11.7	350 ± 190†	NR*	NR*
	China		Chinese (American)	124	NR*	NR*	59.6 ± 12.0	290 ± 180†	NR*	NR*
			Chinese (Northern)	120	NR*	NR*	58.5 ± 10.7	250 ± 130†	NR*	NR*
			Chinese (Southern)	121	NR*	NR*	59.9 ± 11.7	250 ± 140†	NR*	NR*
Leung et al. (2010)	United States of America	Optical coherence tomography	Caucasian	30	14	16	40.2 ± 12.6	450 ± 150†	360 ± 220‡	280 ± 180‡
	China		Chinese	30	15	15	42.6 ± 14.0	460 ± 210†		
TIA										
Leung et al. (2010)	United States of America	Optical coherence tomography	Caucasian	30	14	16	40.2 ± 12.6	36.0 ± 8.5†	29.1 ± 13.9‡	23.5 ± 12.8‡
	China		Chinese	30	15	15	42.6 ± 14.0	36.0 ± 11.9†		
Oh et al. (1994)	United States of America	Gonioscopy	Caucasian	100	39	61	57.1 ± 17.0	32.5 ± 5.5#	33.8‡	31.7‡
			African-American	97	32	65	49.9 ± 18.0	31.8 ± 5.5#		
			Asian	94	40	54	47.5 ± 15.4	33.4 ± 6.8#		

NR* = not reported;
AOD500 = angle-opening distance taken at 500 µm
TIA = trabecular-iris angle
†average of nasal and temporal angle
‡entire group
#superior angle

4.3 FACTORS THAT AFFECT ANTERIOR CHAMBER ANGLE WIDTH VARIABLE MEASUREMENTS

Understanding the influence of demographic and ocular factors on ACA width variable measurements could assist in understanding the mechanisms of ocular anomalies and diseases. Consequently, research studies that have investigated and reported on ACA width variables have associated certain demographic and ocular factors with these variables. Some of the factors that affect ACA width variables include age, gender, race as well as ocular variables and will be briefly discussed below.

a. Age

The relationship between age and ACA width variables has been investigated previously wherein several cross-sectional studies have reported narrower ACA width variables in older individuals (Xu et al. 2008; Amerasinghe et al. 2009; Cheon et al. 2010; Qin et al. 2011; Sun et al. 2012a). It is well established that structural changes in the crystalline lens and consequently the anterior chamber occur with increasing age (Atchison et al. 2008). More specifically as age increases, the crystalline lens becomes thicker and more curved which may account for the narrower ACA variable measurements noted in older individuals (Atchison et al. 2008). Nevertheless, it has been recommended that ACA width variables be investigated in longitudinal studies with follow-ups to document precisely how these variables are affected with advancing age (Cheon et al. 2010).

b. Gender

The relationship between gender and ACA width variables has been investigated in only a few studies. Some studies have noted significantly smaller ACA width variables in females than in males (Friedman et al. 2008; Xu et al. 2008; Amerasinghe et al. 2009). This is in contrast to other studies that have reported no significant gender differences in ACA width variables (Wojciechowski et al. 2003; Dacosta et al. 2008; Hosseini, Abolbashari & Mohidin 2013). Rüfer et al. (2010), using an Orbscan device, reported wider ACA measurements in

female participants than in male participants for the right (31.6 ± 2.1º versus 30.7 ± 1.9º) and left (31.6 ± 2.2º versus 30.7 ± 2.1º) eyes although it was not reported if these gender differences were statistically significant.

c. Race

Wang et al. (2011) noted narrower AOD500 measurements in Chinese individuals than in Caucasian individuals. In contrast, the study by Leung et al. (2010) with a considerably smaller sample size reported similar mean ACA width (AOD500 and TIA) measurements in Chinese and Caucasian individuals. In two earlier studies (Oh et al. 1994; Congdon et al. 2002), similar mean TIA measurements were found in Caucasian, Chinese and African-American individuals.

d. Ocular variables

Ocular variables, including anterior chamber depth and refractive error, have been associated with ACA width variables. Several studies have reported positive associations between ACA width variables and anterior chamber depth (Friedman et al. 2008; Xu et al. 2008; Leung et al. 2010; Rüfer et al. 2010; Wang et al. 2011). An earlier study (Kobayashi et al. 1999), which used an ultrasound biomicroscopy device, noted strong significant associations between anterior chamber depth and the AOD500 (r = 0.890) as well as the TIA (r = 0.913) measurements. The positive associations between these anterior chamber variables (anterior chamber depth and ACA width) have been confirmed more recently in studies using non-contact methods to measure the ACA width variables (Amerasinghe et al. 2009; Rüfer et al. 2010; Hosseini, Abolbashari & Mohidin 2013). Wirbelauer et al. (2005) also reported positive associations between anterior chamber depth and AOD500 (r = 0.71) as well as TIA (r = 0.72) measurements in eyes with glaucoma, cataracts and/or aphakia.

Overall, ACA width variables have been significantly associated with refractive error (Xu et al. 2008; Kim et al. 2011). Some studies have reported inverse associations (r between

–0.16 to –0.30, $p \leq 0.001$) between refractive error and ACA width variables (Amerasinghe et al. 2009; Rüfer et al. 2010). This implies that the ACA width variables are wider when the refractive error is more negative. For example, Dacosta et al. (2008) reported that temporal and nasal ACAs respectively were wider in myopes (28.51 ± 8.21° and 26.96 ± 7.40°) compared with emmetropes (22.18 ± 7.64° and 21.93 ± 7.17°) and hyperopes (17.62 ± 6.21° and 17.71 ± 4.96°). The trend of narrower ACA width variables in hyperopes has also been reported in other studies (Xu et al. 2008; Rüfer et al. 2010) which may relate to why hyperopia has been identified as a major risk factor for primary angle-closure glaucoma (Xu et al. 2008).

Other ocular variables that may influence ACA width variables include axial length and crystalline lens thickness. Some studies have noted positive associations between axial length and ACA width variables (Sihota et al. 2005; Amerasinghe et al. 2009; Leung et al. 2010) although the explanation for this association is unclear. Shallower anterior chambers have been reported in individuals with thicker crystalline lenses (Atchison et al. 2008). Even though these ocular factors (axial length and crystalline lens thickness) were identified in the literature as being associated with ACA width variables, they were not considered within the scope of the current study.

e. Other factors

The process of accommodation alters the shape, thickness and position of the crystalline lens (Atchison et al. 2008). Consequently, fixation targets and pupil size are key factors because they influence the measurement of variables associated with the anterior chamber (Lavanya et al. 2007; Bueno-Gimeno et al. 2013). It is well established that the ACA width variables are different in the various glaucoma disorders with narrower ACAs having been observed in individuals with angle-closure glaucoma and angle-closure suspects (Ramani et al. 2007; Xu et al. 2008; Casson et al. 2009).

4.4 CONCLUSION TO THE CHAPTER

This chapter reviewed the relevant literature on ACA width variables and included selected studies that have investigated and reported on ACA width variable measurements. The review suggests that the majority of studies that have investigated ACA width variables have been clinic-based and conducted in Asian countries. To this extent, normal values for ACA width variables have been reported for Asian countries including China, India, Japan and Singapore. In contrast, no studies involving African samples have reported on ACA width variables implying that there is limited knowledge on the ACA width variable measurements from an African perspective. In Africa, ocular diseases including primary open-angle glaucoma and refractive anomalies are common clinical findings. Consequently, understanding the normal anterior segment ocular biometry is necessary to understand the mechanisms of ocular diseases and anomalies. In light of this knowledge gap related to ACA width variables in African populations, the current study aimed to provide a clinical description of ACA width variables measured using OCT in a South African young adult population. This clinical description facilitated the development of a clinical biometric guideline with normal reference intervals for the ACA width variables.

CHAPTER 5: METHODOLOGY

5.1 INTRODUCTION TO THE CHAPTER

The focus of this study was to produce a clinical description of anterior segment variables, measured using OCT, to facilitate the development of a clinical biometric guideline with normal reference intervals. This chapter presents the methodology used for this study based on the study objectives as shown in Table 5.1. The discussion begins by outlining the positivist paradigm to substantiate the research design used for the study. This is followed by an outline of the study population and sample, which includes the sampling method, sample size and study criteria used to select participants for the study. Thereafter, the data collection instruments, study procedure, data management and analysis techniques are outlined. The chapter ends by highlighting the challenges experienced, validity, reliability and ethical considerations for the study. A structured questionnaire (administered by the researcher) and clinical eye examinations (performed by the researcher) together with descriptive and inferential statistical analysis techniques were used to achieve the objectives of the study (Table 5.1).

Table 5.1: Study objectives, methods and phases

OBJECTIVES		METHODS	PHASES
1	Determine the interocular differences in anterior segment variables measured using OCT.	Clinical eye examination and inferential statistics	1 – Clinical description of anterior segment variables measured using OCT
2	Determine the distribution of anterior segment variables measured using OCT.	Clinical eye examination and descriptive statistics	
3	Investigate racial variations in anterior segment variables measured using OCT.	Clinical eye examination with descriptive and inferential statistics	
4	Investigate gender variations in anterior segment variables measured using OCT.	Clinical eye examination with descriptive and inferential statistics	
5	Determine the effect of spherical equivalent refraction on anterior segment variables measured using OCT.	Clinical eye examination and inferential statistics	
6	Develop a regression tree model to determine which anterior segment variables influence IOP.	Clinical eye examination and inferential statistics	
7	Develop a clinical biometric guideline with normal reference intervals for anterior segment variables measured using OCT.	Clinical eye examination and descriptive statistics	2 – Develop a clinical biometric guideline and compare to anterior segment variables currently available for other healthy African sub-populations
8	Compare the clinical biometric guideline to anterior segment variables currently available for other healthy African sub-populations.	Literature review	

5.2 THE POSITIVIST PARADIGM

A paradigm refers to the way in which a researcher views the world (Maree 2007). This world-view is associated with certain assumptions concerning the nature of reality/truth in the world (ontology) and the relationship between the researcher and reality/truth (epistemology). The world-view and its associated assumptions influence the approach (methodology) a researcher uses to investigate reality/truth in the world.

A quantitative research approach using the positivist paradigm was thought to be most appropriate for this study. Quantitative research is preferred when a systematic and objective research approach is needed to investigate phenomena of interest (Leedy & Ormrod 2005; Terre Blanche, Durrheim & Painter 2006; Maree 2007). Moreover, a quantitative research approach allows research findings, obtained from the analysis of numerical data collected from a subset of a population (sample), to be generalised to the population from which the sample was selected (Maree 2007). Consequently, the quantitative approach is nomothetic as it favours the development of general laws that may be used to explain the research findings that are observed (Cohen, Manion & Morrison 2007). In this study, a quantitative research approach allowed for an investigation of the clinical description of anterior segment variables, measured using OCT, which facilitated the development of a clinical biometric guideline with normal reference intervals.

The positivist paradigm is the favoured approach of natural science and its related disciplines (de Vos et al. 2007). The theory of positivism is attributed to Auguste Comte who was a 19th century French philosopher (Beck 1979). There are certain principles associated with studies adopting a quantitative approach using the positivist paradigm. For example, the positivist paradigm favours methods commonly used in the natural sciences which include performing experiments, obtaining responses to predetermined questions, recording measurements and making structured observations (Bryman 1988; Cohen, Manion & Morrison 2007). Consequently, phenomena within the positivist paradigm are valued as

knowledge only if they are directly observable and measurable. Thus, variables in quantitative studies using the positivist paradigm are usually specific and can be numerically quantified (Fortune et al. 1999).

Research conducted using the positivist paradigm is based on deductive reasoning (Cohen, Manion & Morrison 2007). This implies that scientific knowledge and theories, which already exist, are used as a background for research. Based on existing scientific knowledge and theories, specific research questions and/or hypotheses are generated and subjected to empirical tests. In this way, deductive reasoning moves from 'general to specific' in that what findings are theoretically expected to happen (according to scientific knowledge and theories) are subjected to empirical tests to determine if they do happen (de Vos et al. 2007). Thus, scientific knowledge is tested by formulating research questions and/or hypotheses and collecting data to answer the research questions and/or validate the proposed hypotheses. Consequently, a study adopting this approach will plan its research questions, hypotheses and methods (empirical tests) in advance and follow the proposed methods throughout the research process (Fortune et al. 1999). Lastly, researchers using the positivist paradigm remain objective by ensuring that personal beliefs, opinions and values have no influence over the research process. In this way, the researcher adopts the role of an objective observer (Fortune et al. 1999).

5.3 RESEARCH DESIGN

A research design refers to the structural framework guiding the process by which a study is executed (Drummond & Campling 1996) which for this study entailed using a quantitative observational research design. Observational research designs include case series, case-control studies, cross-sectional studies and cohort studies (Hopkins 2008). For this study, a cross-sectional research design was used. Cross-sectional study designs involve making observations on a cross-section of a population on one single occasion (Babbie 2010; Edmonds & Kennedy 2012). As cross-sectional studies are easier to plan, cheaper to

execute and do not require follow-ups, they are well suited for describing phenomena of interest within a population at one particular period in time (Hulley & Cummings 1988; Walsh 2001).

However, due to its nature, cross-sectional studies only allow for a 'snap-shot' of the phenomena being investigated to be described (Walsh 2001). Thus, cross-sectional studies are unable to detect changes that may occur in the phenomena being investigated over a period of time. Consequently, conclusions and explanations of cross-sectional studies may be limited to one particular period in time and/or the population from which the study sample was selected (Babbie 2010). Therefore, it is recommended that conclusions and explanations resulting from observational cross-sectional studies be considered within the context of similar data collected at different points in time and/or in different populations (Babbie 2010). This implies that the review of other studies, similar to the nature of this study, was important as the results and conclusions from these studies served as the background to interpret the results, conclusions and explanations for the current study.

5.4 STUDY POPULATION AND SAMPLE

5.4.1 Population

The study population comprised of registered students at the University of KwaZulu-Natal (UKZN). A registered student is defined as an individual who is registered to study in one or more modules that form part of a qualification programme offered by the university (College of health sciences 2017). The UKZN comprises of five campuses with four (Edgewood campus, Howard College campus, Nelson Mandela medical school and Westville campus) located in the greater Durban area and one (Pietermaritzburg campus) located in the Pietermaritzburg area (University of KwaZulu-Natal n.d.). As data collection took place at one site in Durban (the eye clinic at the Westville campus), registered students at the Pietermaritzburg campus were excluded from the study population to minimise the travel expenses that participants would need to incur to reach the data collection site. Although

students of all races and ethnicities register at UKZN, the majority of the student population comprises of Black and Indian students of South African ethnicity (I Naidoo, 2012, pers. comm., 1 August). This is consistent with the observed increase in the number of Black and Indian individuals attending educational institutions noted over the last three census periods (1996, 2001 and 2011) in South Africa (Statistics South Africa 2012).

The study population therefore comprised of South African Black and Indian students registered at any one of the four Durban based UKZN campuses. A record of the total number and demographic profile of all South African Black and Indian students registered at any one of the four Durban based campuses was obtained from the UKZN Department of Management Information (DMI). Table 5.2 shows the number of registered students of South African ethnicity, stratified for race and gender, in the study population as obtained from the DMI (I Naidoo, 2012, pers. comm., 1 August). This implies that at the time of conceptualising the study, there were 13259 and 8363 South African Black and Indian students respectively, aged between 17 years and 30 years, registered at any one of the four Durban based UKZN campuses.

Table 5.2: Study population stratified for race and gender

Age (years)	Race	Gender	Total
17-30	Black	Female	7600
		Male	5659
17-30	Indian	Female	5195
		Male	3168

5.4.2 Sampling method and sample size

A sample refers to a subset of a population (Kadam & Bhalerao 2010) while the sampling method refers to the process by which a sample is obtained from a population (Acharya et al. 2013). Aligned to the quantitative approach used in this study, probability sampling was thought to be most appropriate to obtain an unbiased selection of study participants (Maree

2007). Probability sampling is useful as each participant in the population has an unbiased equal chance of being selected for the study sample (Terre Blanche, Durrheim & Painter 2006; Maree 2007). Therefore, with probability sampling, the selection of study participants is an independent process (Cohen, Manion & Morrison 2007). This was necessary as the sample required to execute this study needed to be representative of the population and large enough to allow generalisation of the study findings to the population.

Multistage sampling is a complex form of probability sampling that involves two or more stages of sampling (Daniel 2012; Acharya et al. 2013). Moreover, the sampling units involved in each stage of multistage sampling may be embedded in each other (Acharya et al. 2013). Even though the sampling units share an intertwined relationship, they are fundamentally different at each stage in multistage sampling (Daniel 2012). Multistage sampling is often used when a sampling frame, consisting of all units in the population, does not exist and/or is not available (Acharya et al. 2013). In this study, two-stage random sampling was used to obtain the study sample as random sampling was applied at each of the two stages of sampling. Moreover, a statistician was consulted regarding the number of units required for each stage of sampling. A description of the two stages of sampling used in this study, the sampling units therein and the sample size for each stage is presented in the following section.

5.4.2.1 Stage one of sampling

As the study population was spread across the four Durban based UKZN campuses, stage one of sampling involved the various programmes of study offered at these campuses. Therefore, the sampling units for stage one were the various programmes of study offered at the four Durban based UKZN campuses. A sampling frame of all programmes of study offered at the four Durban campuses was constructed by accessing information available on the UKZN website (www.ukzn.ac.za) and the student prospectus. In addition, the researcher contacted the administrative offices at the different schools across UKZN to

ensure that an accurate sampling frame of all programmes of study offered at these four campuses was constructed. A total of 93 programmes of study were identified across the four Durban campuses.

As the programmes of study were unlikely to influence the ocular characteristics of the study population, selecting one-third of the sampling frame in stage one was judged to be an adequate size to obtain a sample representative of the population (WH Moolman, 2013, pers. comm., 30 May). Using the random number generator function in Microsoft Excel, random numbers between 0 and 1 were assigned to each sampling unit in the sampling frame containing the various programmes of study. Thereafter, the random numbers assigned to each sampling unit were sorted numerically from lowest to highest using the sort function. The first 31 programmes of study that appeared in the sorted sampling frame were selected. Consequently, simple random sampling was used to select the programmes of study in stage one of sampling.

5.4.2.2 Stage two of sampling

The sampling units for stage two were the South African Black and Indian students registered in the programmes of study selected from stage one of sampling. For this stage of random sampling, a sampling frame needed to be constructed because the UKZN Registrar did not allow the researcher access to students' personal information, but consented to the researcher contacting students to be part of a constructed sampling frame by providing their personal information on their own accord (J Meyerowitz, 2013, pers. comm., 28 February). The researcher contacted the respective Deans and Academic Leaders, from the selected programmes of study in stage one of sampling, to request permission to speak to students in lecture, practical and tutorial sessions.

After obtaining permission, students from the selected programmes of study were informed about the research study in numerous lecture, practical and tutorial sessions. Students were

also informed of the associated benefits, risks and nature of the study procedures. Thereafter, students were given the opportunity to seek clarification and enquire about any information supplied to them. In addition, they were informed that their participation was voluntary and that all their information would remain confidential. Students willing to be part of the sampling frame were required to supply their personal, demographic and contact details. They were also asked to supply their unique student registration numbers, known only to the researcher, which was used for identification in the sampling frame thereafter. Therefore, with the permission of the UKZN Registrar, Deans and Academic Leaders, two sampling frames were created over a period of six months. The two sampling frames were stratified for race and gender and comprised a total of 1162 registered students which consisted of 596 Black students (335 females and 261 males) and 566 Indian students (309 females and 257 males).

The sample size for stage two of sampling was determined in consultation with a statistician using two methods. The first method involved a power calculation while the second method involved the use of predetermined sample size estimation tables based on standardised effect sizes (WH Moolman, 2013, pers. comm., 30 May). It was recommended that the sample size for each race and gender group be equal to facilitate comparisons between and within the groups (WH Moolman, 2013, pers. comm., 30 May). This is aligned to the power of a study being maximal when the number of participants in each group is equal (Cohen 1962). Moreover, it was also advised that the number of participants in each group be rounded off to the nearest 50 to optimise the sample size estimation (WH Moolman, 2013, pers. comm., 30 May). The two methods used to estimate the sample size for stage two of sampling are discussed further.

Power calculations in studies with two groups describe the possibility of detecting differences in the phenomena of interest between the groups if such differences exist (Whitely & Ball 2002). Consequently, power calculations should begin by specifying the size

of the difference needed to be detected (Machin & Campbell 2005). The effect size refers to the minimum expected difference (in mean values) needed to be detected and is the most important variable in a power calculation (Cohen 1988; Whitley & Ball 2002; Kadam & Bhalerao 2010). In this way, a power calculation provides guidance on how many participants are required to detect the specified effect size with a particular significance level and statistical power. The significance level (α), also known as a type I error, refers to the possibility of rejecting the null hypothesis when it is true and consequently finding a false positive result (Cohen 1988; Hulley & Cummings 1988; Machin & Campbell 2005). The significance level is often set at 0.05 or 5% (Whitley & Ball 2002; Jones, Carley & Harrison 2003; Machin & Campbell 2005). Type II errors (β) describe the possibility of failing to reject the null hypothesis when it is false and consequently finding a false negative result (Hulley & Cummings 1988; Machin & Campbell 2005; Taborsky 2010). Statistical power is related to type II errors and is determined using the formula $statistical\ power = 1 - \beta$. Statistical power is often set at a minimum of 80% (Eng 2003; Cook & Hatala 2015).

The sample size was determined using the formula $n = \frac{2\sigma^2(z_{1-\alpha/2} + z_{1-\beta})^2}{d^2}$ (Florey 1993; Machin & Campbell 2005; Suresh & Chandrashekara 2012). In this formula, n represents the sample size needed for each group, σ is the pooled standard deviation and d^2 is the effect size that the study would be sensitive to detect. The $z_{1-\alpha/2}$ and $z_{1-\beta}$ denote the values specified for the study's significance level and statistical power respectively. For a 5% and 1% significance level, the values specified for $z_{1-\alpha/2}$ are 1.96 and 2.58 respectively (Eng 2003; Suresh & Chandrashekara 2012). For 80% and 90% statistical power, the values specified for $z_{1-\beta}$ are 0.84 and 1.28 respectively (Eng 2003; Suresh & Chandrashekara 2012). Conceptually, the formula above has a non-directional nature implying that a two-tailed significance test can be employed (Hulley & Cummings 1988; Machin & Campbell 2005).

The sample size was determined using the formula above based on data from the pilot study. Considering that quantitative studies are multifaceted, power calculations should be based on the primary study variable being measured (Hudson 2009). Consequently, the power calculation for this study was based on CCT as the primary anterior segment variable measured using OCT. From the pilot study, the difference in CCT measurements between the two groups (Black and Indian) was 15 µm so an effect size of 5 µm corresponding to one-third of this difference was adopted. The standard deviation for CCT measurements in the two groups corresponded to 17 µm and 18 µm, indicating a pooled standard deviation of 18 µm. Using a 5% significance level with 90% statistical power, a sample size of 272 participants was required in each group for an effect size of 5 µm and pooled standard deviation of 18 µm. Based on the statistician's advice, each group required a total of 300 participants (WH Moolman, 2013, pers. comm., 30 May). This implies that a sample of 600 participants would have a 90% chance of finding an effect size of 5 µm or higher between the two groups, if such differences existed, with a significance level of 5% (Hulley & Cummings 1988; Eng 2003; Suresh & Chandrashekara 2012; WH Moolman, 2013, pers. comm., 30 May).

Inadequate knowledge of any variables necessary for a power calculation may negatively influence the sample size estimation specifically when such calculations are computed at the design stage of a study (Cohen 1988; Hulley & Cummings 1988). Cohen (1988) recommends that using standardised effect sizes may be more appropriate to estimate the sample size particularly in studies with limited information on any of the variables necessary for power calculations. The standardised effect size (Δ) represents a ratio of the expected effect size (E) over the standard deviation (σ) for the variable of interest (Hulley & Cummings 1988; Taborsky 2010). The formula for standardised effect size is $\Delta = \frac{E}{\sigma}$ (Cohen 1988). Furthermore, Cohen (1988) proposed a classification system for the standardised effect size based on the value adopted in a study. For example, $\Delta \geq 0.8$ is considered high, Δ between

0.79 and 0.5 is moderate, Δ between 0.49 and 0.2 is small and Δ ≤ 0.2 is considered negligible (Cohen 1988; Machin & Campbell 2005; Maree 2007). The standardised effect size value adopted by a researcher depends on the preferred sensitivity and nature of the study to detect the estimated effect size. For example, when the study needs to be sensitive enough to detect even a small effect size, a Δ of 0.2 to 0.3 may be adopted (Cohen 1988). Using the concept of standardised effect sizes, Hulley and Cummings (1988) published sample size estimation tables for standardised effect size values with corresponding significance levels and statistical power.

A standardised effect size of 0.25 was adopted to make this study sensitive enough to detect even a small difference between the two groups. Using the tables proposed by Hulley and Cummings (1988) for a 5% significance level and 90% statistical power, a sample size of 336 participants was required for each group (WH Moolman, 2013, pers. comm., 30 May). Based on the statistician's advice, each group required a total of 350 participants (WH Moolman, 2013, pers. comm., 30 May). This implies that a sample of 700 participants would have a 90% chance of detecting a Δ of 0.25 with a significance level of 5%. By adopting a relatively small Δ and if the study finds no difference between the groups, it can be inferred with reasonable confidence that this may be the case in reality (Whitley & Ball 2002; Suresh & Chandrashekara 2012).

The two methods to estimate the sample size for stage two of sampling showed a difference of 50 participants in each group. Therefore, the sample size estimation based on a Δ value of 0.25 was preferred considering that a slightly lower sample size was estimated with the power calculation. This is in accordance with Thabane et al. (2010) who cautioned against relying on data from a pilot study in a power calculation to estimate sample size and recommended the use of power tables. Therefore, the sample size for stage two of sampling

consisted of 700 participants comprising 350 in each group with an equal gender distribution.

Study participants for stage two of sampling were randomly selected out of the two sampling frames that were constructed. Using the random number generator function in Microsoft Excel, random numbers between 0 and 1 were assigned to each of the sampling units in the two sampling frames. Thereafter, the random numbers assigned to each sampling unit were sorted numerally from lowest to highest using the sort function. The researcher contacted participants for the study according to the order in which they appeared in the sorted sampling frames, starting with the first sampling unit (registered student). When a selected registered student declined to participate or was unavailable for the study, the next registered student in the sorted sampling frame was contacted to participate in the study. The researcher proceeded moving down the sampling frame until the required sample size of 350 participants in each group was obtained. In this way, simple random sampling was used to select participants from the two sampling frames in stage two of sampling.

5.4.3 Inclusion and exclusion criteria

Considering the aim of this study, normal healthy individuals were included in the study sample as an understanding of anterior segment variables in normal individuals is necessary to interpret anterior segment variables in individuals with ocular diseases and/or post-ocular surgeries. Moreover, a young adult sample with a specified age range (17 to 30 years) was preferred because anterior segment variables may vary with age (Aghaian et al. 2004; Xu et al. 2008; Su et al. 2009; Vijaya et al. 2010; Wang et al. 2012).

Consequently, study participants who satisfied the following criteria were included:

i. South African Black or Indian young adults.
ii. male or female aged 17 years to 30 years.

iii. registered student at UKZN Edgewood campus, Howard college campus, Nelson Mandela medical school or Westville campus.

Study participants were excluded based on the following criteria:

i. history of ocular trauma and/or surgery.
ii. history of systemic and/or ocular diseases.
iii. current use of systemic and/or ocular medication.
iv. history and/or current use of rigid gas permeable contact lenses.
v. soft contact lens wearers with last reported use of contact lenses within 21 days prior to data collection. A three week period without soft contact lenses was considered as a suitable 'washout period' even though two days is sufficient for any induced corneal oedema to dissipate (Holden, Mertz & McNally 1983; Johnson, Boltz & Godio 1985).
vi. unaided or best corrected distance visual acuity (VA) worse than 0 logarithm of the minimum angle of resolution (LogMAR).
vii. IOP greater than 21 mmHg with a non-contact tonometer.
viii. corneal astigmatism greater than 2.50 D because Goldmann applanation tonometry results may be erroneous when corneal astigmatism exceeds three dioptres (Goldmann & Schmidt 2000).
ix. ocular abnormalities that may hinder viewing the ACA structures.

5.5 DATA COLLECTION INSTRUMENTS

Data collection was divided into two stages and the instruments used therein are shown in Figure 5.1. Stage one of data collection involved conducting screening procedures to determine participants' eligibility according to the study criteria. Stage two of data collection involved data gathering on eligible participants. Instruments used in stage one for screening consisted of a questionnaire, distance LogMAR VA chart, non-contact tonometer (Nidek NT-

530P), autorefractor (Nidek AR-1), trial case and frame, slit lamp biomicroscope (Nikon NS-1) and Wellch Allyn ophthalmoscope (Figure 5.1). Instruments used in stage two for data gathering consisted of the Optovue iVue100 Optical Coherence Tomographer, Oculus Keratograph 3 corneal topographer, Goldmann applanation tonometer and Nidek US-500 ultrasound device (Figure 5.1).

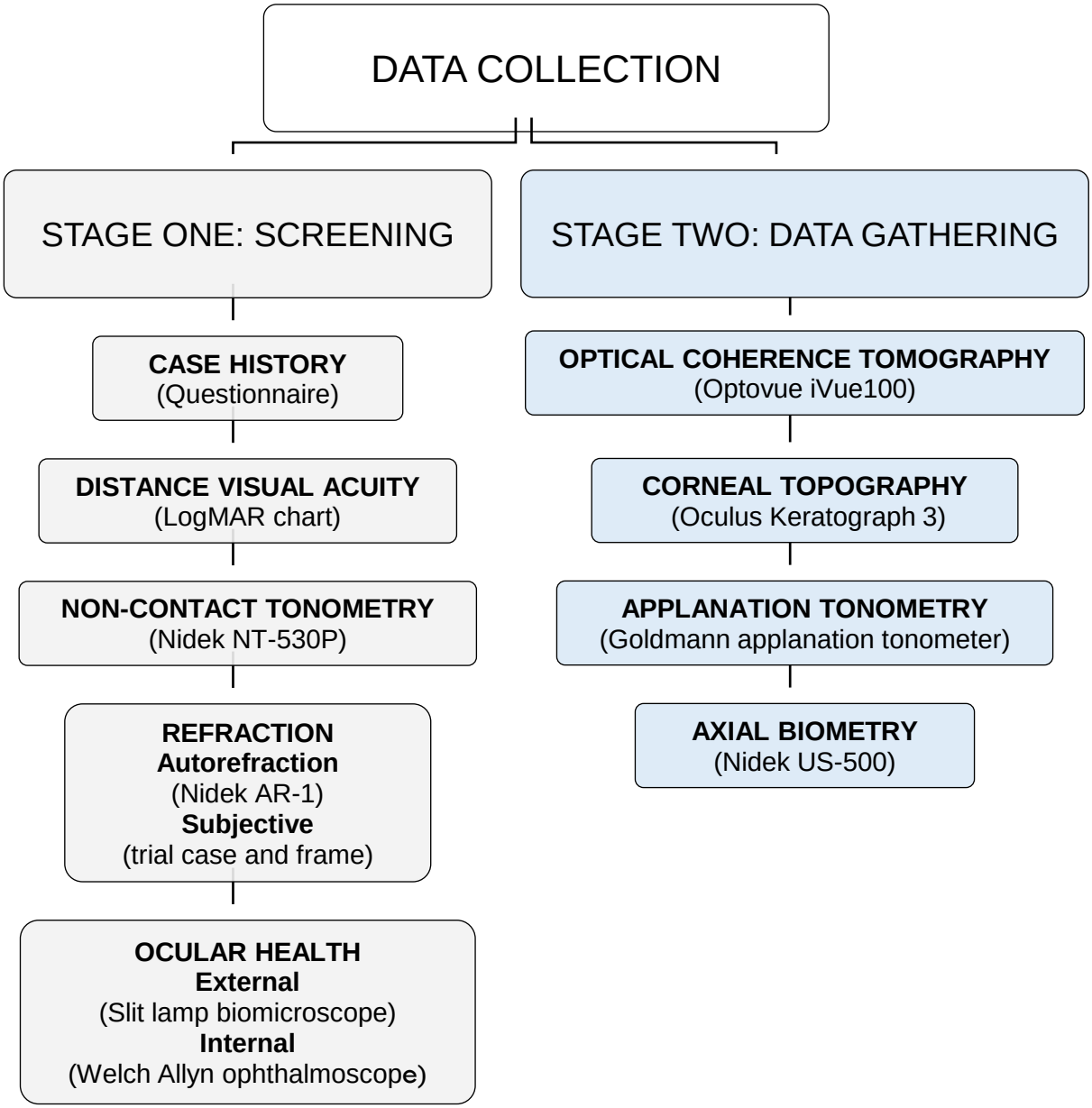


Figure 5.1: The two stages of data collection and instruments used therein

5.5.1 Instruments used in stage one for screening

The screening procedures consisted of an interview-administered structured questionnaire and a clinical eye examination (Appendix I). The questionnaire consisted of close- and open-ended questions to determine participants' demographic information and ocular as well as medical history. The majority of the close-ended questions were dichotomous in nature and required a nominal response. For example, the question 'Do you wear glasses/spectacles?' required a nominal 'yes' or 'no' response. The open-ended questions required word-based responses and were related to use of ocular and/or systemic medication. After the interview, distance VA was assessed using a LogMAR chart, which is accurate and reliable for assessing VA (Hussain et al. 2006). A distance LogMAR VA chart has 14 lines consisting of five letters each totalling 70 letters with a VA range from 1.0 LogMAR to –0.3 LogMAR. Autorefraction was performed with the Nidek AR-1 (sphere range: –30.00 D to +25.00 D; cylinder range: 0 ± 12.00 D; axis range: 0 to 180 degrees) and subsequently refined using subjective refraction to determine the refractive error. A Nikon NS-1 slit lamp biomicroscope and Welch Allyn ophthalmoscope were used to assess the health of the external and internal ocular structures respectively. Non-contact IOP was measured with the Nidek NT-530P tonometer which has good reliability and agreement with Goldmann applanation tonometry (Mashige et al. 2012; Fujimura et al. 2013; García-Resúa et al. 2013).

5.5.2 Instruments used in stage two for data gathering

The data gathering procedure consisted of a clinical eye examination (Appendix II). The four data collection instruments and associated ocular variables measured herewith were the Optovue iVue100 Optical Coherence Tomographer for corneal thickness as well as ACA width variable measurements, Oculus Keratograph 3 for corneal curvature as well as diameter measurements, Goldmann applanation tonometer for IOP measurements and Nidek US-500 ultrasound device for axial biometry measurements. The following section will discuss each data collection instrument in terms of its operating/theoretical principles, instrumentation and technical specifications, calibration as well as measurement of the

associated ocular variables. However, more attention will be focused on OCT and the iVue100 Optical Coherence Tomographer as this served as the primary data gathering instrument.

5.5.2.1 Optical coherence tomography

a. Operating/theoretical principles

Optical coherence tomography, first described in 1991 (Huang et al. 1991), is a non-invasive method of producing high-resolution cross-sectional images of ocular structures in real time (Hirano et al. 2001; Swartz, Marten & Wang 2007). It works on a principle similar to B-mode ultrasonography except that OCT uses reflected light waves instead of sound waves to create the cross-sectional images (tomograms) (Huang et al. 1991; Fujimoto et al. 2000). The ocular tomograms can be displayed in a false-colour scale or grayscale (Fujimoto et al. 2000; Wojtkowski 2010). In the ocular tomograms, areas of high reflectivity are shown as red and white in the false-colour and grayscale tomograms respectively. In contrast, areas of low reflectivity are shown as blue and black in the false-colour and grayscale tomograms respectively. Since its introduction in the early 1990s, OCT has undergone several technological improvements and is being widely used to provide quantitative and qualitative assessment of ocular structures (Goldsmith et al. 2005).

The non-contact nature of OCT is advantageous especially for assessing the anterior segment ocular variables as it minimises the influence of mechanical distortion, reduces the risk of infections and abrasions, is non-threatening and facilitates patient comfort (Radhakrishnan, Huang & Smith 2005). Moreover, OCT devices allow for better control of pupil size and accommodation when imaging the ACA (Leung et al. 2008). Since the first reported use of OCT to image the anterior segment in 1994 (Izatt et al. 1994), this method has gained popularity and is being extensively used for the clinical imaging and quantitative assessment of anterior segment ocular structures (Radhakrishnan et al. 2001; Goldsmith et al. 2005; Radhakrishnan, Huang & Smith 2005).

Light transmitted into the eye undergoes reflection at the various structures therein. Consequently, the distances and relative positions of the various ocular structures can be determined by measuring the intensity and echo time delay of the reflected light from these structures (Fujimoto et al. 2000; Wojtkowski, Kaluzny & Zawadzki 2012). As the speed of light (~3 x 108 m/sec) is faster than the speed of sound (~1500 m/sec), low-coherence interferometry is used to measure the intensity and echo time delay of the reflected light (Fujimoto et al. 2000; Wojtkowski 2010). Interferometry is the measurement of the interaction or interference of reflected light to detect information related to the distances and relative positions of structures (Hariharan 2003). In low-coherence interferometry, the reflected light from the tissue of interest is measured by correlating it with light that has travelled through a known reference pathway (Huang et al. 1991; Fujimoto et al. 2000). Thus, an interferometer is central to OCT as it performs the low-coherence interferometry measurements (Huang et al. 1991). The Michelson interferometer is the most commonly used interferometer configuration (Schmitt 1999).

In an OCT device, a broadband superluminescent diode emits a low-coherence light beam which is split into two beams, including a reference and sample beam, by means of a beam splitter (Huang et al. 1991; Tearney et al. 1997). The reference beam travels to a reference mirror via a known reference pathway whereas the sample beam travels to the ocular tissue of interest. Light from the sample beam is reflected off the various surfaces within the eye giving rise to multiple echoes of reflected light. Both the reference and sample beams of light travel back to the splitter after which two methods of OCT may be used to detect and process the reflected light, these being time-domain OCT and Fourier-domain OCT (Ţălu et al. 2011).

In time-domain OCT, the light from the two beams combine or interfere with each other resulting in an interference pattern. The resulting interference pattern reaches the photodetector and is processed into a signal which is further processed and gives rise to a

depth profile (A-scan) of a specific point in the tissue of interest (Singh et al. 2014). In time-domain OCT, the reference mirror moves throughout the scanning process for each A-scan that is created. Thus, multiple A-scans of adjacent points are created sequentially which when combined result in a cross-sectional image (Huang et al. 1991). In Fourier-domain OCT, the light from the reference and sample beams also undergo interference, although, the resulting interference pattern is collected by an array detector simultaneously as a spectrum. This is because the reference mirror, in Fourier-domain OCT, is stationary throughout the scanning process. The spectral interference pattern (interferogram) is processed using a spectrometer (Singh et al. 2014). Using Fourier transformation, the spectral interferogram is converted into A-scans which are combined and displayed as a cross-sectional image.

Fourier-domain OCT devices have scanning speeds that are more than 100 times faster than traditional time-domain OCT devices (Wojtkowski 2010). This difference in scanning speed is attributed to the role of the reference mirror in the two methods of detecting and processing the reflected light. In the time-domain OCT devices, the movement of the reference mirror limits the scanning speed to approximately 400 A-scans per second whereas the Fourier-domain OCT devices have scanning speeds of ~27000 A-scans per second (Nadler et al. 2012). Faster scanning speeds are advantageous as the resulting cross-sectional images have higher resolution when more A-scans are created. Consequently, the axial resolutions of Fourier-domain OCT devices (3 µm to 6 µm) are better than time-domain OCT devices (10 µm to 15 µm) (Townsend, Wollstein & Schuman 2009). Moreover, the faster scanning speeds associated with Fourier-domain OCT devices minimise the influence of motion artifacts due to involuntary eye and patient movements (Bald, Li & Huang 2012). For this reason, Fourier-domain OCT devices have better repeatability and produce more accurate measurements than time-domain OCT devices (Prakash et al. 2009; Ishibazawa et al. 2011).

b. Instrumentation and technical specifications

The Optovue iVue100 Optical Coherence Tomographer is a Fourier-domain OCT device capable of clinical imaging and quantitative assessment of anterior and posterior segment ocular structures (Optovue 2011). The iVue100 Optical Coherence Tomographer has a scanning speed of 26 000 A-scans per second, frame rate of 256 to 4096 A-scans per frame and operates at a wavelength of 830 nm to 850 nm (Optovue 2011). The axial and transverse resolutions of this device are 5 µm and 15 µm respectively (Optovue 2011). A corneal adaptor module (CAM) auxiliary lens, which uses a telecentric scanning pattern and is attached to the scanner head of iVue100 Optical Coherence Tomographer, is required for anterior segment imaging and assessment (Optovue 2011).

c. Calibration

As the calibration of the iVue100 Optical Coherence Tomographer is difficult to check without specialised equipment, precautionary steps were taken to ensure its proper functioning prior to and during the data collection period. Prior to data collection, qualified technicians (one of which is an optometrist) assessed the iVue100 Optical Coherence Tomographer to verify that it was in a proper working condition. In addition, a pilot study was undertaken to verify that the data collection procedure and measurements obtained with the optical coherence tomographer were optimal. Moreover during the data collection period, the same technicians routinely checked and cleaned the optical coherence tomographer which included testing the internal components and software algorithms. In addition, only one researcher performed all the data collection procedures with the optical coherence tomographer and the device and/or its measurements were not erratic at any point during the data collection period.

d. Measurement of ocular variables

Corneal thickness and ACA width were scanned and measured using the iVue100 Optical Coherence Tomographer. All OCT scans were captured in standardised lighting conditions

wherein the room lights were switched off and only the unavoidable minimal light from the laptop screen was present. In accordance with the manufacturer's recommendations, repeat scans were taken when the scan had a scan quality index of less than 27 or was labelled as poor on the laptop screen (Optovue 2011). Prior to each scan, participants were instructed to blink completely to ensure that an optically smooth tear layer was present over the anterior corneal surface. The cornea pachymetry scan protocol was used to map the cornea and measure corneal thickness. This scan protocol consists of eight radial (6 mm) line scans of 1024 A-scans each. When scanning the cornea, participants were instructed to look at the internal fixation target while the real-time image of the participant's eye and corresponding cornea were monitored on the laptop screen. The iVue100 Optical Coherence Tomographer has a pre-programmed algorithm that defines the corneal epithelium as the anterior boundary and the corneal endothelium as the posterior boundary (Optovue 2011). Consequently, corneal thickness is automatically determined as the distance between these two boundaries.

The cornea pachymetry scan protocol produces a 6 mm x 6 mm pachymetry map which displays the average corneal thickness (Figure 5.2). Moreover, the pachymetry map (Figure 5.2) is divided by rings into three corneal sections (central, paracentral and peripheral). The CCT measurement is defined as the average thickness in the central 2 mm ring. The middle and outermost rings, of 5 mm and 6 mm diameter, correspond to the paracentral and peripheral corneal sections respectively. Moreover, the paracentral and peripheral cornea are further divided into eight zones (superior, superior-temporal, temporal, inferior-temporal, inferior, inferior-nasal, nasal and superior-nasal). The average thickness in the central, paracentral and peripheral cornea (17 zones) are presented accordingly in the corneal pachymetry map using a false-colour display (Figure 5.2). In this study, the average paracentral corneal thickness (AveParaCT) and average peripheral corneal thickness (AvePeriCT) were computed as the average of the four cardinal zones/quadrants (superior, inferior, nasal and temporal) therein.

The location of the thinnest point on the pachymetry map (minimum corneal thickness) is shown with a blue asterisk (Figure 5.2). The corneal thickness at this point is displayed in the pachymetry assessment box (Figure 5.2). The iVue100 Optical Coherence Tomographer records the minimum corneal thickness as a single point measurement (Optovue 2011). This is in contrast to the thickness measurements for the central, paracentral and peripheral corneal zones which represent the average thickness measurement for multiple data points located therein (Optovue 2011).

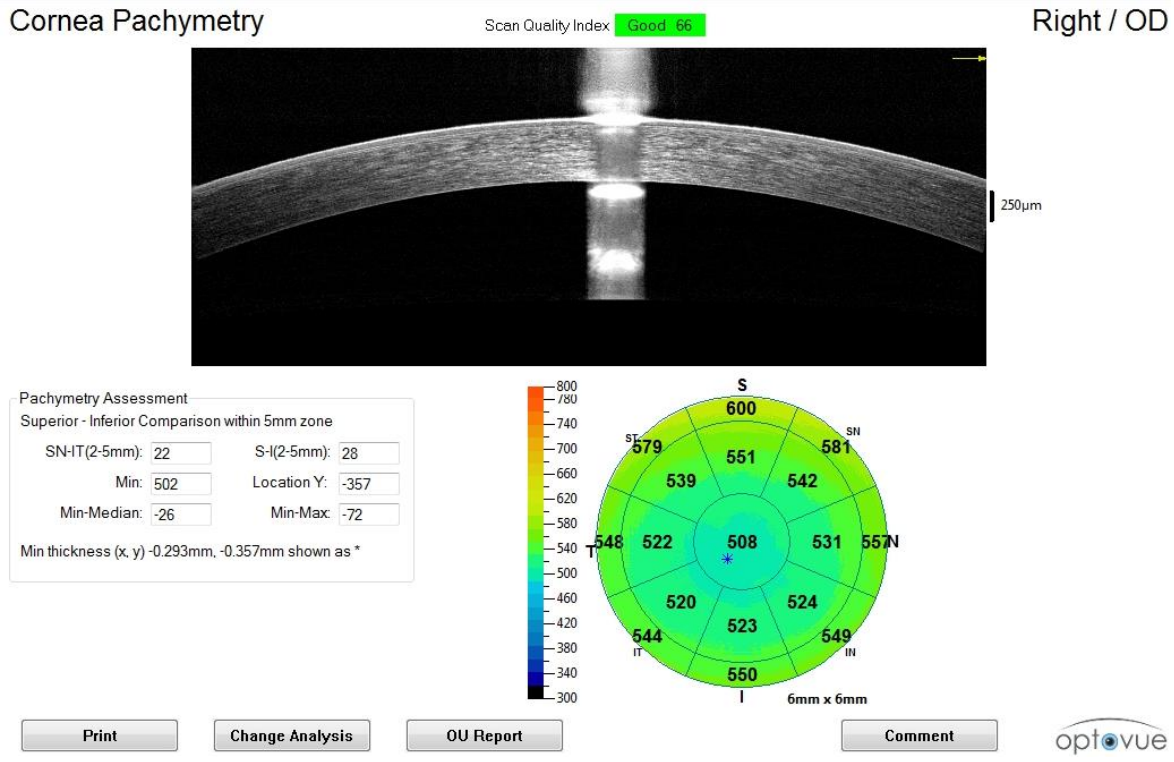


Figure 5.2: Corneal pachymetry map showing the mean corneal thickness (µm) in the centre and the different zones in the paracentral and peripheral cornea

The cornea angle scan protocol was used to image and measure the ACA width. This scan protocol consists of a single 5 mm line scan of 1024 A-scans. The iVue100 Optical Coherence Tomographer automatically averages 16 consecutive scans to create the single 5 mm line scan (Optovue 2011). The ACA width was quantified as a linear distance and angular measurement. Angle-opening distance taken at 500 µm was measured as the linear

distance variable. Trabecular-iris angle was measured as the angular measurement variable. The ACA width variables (AOD500 and TIA) were measured using the inbuilt measuring tools (distance and angle) in the iVue100 Optical Coherence Tomographer. The ACAs in the horizontal meridian (nasal and temporal) were imaged and measured as they are easier to access and are unlikely to be distorted by the eyelids (Wang et al. 2009). Moreover, ACA width variables in the horizontal meridian have better repeatability than the ACA width variables in the vertical meridian (Radhakrishanan et al. 2007; Kim et al. 2011; Quek et al. 2012) and the location of the scleral spur is more frequently identified in the horizontal meridian (Sakata et al. 2008).

When scanning the ACA, participants were instructed to look at the inbuilt external fixation target mounted on the side of the iVue100 Optical Coherence Tomographer while the line scan was centred on the limbus (nasal or temporal). This ensured that the limbal surface was aligned to the iVue100 Optical Coherence Tomographer light beam and that the cornea appeared flattened to minimise distortion and diffraction (Wirbelauer et al. 2005; Müller et al. 2006; Wang et al. 2009). During ACA scanning, the real-time image of the participant's eye and corresponding ACA were monitored on the laptop screen. As the iVue100 Optical Coherence Tomographer uses reflected near infrared light that does not alter the pupil size (Dacosta et al. 2008), the ACA was imaged under optimal uniform lighting conditions that minimised the effect of pupil size on the ACA images.

The ACA width variables (AOD500 and TIA) were determined using the method described by Pavlin, Harasiewicz and Foster (1992) and subsequently used in several other studies (Narayanaswamy et al. 2004; Radhakrishnan et al. 2005; Sihota et al. 2005; Ramani et al. 2007; Amerasinghe et al. 2009). This method involved identifying landmark ACA structures including the angle recess, scleral spur, point on the trabecular meshwork 500 µm anterior to the scleral spur and the corresponding perpendicular point on the anterior iris surface (Müller et al. 2006; Li et al. 2007). The ACA width variables including the AOD500 and TIA

have become standard measurements that are used to assess the ACA width as they allow for comprehensive evaluation of the ACA anatomy (Li et al. 2007; Lozano et al. 2018). This may be the case, as these two ACA width variables are most sensitive in distinguishing between individuals with non-occludable ACAs and those with primary angle closure as well as primary angle closure suspects (Henzan et al. 2011).

The scleral spur is the anatomical reference point for measuring ACA width variables as it is easy to identify, has a distinctive outline and increased reflectivity compared with adjacent ACA structures (Pavlin et al. 1991; Ishikawa, Liebmann & Ritch 2000; Hoerauf et al. 2002). Moreover, using the scleral spur as a reference point helps to orientate the researcher to determine which ACA structures are being viewed and the relative position of the trabecular meshwork (Pavlin et al. 1991; Sakata et al. 2008). Consequently, the first step for measuring ACA width variables involves identifying the scleral spur (Sakata et al. 2008). The scleral spur is identified manually as objective automated methods for identification of the scleral spur are elusive (Cumba et al. 2012). Nevertheless, several studies have used manual methods to identify the scleral spur and have reported good repeatability for the identification of the scleral spur (Console et al. 2008; Sakata et al. 2008; Cumba et al. 2012) as well as ACA width variable measurements (Li et al. 2007; Radhakrishnan et al. 2007; Kim et al. 2011; Tan et al. 2011; Cumba et al. 2012; Lozano et al. 2018).

To facilitate easier identification of the scleral spur in this study, the researcher adjusted the brightness and/or contrast of the ACA images produced by the cornea angle scan (Figure 5.3). In the majority of the images, the brightness and/or contrast was increased to enhance the appearance of the ACA structures. The scleral spur was identified by following the inner surface of the cornea and sclera to the point at which they intersected. This point of intersection is characterised by a change in curvature, which appears as a prominent inward protrusion of the sclera, noted along the inner surface of the ACA wall (Sakata et al. 2008; Yuen et al. 2010; Cumba et al. 2012). Thereafter, the other landmark ACA structures were

identified using the inbuilt distance-measuring tool in the iVue100 Optical Coherence Tomographer. A point 500 µm away from the scleral spur was identified (Müller et al. 2006; Li et al. 2007; Leung et al. 2010). This point, which is located along the posterior corneal surface, corresponds to the relative position of the trabecular meshwork (Sakata et al. 2008; Campa et al. 2011). Thereafter, the point located on the anterior iris surface perpendicular to the trabecular meshwork was identified (Müller et al. 2006; Li et al. 2007; Leung et al. 2010).

The AOD500 represents the linear distance (in µm) from the point on the trabecular meshwork to the perpendicular point on the anterior iris surface (Pavlin, Harasiewicz & Foster 1992; Müller et al. 2006; Campa et al. 2011). To determine the AOD500, the two ends of the inbuilt distance-measuring tool were placed on the points corresponding to the trabecular meshwork and anterior iris surface. The AOD500 measurement was displayed when placement of the distance-measuring tool was completed (Figure 5.3). In this study, the average AOD500 measurement (AveAOD500) was computed as the average of the nasal and temporal AOD500 measurements.

The TIA represents the angular measurement (in degrees) of the triangle formed by the angle recess, point on the trabecular meshwork and the perpendicular point on the anterior iris surface (Pavlin, Harasiewicz & Foster 1992; Müller et al. 2006; Campa et al. 2011). To determine the TIA measurement, the inbuilt angle-measuring tool was used where the apex of the triangle was placed in the angle recess and the two ends were placed on the points corresponding to the trabecular meshwork and anterior iris surface (Cheon et al. 2010; Dilworth & Alexander 2013). The TIA measurement was displayed when placement of the angle-measuring tool was completed (Figure 5.3). In this study, the average TIA measurement (AveTIA) was computed as the average of the nasal and temporal TIA measurements. Any ACA image in which the scleral spur could not be clearly identified was excluded from measurement of the ACA width variables and data analysis.

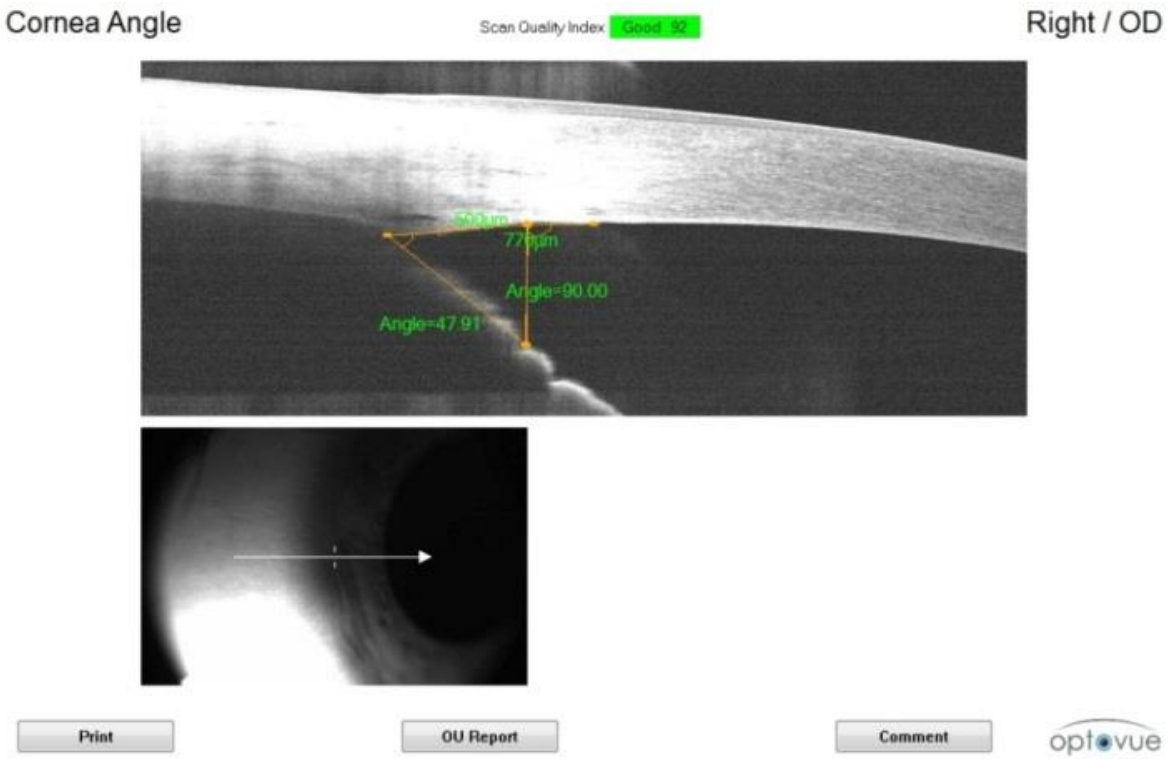


Figure 5.3: Cornea angle analysis showing the ACA width variables (AOD500 and TIA)

5.5.2.2 Corneal topography

a. Operating/theoretical principles

Corneal topography implies knowledge of the shape of the corneal surface (Belin & Khachikian 2009). Unlike traditional keratometers, corneal topographers evaluate corneal shape comprehensively by assessing a larger area of the cornea and producing topographical maps (Courville & Klyce 2005; Horner, Salmon & Soni 2006). The anterior corneal surface and overlying tear film act as a convex mirror and give rise to a reflected image (Purkinje-Sanson image I). The characteristics (shape and size) of this reflected image provides information related to the corneal shape. Corneal topographers are classified according to the optical principles used and include systems based on Placido-disc, slit-imaging, digital rasterstereography and laser holographic interferometry (Klein 2000; Mejía-Barbosa & Malacara-Hernández 2001; Khurana 2008). The majority of corneal topographers are based on the Placido-disc optical principle (Mejía-Barbosa & Malacara-

Hernández 2001; Khurana 2008). Quantitatively, corneal topographers express corneal curvature in millimetres or dioptres (Courville & Klyce 2005).

b. Instrumentation and technical specifications

The Oculus Keratograph 3 is a contemporary topographic device capable of providing quantitative and qualitative information related to corneal shape (Oculus Optikgeräte GmbH 2006). The Oculus Keratograph 3 evaluates 22 000 data points on the cornea with an illuminated Placido-disc target containing 22 concentric rings (Oculus Optikgeräte GmbH 2006). It has inbuilt software programmes that process the information from the data points and display various topographical maps including the overview display, refractive display and Fourier analysis. The Oculus Keratograph has an accuracy of 0.1 D and a measurement range of 9 D to 99 D (Oculus Optikgeräte GmbH 2006).

c. Calibration

The calibration of the Oculus Keratograph 3 was checked using a calibration globe of radius 8.00 mm. Prior to data collection, ten automated keratometry measurements were taken using the calibration globe. To take the measurements, the immobilisation arm of the calibration globe was attached to the combination chin and forehead rest bar and five measurements were taken in the right eye position. Thereafter, the calibration globe was rotated by 180 degrees and five measurements were taken in the left eye positon. The automated keratometry measurements for each attempt were within 0.05 mm of the reference 8.00 mm measurement. Moreover, the amount of corneal astigmatism did not exceed 0.1 D for any of the ten measurements. In addition, a pilot study was undertaken to verify that the data collection procedure and measurements obtained with the Oculus Keratograph 3 were optimal.

The calibration of the Oculus Keratograph 3 was also confirmed weekly during the data collection period. The researcher took two automated keratometry measurements each in

the right and left eye positions using the calibration globe. The keratometry measurements in each meridian did not exceed 0.05 mm of the reference 8.00 mm measurement. Moreover, the amount of corneal astigmatism was less than 0.1 D during the data collection period.

d. Measurement of ocular variables

The corneal curvature and diameter were measured with the Oculus Keratograph 3. When scanning the cornea, participants were instructed to look at the inbuilt fixation target located at the centre of the Placido-disc target while the image of the participant's eye was monitored on the computer screen. Prior to each scan, participants were instructed to blink completely to ensure that an optically smooth tear layer was present over the anterior corneal surface. In this corneal topographer, a reflected image (Purkinje-Sanson image I) of the illuminated Placido-disc target is created on the participant's anterior ocular surface. The Oculus Keratograph 3 automatically captures the image of the participant's eye when the reflected image is sharply focused and properly aligned (Oculus Optikgeräte GmbH 2006). The corneal topography scans were assessed for missing data points and irregularities due to tear film anomalies and/or eyelid infringements particularly within the central 3 mm zone. The Oculus Keratograph 3 has inbuilt software programmes that process the shape and location of the reflected image to calculate the corneal curvature and display the various topographical maps (Oculus Optikgeräte GmbH 2006).

The overview display map provides a summary of the corneal topography and shows the camera image of the eye, coloured topographic image (with a standardised scale) and keratometer data (Figure 5.4). The keratometer data includes the simulated corneal curvature measurements along the two principal meridians and the corneal astigmatism (amount and axis). The K1 and K2 measurements represent the simulated corneal curvature measurements, within the central 3 mm zone, along the flattest and steepest meridians respectively (Oculus Optikgeräte GmbH 2006). The Oculus Keratograph 3 calculates

corneal curvature in dioptres using the formula $corneal\ curvature = \frac{n_k - n_a}{corneal\ radius\ (m)}$ (Oculus Optikgeräte GmbH 2006). In this formula n_k and n_a represent the standard keratometric index (1.3375) and refractive index of air (1) respectively. The standard keratometric index is slightly lower than the refractive index of the cornea (1.376) to account for the negative power associated with the posterior corneal surface and the corneal thickness (Courville & Klyce 2005; Horner, Salmon & Soni 2006). In this study, the average corneal curvature was computed as the average of the K1 and K2 measurements. The corneal astigmatism represents the numerical difference in corneal curvature between the two principal meridians and is shown with its corresponding axis. The overview display map also shows the corneal diameter measurement (Figure 5.4).

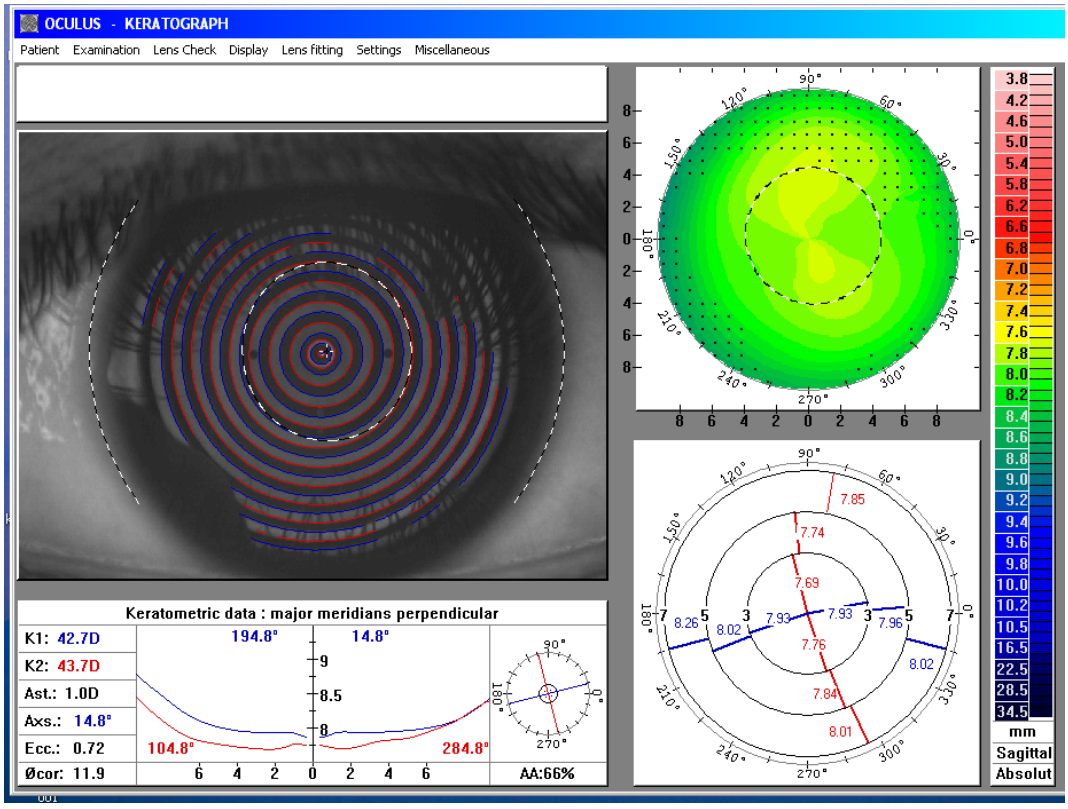


Figure 5.4: Overview display map showing the corneal curvature and diameter measurements

5.5.2.3 Applanation tonometry

a. Operating/theoretical principles

Clinical tonometers indirectly measure the tension within the eye (IOP). Goldmann applanation tonometry is the gold standard method for measuring IOP (Schneider & Grehn 2006; Avitabile et al. 2010). The Goldmann applanation tonometer is based on the Imbert-Fick principle which states that the pressure (P) inside a sphere is equal to the force (F) needed to flatten its surface divided by the area (A) of flattening ($P = F/A$) (Moses 1958; Kanski 2008). However, the characteristics of the eye prevent it from behaving like a perfect sphere. For example, the cornea is a rigid structure and the walls of the eye are neither infinitely thin nor in a dry state (Kanski 2008). Consequently, the cornea resists deformation during flattening, which decreases the internal volume within the eye, increasing the overall pressure (Cockburn 1991b). Moreover, the probe used to produce the flattening gets attracted to the corneal surface due to capillary attraction of the tear film decreasing the overall pressure (Cockburn 1991b; Kanski 2008).

The design of the Goldmann applanation tonometer manipulates these two factors such that when the diameter of the flattened area is 3.06 mm, the effect of the corneal rigidity and capillary attraction of the tear film are cancelled (Cockburn 1991b; Kanski 2008). Moreover, this specific diameter for the flattened area (3.06 mm) allows for a simple relationship between the grams of force needed to flatten the cornea and the IOP. For example, a force of 1.5 grams needed to flatten the cornea corresponds to an IOP measurement of 15 mmHg.

b. Instrumentation and technical specifications

The Goldmann applanation tonometer A900 (CSO, Firenze, Italy) is a manual contact tonometer capable of measuring IOP. This Goldmann applanation tonometer has a measurement range from 0 to 80 mmHg.

c. Calibration

The researcher checked the calibration of the Goldmann applanation tonometer prior to and weekly during the data collection period. The calibration of the applanation tonometer was checked at three dial positions corresponding to 0, 2 and 6. Throughout the data collection period, the Goldmann applanation tonometer remained accurate because the pressure arm moved towards and away from the researcher when the dial was moved backward and forward, from the calibration dial positions, respectively (Cordero 2012).

d. Measurement of ocular variables

The Goldmann applanation tonometer was mounted onto the peg found on the Nikon NS-1 slit lamp biomicroscope. Prior to the IOP measurements, participants' eyes were anesthetised and fluorescein was instilled. Thereafter, they were instructed to look straight ahead while the slit lamp, with the cobalt blue filter in place, was moved towards the participant until the measurement prism made contact with the corneal centre. The slit lamp was adjusted to ensure that two fluorescein semi-circles were seen. Thereafter, the dial was adjusted so that the inner borders of the two semi-circles were in contact. The IOP measurement in mmHg was determined by multiplying the value on the dial by ten.

5.5.2.4 Axial biometry

a. Operating/theoretical principles

Ultrasonography is the gold standard method used for measuring axial dimensions of the eye (Goyal, North & Morgan 2003; Holzer, Mamusa & Auffarth 2009). Ultrasound devices, used for measuring axial biometry, emit high frequency sound waves (10-20 MHz) that are above the range perceivable by the human ear (Rabbetts & Mallen 2007). In A-mode ultrasonography (time-amplitude), the time taken for a sound wave to return back to its origin after being reflected from a surface is measured and used to determine the axial distance (Rabbetts & Mallen 2007).

In this technique, a high frequency sound wave is emitted into the eye by an ultrasound probe (DiBernardo & Greenberg 2007). Similar to light waves, sound waves also undergo reflection at the various structures within the eye (Rosenfield 2006). The reflected sound wave gives rise to various echoes that travel back in the direction of the probe. A transducer detects the echoes and converts them into acoustic signals. Software programmes, inbuilt in the ultrasound device, process the echoes and produce a one-dimensional A-mode waveform that shows various deflections along a baseline (DiBernardo & Greenberg 2007). In a phakic eye, the deflections on the waveform correspond to the cornea, lens, retina, choroid and sclera. The separation or axial distance of each ocular structure is determined by considering the time difference of each deflection and the known velocity of sound through each ocular structure (Pavlin & Foster 1998).

b. Instrumentation and technical specifications

The Nidek US-500 is an ultrasound device capable of recording axial biometry measurements for axial length, anterior chamber depth (ACD), lens thickness and vitreous body thickness (Nidek 2012). A solid probe, with a frequency of 10 MHz, is used for the axial biometry measurements (Nidek 2012). The Nidek US-500 ultrasound device has a measurement range from 12.00 mm to 40.00 mm (Nidek 2012). The Nidek US-500 uses different sonic velocities to calculate distance that are 1532 m/s, 1641 m/s and 1532 m/s for ACD, lens thickness and vitreous body thickness measurements respectively (Nidek 2012). The axial length is calculated as the sum of the ACD, lens thickness and vitreous body thickness (Nidek 2012).

c. Calibration

The researcher checked the calibration of the Nidek US-500 device prior to and weekly during the data collection period. The calibration of the Nidek US-500 was checked using the test piece supplied with the ultrasound device. Throughout the data collection period,

the US-500 remained accurate as the axial measurements obtained with the test piece were within the range (21.00 ± 0.15 mm) specified on the test piece.

d. Measurement of ocular variables

Axial biometry measurements for axial length and axial ACD were measured using the Nidek US-500 ultrasound device. The device was set on the automatic method of measurement where the device recorded the axial biometry measurements only when acceptable measurement conditions persisted for a determined duration (Nidek 2012). Moreover, this ultrasound device automatically stops measuring when ten sets of acceptable measurements with a stability of ±0.05 mm are obtained (Nidek 2012). The phakic eye 2 scan was selected where the various axial biometry measurements were determined using different sonic velocities (Nidek 2012).

When measuring the axial biometry, participants were instructed to look at a spot of light located six metres away that was aligned to the visual axis of the eye not being measured. Distant fixation targets are recommended for axial biometry measurements to minimise errors associated with accommodation (Steele, Crabb & Edgar 1992). The ultrasound probe was then centred over the participant's pupil to ensure perpendicular scanning. The resulting waveform and axial biometry measurements in millimetres (to two decimal places) were then displayed on the LCD screen of the device. The Nidek US-500 device displays the ten sets of measurements, their mean and standard deviation (Nidek 2012).

5.6 STUDY PROCEDURE

This section will outline the study procedure with detailed descriptions of the pilot study and data collection procedures. The events of the study procedure occurred in the sequence outlined below.

5.6.1 Ethical approval and gatekeeper permission

A research proposal was submitted to the Biomedical Research and Ethics Committee of the UKZN. Ethical approval (reference number BE 289/12) was granted prior to commencing data collection (Appendix III). The researcher obtained permission from the UKZN Registrar to include students in the research study (Appendix IV). Permission was also obtained from the Dean and Head of School (Health Sciences) and Academic Leader of Research (Health Sciences) to use the optometry clinic and equipment therein for data collection (Appendix V).

5.6.2 Construction of sampling frames

The researcher constructed a sampling frame of all programmes of study offered at the four Durban based UKZN campuses. This sampling frame comprised of 93 sampling units. In addition, two sampling frames consisting of registered students, from the selected programmes of study, were created over a period of six months. These sampling frames were stratified for race and gender and comprised of 1162 sampling units

5.6.3 Pilot study

Prior to data collection, a pilot study was undertaken to assess the feasibility of the study procedure and validate the data collection instruments. A pilot study serves as a 'test run' to assess the data collection procedures, study instruments and criteria in a research study (Lancaster, Dodd & Williamson 2004). Thus, any insufficiencies in the study procedure can be identified and rectified prior to data collection (Leedy & Ormrod 2005). A pilot study was conducted on 10 participants who were not included in the data collection. The pilot study revealed that the chair used for the axial biometry measurements needed to be changed to ensure that the headrest provided firm support for the participant's head. In addition, the results were used to estimate the sample size for the power calculation performed in consultation with the statistician. Moreover, the pilot study confirmed that the study procedure and instruments were appropriate for the study.

5.6.4 Data collection

Data collection involved two stages (screening and data gathering) and was undertaken over a period of nine months. The clinical setting, illumination, test distances, procedures, instructions to participants and instruments used throughout the data collection period were standardised. Moreover, one researcher performed all measurements to promote standardisation.

5.6.4.1 Screening

The screening procedures consisted of an interview-administered structured questionnaire and standard optometric tests to evaluate VA, refractive error, ocular health and IOP. The purpose of screening was to ensure participants' eligibility according to the study criteria. The tests for screening were completed in approximately 10 to 15 minutes and consisted of:

i. Case history: a comprehensive case history was taken to ascertain participants' demographic information and ocular as well as medical history. Participants' ocular history was evaluated by obtaining information related to use of spectacles and/or contact lenses, previous eye examinations, history of ocular injuries and/or surgeries and ocular conditions. Participants' medical history was evaluated by obtaining information related to medical conditions and use of medication.

ii. Visual acuity: distance VA of the right, left and both eyes were measured using a LogMAR VA chart at a test distance of four meters. The unaided distance VA was measured for all participants. The aided distance VA was also measured for participants who wore spectacles.

iii. Refraction: both autorefraction and subjective refraction were performed to determine refractive error. The autorefraction findings, with the Nidek AR-1, were used as the starting point for the subjective refraction. The subjective refraction,

performed with a trial case and frame, was converted to a spherical equivalent. Refractive astigmatism was analysed based on the negative cylinder which was defined as less than or equal to –0.25 D. The refractive astigmatism was classified as with-the-rule (WTR) if the axis of the negative cylinder was within 15º of 180º, against-the-rule (ATR) if the axis was within 15º of 90º or oblique astigmatism when it was neither WTR or ATR (Gwiazda et al. 1984). The spherical equivalent was calculated as the sphere power added to half the negative cylinder power (Stephens 2006). The resulting spherical equivalents were classified as emmetropia (spherical equivalent between +0.50 D and –0.50 D), myopia (spherical equivalent less than –0.50 D) or hyperopia (spherical equivalent more than +0.50 D) which corresponds to the refraction classification used in other studies (Rüfer et al. 2009; Fotedar et al. 2010).

iv. Ocular health: slit lamp examination and ophthalmoscopy were used to assess the health of the external and internal ocular structures respectively. The cornea and lens were examined for any abnormalities using the relevant slit lamp settings. The nasal and temporal limbal ACA widths were assessed using the van Herick's technique.

v. IOP: a non-contact tonometer (Nidek NT-530P), which has good reliability and agreement with Goldmann applanation tonometry (Mashige et al. 2012; Fujimura et al. 2013; García-Resúa et al. 2013), was used to assess IOP for screening.

5.6.4.2 Data gathering

The data gathering procedures consisted of scanning and measurements with the Optovue iVue100 Optical Coherence Tomographer, Oculus Keratograph 3, Goldmann applanation tonometer and Nidek US-500 ultrasound device. The order of the data gathering procedures was selected to minimise the effect of a prior measurement on a subsequent measurement.

Corneal tomography and topography were performed prior to installation of anaesthetic to prevent any disturbance of the tear film that may influence the measurements obtained (Courville & Klyce 2005). Moreover, corneal tomography and topography are non-contact tests that allow for rapid image acquisition and measurements. Applanation tonometry and axial biometry measurements were performed thereafter as they required the use of anaesthetic. Prior to measuring the IOP, topical anaesthetic (Novesin Wander 0.4% by Novartis) was instilled into the participant's eyes. Thereafter, the researcher ensured that anaesthesia was achieved, by using a cotton wisp, before continuing with the data collection procedures. Prior to and after the IOP measurement, the integrity of the cornea was assessed with a slit lamp biomicroscope using white light and a cobalt blue filter. Artificial tear supplements (tear gel) was administered (if required) after the data gathering procedures to minimise the effect of tear film changes on the measurement of ocular variables. The tests for data gathering were completed in approximately 15 to 20 minutes and consisted of:

i. Corneal tomography: Corneal thickness and ACA width were scanned and measured using the Optovue iVue100 Optical Coherence Tomographer. Scans were taken in a standardised dark room after dark adapting for at least 30 seconds. This was done to ensure that the ACA configuration was not affected by varying illumination (Li et al. 2007; Friedman & He 2008). Both vertex and pupil centring were used to align the iVue 100 Optical Coherence Tomographer before image capturing (Optovue 2011). Three measurements for corneal pachymetry and ACA width, for both the nasal and temporal ACAs, were recorded and the averages computed. This was done to minimise any corneal pachymetry measurement errors and ensure that accurate ACA width variable measurements were recorded (Kohnen et al. 2006; Müller et al. 2006; Nam et al. 2010). Even though multiple scans were taken, the optical coherence tomographer was reset and realigned before capturing for each scan. All corneal tomography scans were taken at least two hours after

awakening to minimise the influence of closed-eye corneal swelling on pachymetry measurements (Hamilton et al. 2007; Read & Collins 2009).

ii. Corneal topography: Corneal curvature and diameter were measured with the Oculus Keratograph 3. Corneal scanning was performed in a standardised dark room. Three measurements for corneal curvature and diameter were recorded and the average computed. Despite multiple scans being taken, the corneal topographer was reset and realigned before each measurement was recorded.

iii. Applanation tonometry: The IOP was measured with a Goldmann applanation tonometer. Three IOP measurements were recorded and the average computed.

iv. Axial biometry: Three axial biometry measurements were recorded and the average computed. For axial biometry measurements, the researcher inspected the resulting waveform of each measurement on the LCD screen of the US-500 device. The waveform was accepted if three deflections were visible on the left (corresponding to the cornea, anterior lens and posterior lens) and the retinal deflection was separated from the smaller scleral deflection on the right (Nidek 2012). Moreover, the position of the four gates on the waveform was inspected and adjusted if needed (Nidek 2012).

5.6.5 Data capturing

Three measurements each were recorded for corneal pachymetry, ACA width variables, corneal curvature, corneal diameter, contact tonometry and axial biometry on the data collection sheet (Appendix II). Thereafter, the average of the three measurements was computed, double checked and captured on a worksheet. Data were captured weekly and the researcher double checked each data entry at a subsequent time to ensure accuracy of data capturing. Any discrepancies detected during data checking were compared against

the three measurements and their average recorded on the data collection sheet and corrected.

5.7 DATA HANDLING AND STORAGE

Quantitative data (nominal and ratio) were collected in paper and digital format. The paper format included the screening questionnaire and data collection sheets (Appendix I and II) which were compiled into a participant folder labelled with each participant's unique participant number. The digital data were retrieved directly from the internal hard drive inbuilt in each imaging device. The digital data were stored and identified by each participant's unique participant number. Moreover, all digital data were copied onto an external hard drive and stored as backup.

All consent forms, screening questionnaires, data collection sheets and the external hard drive were stored in a locked cupboard to which only the researcher had access. The worksheets used for data capturing were stored in a password protected computer. All data in paper format will be stored for a minimum of five years and thereafter will be destroyed. All data in digital format will be stored for a minimum of five years and thereafter will be permanently deleted.

5.8 DATA ANALYSIS

Data were captured and analysed with two software packages namely the IBM Statistical Package for Social Sciences (version 25) and the R Package. The data were analysed using descriptive and inferential statistical tests in consultation with a statistician. Both parametric and non-parametric statistical tests were used to analyse the data. All results, presented in the subsequent chapter, are reported in narrative form in conjunction with tables and figures. The study adopted a 95% significance level where p-values ≤ 0.05 were considered statistically significant. The various statistical tests used to analyse the data are outlined below with respect to the study objectives.

a. Demographic and ocular characteristics of the sample

Categorical data related to the demographic and ocular characteristics of the study sample are described using frequency counts and percentage statistics in a contingency table. The Pearson's chi-squared test was used to test the associations between the categorical variables. Continuous data for mean age and measurement of ocular variables are described using the mean ± standard deviation (SD). The Mann-Whitney U and Wilcoxon signed ranks tests were used to assess gender differences in mean age and interocular differences in ocular variable measurements respectively.

b. Objective 1: Interocular differences in anterior segment variables measured using OCT

Measurements for the corneal thickness and ACA width variables are presented as mean ± SD. Interocular symmetry was assessed using the intraclass correlation coefficient (ICC) (Armstrong 2013). Moreover, the mean interocular difference and Bland Altman lower and upper limits of agreement (LoA) were calculated for each corneal thickness and ACA width variable measurement. In this instance, the LoAs were particularly useful as they are not influenced by paired measurements of the right and left eyes (McAlinden, Khadka & Pesudovs 2011).

c. Objective 2: Distribution of anterior segment variables measured using OCT

The corneal thickness and ACA width variable measurements are summarised using descriptive statistics including the mean ± SD, median, range and 95% confidence intervals. The Shapiro-Wilk's test, kurtosis statistic, skewness statistic and graphical inspection of histograms were used to assess the distribution of the anterior segment ocular variables. The distribution was considered Gaussian when the p-value of the Shapiro-Wilk's test was greater than 0.05. Frequency counts were used to describe the location of the thinnest point on the cornea for the entire sample. The dependent sample *t*-test was used to assess differences in corneal thickness measurements between the centre (CCT) and thinnest point (minimum).

d. Objective 3: Racial variations in anterior segment variables measured using OCT

Data on the corneal thickness and ACA width variable measurements in the two race groups are described using descriptive statistics including the mean ± SD, 95% confidence interval, median and interquartile range. The independent sample *t*-test and Mann-Whitney U test were used to compare the corneal thickness and ACA width variable measurements respectively in the two race groups. These differences were considered significant if the resulting p-value was ≤ 0.05. Descriptive statistics (frequency counts and percentages) were used to present the location of the thinnest point on the cornea in the two race groups.

e. Objective 4: Gender variations in anterior segment variables measured using OCT

Descriptive statistics including the mean ± SD, 95% confidence interval, median and interquartile range were used to describe the corneal thickness and ACA width variable measurements in the two gender groups. Gender differences in cornea and ACA width variable measurements were assessed using the independent sample *t*-test and Mann-Whitney U test respectively where a p-value ≤ 0.05 was considered statistically significant. The location of the thinnest point on the cornea in the two gender groups are presented using frequency counts and percentage statistics.

f. Objective 5: Effect of spherical equivalent refraction on anterior segment variables measured using OCT

Anterior segment (cornea and ACA) variable measurements in the three refractive error groups (emmetropes, myopes and hyperopes) are described using the mean ± SD and median. Differences in corneal thickness measurements among the three groups were tested using the one-way analysis of variance (ANOVA) test. A post-hoc (Gabriel) analysis was performed for between group comparisons. The Kruskal-Wallis test was used to assess differences in ACA width variable measurements among the three refractive error groups. Pearson's and Spearman's correlation coefficients were used to assess the relationship between the anterior segment variables and spherical equivalent refraction with a p-value

of ≤ 0.05 being considered statistically significant. Linear regression analysis was used to assess the relationship between spherical equivalent refraction and CCT, AveAOD500 as well as AveTIA.

g. Objective 6: Regression tree model for the influence of anterior segment variables on IOP

The RPART function in the R Package was used to automatically generate the regression tree models. Eleven independent variables, consisting of demographic and ocular variables, were entered into the classification and regression tree (CART) analysis method. The three demographic variables were age, gender and race. The eight anterior segment ocular variables were CCT, AveParaCT, AvePeriCT, corneal diameter, average corneal curvature, axial ACD, AveAOD500 and AveTIA. Cross-validation was used to prune the initial unpruned regression tree model to generate an optimal sized regression tree model (pruned regression tree model).

h. Objective 7: Develop a clinical biometric guideline with normal reference intervals for anterior segment variables measured using OCT

The reference intervals in the clinical biometric guideline were computed using the non-parametric method endorsed by the Clinical and Laboratory Standards Institute (CLSI). The 2.5 percentile or lower limit of the normal reference interval corresponded to the reference value with the rank equivalent to $0.025 \times (n + 1)$ (Harris & Boyd 1995; Horowitz 2008; Jung & Adeli 2009; Köseoğlu et al. 2010). The 97.5 percentile or upper limit of the normal reference interval corresponded to the reference value with the rank equivalent to $0.975 \times (n + 1)$ (Harris & Boyd 1995; Horowitz 2008; Jung & Adeli 2009; Köseoğlu et al. 2010).

5.9 CHALLENGES EXPERIENCED AND ADDRESSED

The researcher experienced a challenge accessing personal information of the registered students at UKZN as the Registrar did not allow the researcher access to this information. Personal information, such as demographic characteristics, contact information, programme

of study and campus of registration, would have been useful for the sampling frames needed in stage two of sampling. To overcome this challenge, the researcher created two sampling frames as the UKZN Registrar consented to the researcher approaching students to be part of a constructed sampling frame (J Meyerowitz, 2013, pers. comm., 28 February) (Appendix IV). Every effort was made to contact all students in the selected programmes of study in stage one of sampling to inform them of the study and invite them to participate. As advised by the statistician, the sampling frames were created over a specified time period of six months and consisted of the total number of possible participants who showed interest in the study and supplied their personal information (WH Moolman, 2013, pers. comm., 30 May). The construction of the sampling frames increased the duration of the study procedure and volume of work for the researcher but also allowed for obtaining accurate personal information of study participants.

The researcher experienced a challenge measuring the ACA width variables as the iVue100 Optical Coherence Tomographer does not allow for objective automatic measurements. Some studies, using a Visante time-domain OCT device, reported using special mathematical programmes to measure the ACA width variables after manually identifying the scleral spur (Li et al. 2007; Leung et al. 2010). The researcher contacted the corresponding authors of these articles to request access to the mathematical programmes to semi-automatically analyse the ACA images produced with the iVue100 Optical Coherence Tomographer. Only one corresponding author responded and rejected the request due to research rights governing their study group (CK Leung, 2014, pers. comm., 28 November) (Appendix VI).

To overcome this challenge, the researcher adopted two strategies to ensure that the ACA width variables measured were optimal. The researcher verified the process used to capture the cornea angle scans and measure the ACA width variables with an established Optovue consultant (LJ Alexander, 2014, pers. comm., 31 January). As the ACA width variables were

measured manually, the researcher re-measured the ACA width variables on 10 randomly selected participants after data collection and ACA width variable measurement. The re-measured ACA width variable measurements showed good agreement with the original measurements with ICCs of 0.965 or greater for both the right (nasal AOD500 = 0.965, nasal TIA = 0.981, temporal AOD500 = 0.988 and temporal TIA = 0.996) and left (nasal AOD500 = 0.968, nasal TIA = 0.991, temporal AOD500 = 0.970 and temporal TIA = 0.989) eyes. Moreover, it has been shown that there is no clinically significant difference for ACA width variables that are measured manually or semi-automatically with an OCT device (Sihota et al. 2012)

5.10 VALIDITY AND RELIABILITY

a. Validity

Validity may be described as the extent to which a study measures what it is supposed to measure with the study instruments being an important aspect of a research study (Leedy & Ormrod 2005). The instruments used in the current study have either been documented as gold standards or used extensively in previous studies (Schneider & Grehn 2006; Zhang, et al. 2008; Chen et al. 2009; Leung et al. 2010; Vijaya et al. 2010; Wang et al. 2012; Yannakorpantana 2012). Moreover, the instruments and procedures used in this study are standard optometric instruments and within the scope of the optometry profession. Prior to data collection, a pilot study was undertaken to validate the study procedure and data collection instruments.

b. Reliability

Reliability may be described as the extent to which a study will yield the same consistent measurements when it is repeated with no alterations (Leedy & Ormrod 2005). Consequently, the study instruments, procedures and environment are important considerations. Previous studies have shown that OCT devices have good repeatability and reproducibility for measuring corneal thickness (Mohamed et al. 2007; Li et al. 2010) and

ACA width variables (Li et al. 2007; Radhakrishnan et al. 2007). The Oculus Keratograph 3 is a reliable instrument for corneal curvature and diameter measurements (Best, Drury & Wolffsohn 2012; Mao et al. 2013). Studies have reported good repeatability for IOP and axial biometry measurements with the Goldmann applanation tonometer (Avitabile et al. 2010) and ultrasound devices (Nemeth et al. 2007; Rončević et al. 2011) respectively.

All instruments used for data gathering were subjected to calibration checks throughout the data collection period. The order of the data gathering procedures and clinical environment, particularly the lighting, were kept constant throughout the data collection period. To ensure standardisation, all measurements were performed by one researcher wherein three measurements for each variable (in data gathering) were recorded and the averages computed.

5.11 ETHICAL AND LEGAL CONSIDERATIONS

a. Ethical approval and gatekeeper permission

Approval to conduct this study was obtained from the UKZN Biomedical Research and Ethics Committee (Appendix III). Gatekeeper permission was obtained from the UKZN Registrar, Dean and Head of School (Health Sciences) and Academic Leader of Research (Health Sciences) (Appendix IV and V).

b. Informed consent

Written informed consent was obtained from all participants prior to participation in the study via a consent form (Appendix VII). All participants received an information document (Appendix VIII) which outlined the study purpose, procedures involved, anticipated consequences and risks. Both the consent form and information document were translated into isiZulu (Appendix IX and X) and made available to participants if needed. In addition, both the consent form and information document indicated that participation in the study

was voluntary and that participants could withdraw from the study at any time without any consequences.

c. Beneficence and protection from harm

The anticipated benefit from participating in the study was that participants were informed of their visual and ocular status. Referrals were made to the UKZN optometry clinic if any participant required additional optometric management or if any ocular condition was detected. The results of the screening and data gathering tests were explained to each participant with the use of eye diagrams.

In order to prevent the spread of infection, the researcher ensured that all necessary equipment (chin rests, forehead rests and probes for the tonometer and ultrasound device) were disinfected with the use of alcohol between participants. When performing tests that required contact with the eye, participants were directly observed during the procedure and advised to inform the researcher of any adverse sensations. In the event of a corneal abrasion, tear gel was available to be instilled on the cornea and given to participants for further application. Pressure patches were also available but none of the participants required patching. The standard protocol was to monitor the anterior ocular surface daily with slit lamp evaluation until the abrasion healed.

d. Confidentiality and anonymity

All participants were informed that their test results would remain confidential. Moreover, all participants were assured of anonymity of their identities. This was achieved by assigning each participant with a unique participant number which was used to refer to them thereafter in the study. Furthermore, participant confidentiality and anonymity were also maintained in the reporting of the study because data analysis and presentation of results were grouped to include all study participants. As mentioned above, all paper and digital data will be stored securely for a minimum of five years and thereafter be destroyed.

5.12 CONCLUSION TO THE CHAPTER

This chapter reviewed the methodology and methods used to execute this study. This included reviewing the study design, population, sampling method and sample size. Thereafter, the data collection instruments and procedures were discussed in detail together with the methods used to manage and analyse the data. Lastly, the chapter ended by highlighting the challenges experienced, validity, reliability and ethical considerations for the study. The next chapter presents the results of the study.

CHAPTER 6: RESULTS

6.1 INTRODUCTION TO THE CHAPTER

This chapter presents the results of the data analysis for the study. Initially the demographic and ocular characteristics of the study sample are outlined. Thereafter, the results for phase one of the study, which consisted of the first six study objectives (1, 2, 3, 4, 5 and 6) are presented. This phase of the study focused on the clinical description of anterior segment variables, measured using OCT, in a South African young adult population. The anterior segment variables were measured using the iVue100 OCT device. The results from phase one of the study are presented according to the six study objectives.

6.2 DEMOGRAPHIC AND OCULAR CHARACTERISTICS

Of the 1162 eligible individuals from the two sampling frames, 806 participants (69.4%) were recruited for this study. Of the 806 participants, 106 were excluded as they failed to meet one or more of the study inclusion criteria. Thus, the sample consisted of 700 participants with an equal distribution of male (n = 350) and female (n = 350) participants. Table 6.1 summarises the demographic and ocular characteristics of the study sample. Almost 75% of the sample were aged between 17 and 21 years. The mean age of all participants was 20.4 ± 1.8 years and ranged from 17 years to 29 years. The male participants were marginally older than the female participants (20.6 ± 1.9 versus 20.3 ± 1.6 years). However, this difference in mean age was not statistically significant (p = 0.093). There was an equal number of participants in each of the two race groups (n = 350). Overall, the participants were asymmetrically distributed across the academic levels of study with the majority being in their first year of study (39.0%) and the minority in fourth year or higher (17.0%). A similar trend was observed when level of study was stratified according to gender although there was no significant association between gender and level of study (p = 0.571). The majority of participants were from urban areas (n = 416) as compared to township (n = 150) and rural

(n = 134) areas. There was no significant association between gender and hometown classification (p = 0.628).

The majority of participants (n = 437, 62.4%) reported having had a previous eye examination. There was a significant association between gender and likelihood of a previous eye examination ($p < 0.05$) wherein a greater proportion of females (n = 235, 67.1%) reported having had a previous eye examination than males (n = 202, 57.7%). Furthermore, in the participants who had a previous eye examination, the majority (81.0%) reported that the most recent eye examination was conducted within the last two years prior to data collection for the study. Only 200 participants reported wearing spectacles, of which there were significantly more female (n = 112) than male (n = 88) participants (p = 0.045). The use of contact lenses was relatively low wherein less than 10% of all participants reported to be wearing them with no significant gender difference (p = 0.077). Furthermore, in the participants who reported wearing contact lenses, none wore rigid gas permeable lenses and the last use of contact lenses was at least three weeks prior to data collection.

Table 6.1: Demographic and ocular characteristics of young adults

Demographic and ocular characteristic	Total (n = 700)	Gender		p-value
		Male (n = 350)	Female (n = 350)	
Age n (%)				0.004*
17 to 21	521 (74.4)	244 (69.7)	277 (79.1)	
≥ 22	179 (25.6)	106 (30.3)	73 (20.9)	
Mean age (years)	20.4 ± 1.8	20.6 ± 1.9	20.3 ± 1.6	0.093†
Race n (%)				1.000
Black	350 (50.0)	175 (50.0)	175 (50.0)	
Indian	350 (50.0)	175 (50.0)	175 (50.0)	
Level of study n (%)				0.571
First	273 (39.0)	145 (41.4)	128 (36.6)	
Second	140 (20.0)	65 (18.6)	75 (21.4)	
Third	168 (24.0)	83 (23.7)	85 (24.3)	
Fourth or more	119 (17.0)	57 (16.3)	62 (17.7)	
Hometown n (%)				0.628
Urban	416 (59.4)	202 (57.7)	214 (61.1)	
Township	150 (21.4)	77 (22.0)	73 (20.9)	
Rural	134 (19.1)	71 (20.3)	63 (18.0)	
Previous eye examination n (%)				0.010*
Yes	437 (62.4)	202 (57.7)	235 (67.1)	
No	263 (37.6)	148 (42.3)	115 (32.9)	
Spectacle use n (%)				0.045*
Yes	200 (28.6)	88 (25.1)	112 (32.0)	
No	500 (71.4)	262 (74.9)	238 (68.0)	
Contact lens use n (%)				0.077
Yes	59 (8.4)	23 (6.6)	36 (10.3)	
No	641 (91.6)	327 (93.4)	314 (89.7)	

* = statistically significant p-value (chi-squared test)
† = Mann-Whitney U test

Table 6.2 shows the means and standard deviations for ocular variables in the right and left eyes of the study sample (n = 700). The mean measurements for the ocular variables corneal diameter, average corneal curvature, axial length and axial ACD were identical in the right and left eyes ($p \geq 0.071$). The mean corneal astigmatism was 0.1 D higher in the left eye and this difference was not statistically significant ($p = 0.202$). The mean IOP measurements were 14.6 mmHg and 14.4 mmHg in the right and left eyes respectively (Table 6.2). Even though this difference achieved statistical significance ($p < 0.001$), it was only 0.20 mmHg, which can be considered marginal and thus unlikely to be clinically important.

Table 6.2: Means and standard deviations for ocular variables in the right and left eyes of young adults

Ocular variable	Right eye (n = 700)	Left eye (n = 700)	p-value†
Corneal diameter (mm)	12.0 ± 0.4	12 ± 0.4	0.114
Average corneal curvature (D)	43.2 ± 1.5	43.2 ± 1.5	0.387
Corneal astigmatism (D)	0.9 ± 0.6	1.0 ± 0.6	0.202
Axial length (mm)	23.4 ± 0.9	23.4 ± 0.9	0.728
Axial ACD (mm)	3.4 ± 0.2	3.4 ± 0.2	0.071
IOP (mmHg)	14.6 ± 2.4	14.4 ± 2.4	<0.001*
Spherical equivalent (D)	–0.72 ± 1.3	–0.71 ± 1.3	0.143

† = Wilcoxon signed ranks test
* = statistically significant

The mean spherical equivalent was similar in the right (–0.72 ± 1.3 D) and left (–0.71 ± 1.3 D) eyes (p = 0.143) (Table 6.2). Figure 6.1 shows the distribution of spherical equivalent refractive error in the right and left eyes for the study sample. Based on the spherical equivalent classification system used in this study, emmetropia (70.3%) was more prevalent than ametropia (29.7%). In addition, almost all participants with ametropia had myopia with a low frequency of hyperopia in the total sample (<1%).

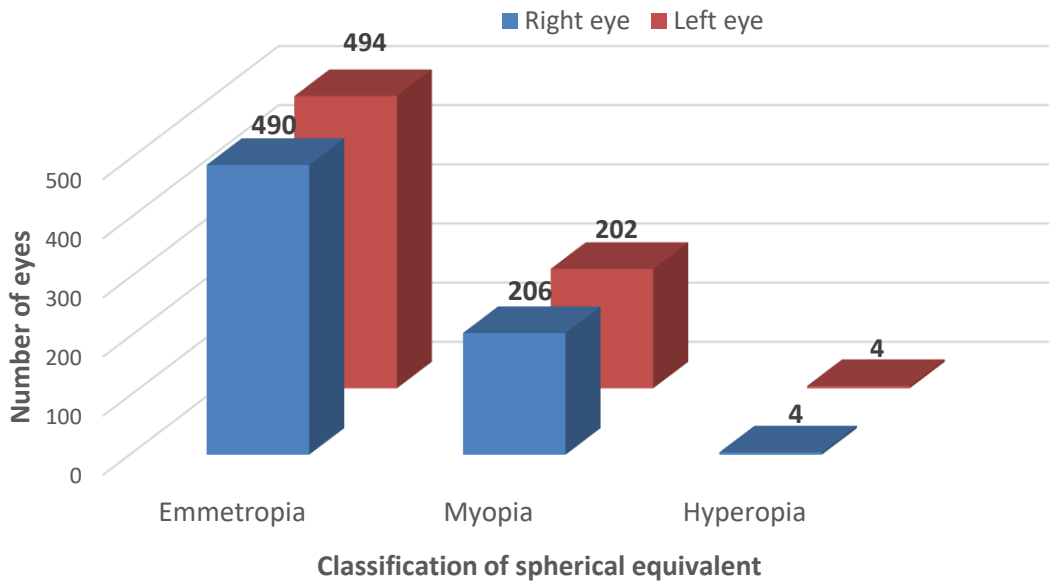


Figure 6.1: Distribution of spherical equivalent refractive error in the right and left eyes

Refractive astigmatism of at least –0.25 D was present in less than half of the total sample for either the right (n = 296, 42.3%) or left (n = 310, 44.3%) eyes. Moreover, WTR astigmatism was most common whereas ATR astigmatism was least common (Figure 6.2).

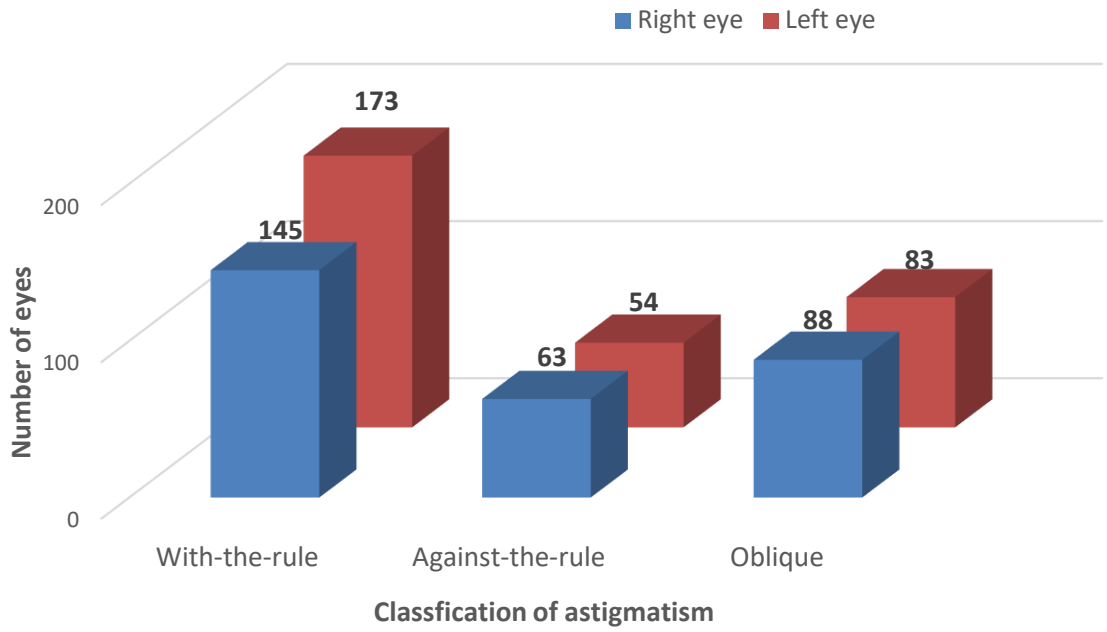


Figure 6.2: Distribution of refractive astigmatism in the right and left eyes

6.3 OBJECTIVE 1: INTEROCULAR DIFFERENCES IN ANTERIOR SEGMENT VARIABLES MEASURED USING OCT

Table 6.3 shows corneal thickness measurements of the right (n = 700) and left (n = 700) eyes for the centre (CCT), thinnest point (minimum) and four (superior, inferior, nasal and temporal) paracentral and peripheral quadrants together with the measures of interocular symmetry. Corneal thickness measurements in the right and left eyes were similar in the different zones with ICCs ≥ 0.975. Overall, the mean interocular differences were less than 2 µm in all zones except the nasal and temporal quadrants of the paracentral and peripheral cornea. The interocular difference for the paracentral nasal and temporal quadrants (~5.0 µm) were slightly lower than the peripheral nasal and temporal quadrants (~6.4 µm). Table 6.3 also shows the Bland Altman lower and upper LoA for the corneal thickness

measurements in the right and left eyes for each zone. For CCT, the mean interocular difference was –0.23 µm with 95% of the interocular differences between –11.53 µm (lower LoA) and 11.07 µm (upper LoA).

Table 6.3: Corneal thickness (µm) of the right and left eyes and measures of interocular symmetry

Cornea variable (µm)	Right eye Mean ± SD	Left eye Mean ± SD	Measures of symmetry			
			ICC	Interocular difference		
				Mean	Lower LoA	Upper LoA
CCT	501.91 ± 33.74	502.14 ± 33.61	0.993	–0.23	–11.53	11.07
Minimum	495.73 ± 33.89	495.25 ± 33.84	0.994	0.47	–9.91	10.85
Paracentral superior	534.24 ± 35.15	533.91 ± 34.98	0.992	0.34	–11.77	12.44
Paracentral inferior	513.21 ± 35.15	513.47 ± 35.24	0.993	–0.25	–11.42	10.92
Paracentral nasal	522.92 ± 34.34	527.90 ± 34.68	0.983	–4.98	–19.78	9.83
Paracentral temporal	513.85 ± 34.94	508.86 ± 34.62	0.983	4.99	–9.82	19.81
Peripheral superior	567.64 ± 37.24	565.75 ± 37.09	0.983	1.88	–16.62	20.39
Peripheral inferior	536.66 ± 36.87	536.88 ± 36.98	0.993	–0.21	–12.38	11.95
Peripheral nasal	548.86 ± 35.71	555.17 ± 36.07	0.975	–6.30	–24.44	11.84
Peripheral temporal	534.10 ± 35.80	527.61 ± 35.76	0.976	6.49	–10.83	23.81

SD = standard deviation
ICC = intraclass correlation coefficient
LoA = Bland Altman limit of agreement

Table 6.4 summarises the mean nasal and temporal AOD500 and TIA measurements for the right (n = 697) and left (n = 698) eyes together with the measures of interocular symmetry. The ACA width variables could not be determined in less than 1% of the total sample (three and two participants for the right and left eyes respectively) due to poor quality ACA images (poor visibility of the scleral spur and/or motion artifacts). The nasal and temporal AOD500 and TIA measurements were similar in the right and left eyes with ICCs ≥ 0.934. Interocular differences in mean nasal and temporal AOD500 and TIA measurements were less than 2.5 µm and 1° respectively. Table 6.4 also shows the Bland Altman lower and upper LoA for nasal and temporal ACA width variable measurements in the right and left eyes. For the AOD500 measurements, the mean interocular differences were 0.93 µm and 2.47 µm for the nasal and temporal ACAs respectively. The Bland Altman lower and upper LoA were –104.44 µm and 102.58 µm for the nasal ACA and –117.32 µm and 112.38 µm for the temporal ACA. For the TIA measurements, the mean interocular

differences for the nasal and temporal ACAs were 0.05º and 0.10º respectively. The Bland Altman lower and upper LoA were –3.25º and 3.34º for the nasal ACA and –3.68º and 3.88º for the temporal ACA.

Table 6.4: Anterior chamber angle variables of the right and left eyes and measures of interocular symmetry

Anterior chamber angle variable	Right eye Mean ± SD	Left eye Mean ± SD	Measures of symmetry			
			ICC	Interocular difference		
				Mean	Lower LoA	Upper LoA
Nasal AOD500 (µm)	552.79 ± 112.12	553.72 ± 114.59	0.943	–0.93	–104.44	102.58
Nasal TIA (°)	36.61 ± 4.59	36.56 ± 4.64	0.966	0.05	–3.25	3.34
Temporal AOD500 (µm)	553.01 ± 117.55	555.48 ± 117.37	0.934	–2.47	–117.32	112.38
Temporal TIA (°)	36.78 ± 4.86	36.68 ± 4.72	0.958	0.10	–3.68	3.88

AOD500 = angle-opening distance taken at 500 µm
TIA = trabecular-iris angle
SD = standard deviation
ICC = intraclass correlation coefficient
LoA = Bland Altman limit of agreement

Overall, the anterior segment variables were similar for the right and left eyes and showed high levels of interocular symmetry with ICCs close to 1. As a result of the high levels of interocular symmetry, data from only the right eyes of the 700 participants were analysed for the remaining objectives (McAlinden, Khadka & Pesudovs 2011; Armstrong 2013).

6.4 OBJECTIVE 2: DISTRIBUTION OF ANTERIOR SEGMENT VARIABLES MEASURED USING OCT

Table 6.5 shows the distribution of corneal thickness measurements in the different zones of the right eye for the total sample (n = 700). The mean CCT measurement, which ranged from 413 µm to 618 µm, was 501.91 ± 33.74 µm. Just less than half of the total sample (n = 326, 46.6%) had mean CCT measurements less than 500 µm. Only two participants presented with mean CCT measurements greater than 600 µm. The CCT and minimum corneal thickness measurements were the least variable with lower standard deviations relative to the four quadrants of both the paracentral and peripheral cornea (Table 6.5). The range of measurements for the CCT and minimum corneal thickness varied by 1.50-fold

while the four quadrants of the paracentral and peripheral cornea varied between 1.48- to 1.51-fold.

In the paracentral cornea, the superior quadrant (534.24 µm) was the thickest followed by the nasal (522.92 µm), temporal (513.85 µm) and inferior (513.21 µm) quadrants. The difference between the thickest and thinnest quadrants of the paracentral cornea was 21.03 µm. The mean AveParaCT, which ranged from 430 µm to 643 µm, was 521.06 ± 34.56 µm. The thickness difference between the mean CCT and AveParaCT was 19.15 µm ($p < 0.001$). In the peripheral cornea, corneal thickness was greatest in the superior quadrant, followed by the nasal, inferior and temporal quadrants (Table 6.5). The difference between the thickest and thinnest quadrants of the peripheral cornea was 33.54 µm. The mean AvePeriCT was 546.82 ± 35.71 µm and ranged from 453 µm to 675 µm. Furthermore, the AvePeriCT was 44.91 µm significantly thicker than the mean CCT measurement ($p < 0.001$). As expected, the mean CCT was significantly thinner than each quadrant of both the paracentral and peripheral cornea ($p < 0.001$). This relates to the overall increase in thickness from the central cornea (CCT) to all quadrants of the paracentral and peripheral cornea. Moreover, the standard deviations associated with the corneal thickness measurements increased as the distance away from the central cornea increased (Table 6.5).

Table 6.5 Distribution of corneal thickness measurements (µm) in the different zones of the right eye for the sample

Cornea variable (µm)	Mean ± SD	Median	CI (95% of mean)	Range	Kurtosis	Skewness	S-W
CCT	501.91 ± 33.74	503	499.40 to 504.41	413 to 618	–0.09	0.09	0.193
Minimum	495.73 ± 33.89	496	493.21 to 498.24	408 to 612	–0.12	0.09	0.175
Paracentral superior	534.24 ± 35.15	534	531.64 to 536.85	442 to 656	–0.07	0.07	0.215
Paracentral inferior	513.21 ± 35.15	514	510.61 to 515.82	423 to 637	–0.06	0.12	0.114
Paracentral nasal	522.92 ± 34.34	523	520.37 to 525.47	428 to 642	–0.03	0.12	0.314
Paracentral temporal	513.85 ± 34.94	514	511.26 to 516.44	425 to 635	–0.12	0.10	0.157
Peripheral superior	567.64 ± 37.24	569	564.87 to 570.40	471 to 695	–0.04	0.10	0.234
Peripheral inferior	536.66 ± 36.87	537	533.93 to 539.40	445 to 667	-–0.03	0.14	0.095
Peripheral nasal	548.86 ± 35.71	549	546.21 to 551.51	452 to 674	–0.01	0.15	0.160
Peripheral temporal	534.10 ± 35.80	535	531.45 to 536.76	442 to 662	–0.05	0.11	0.221

CCT = central corneal thickness
SD = standard deviation
CI = confidence interval
S-W = Shapiro-Wilk's test for normality p-value

The location of the thinnest point on the cornea was most often located central, followed by the inferotemporal, inferior and temporal quadrants (Figure 6.3). The mean minimum corneal thickness was 495.73 µm (Table 6.5), which was 1.23% thinner than the mean CCT measurement ($p < 0.001$). On average, the difference in corneal thickness between the CCT and minimum corneal thickness was 6.18 µm (range, 2 to 31 µm). Furthermore, the thickness difference between these two points was 9 µm or lower in most participants (n = 668, 95.4%). The small extent of this difference in corneal thickness implies that few participants had unusually thin measurements at the point of minimum corneal thickness relative to the CCT measurement.

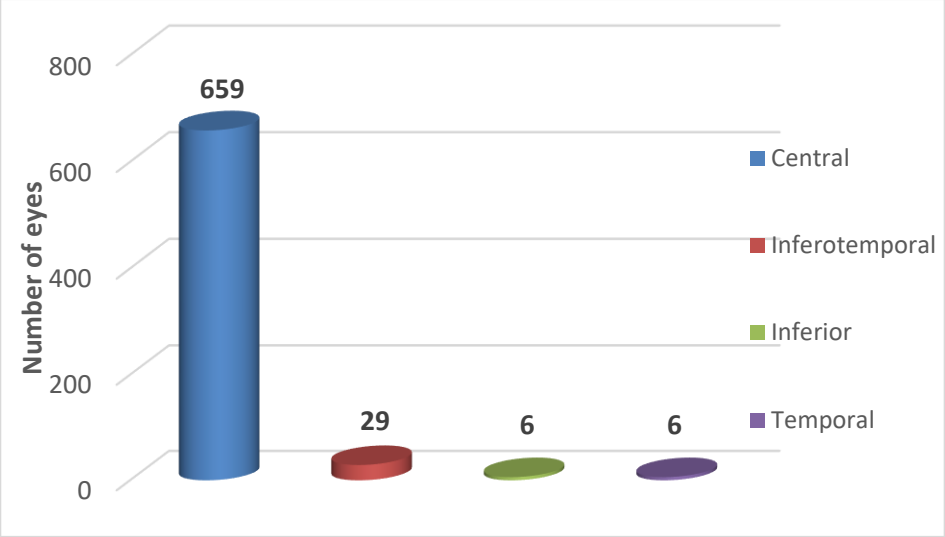
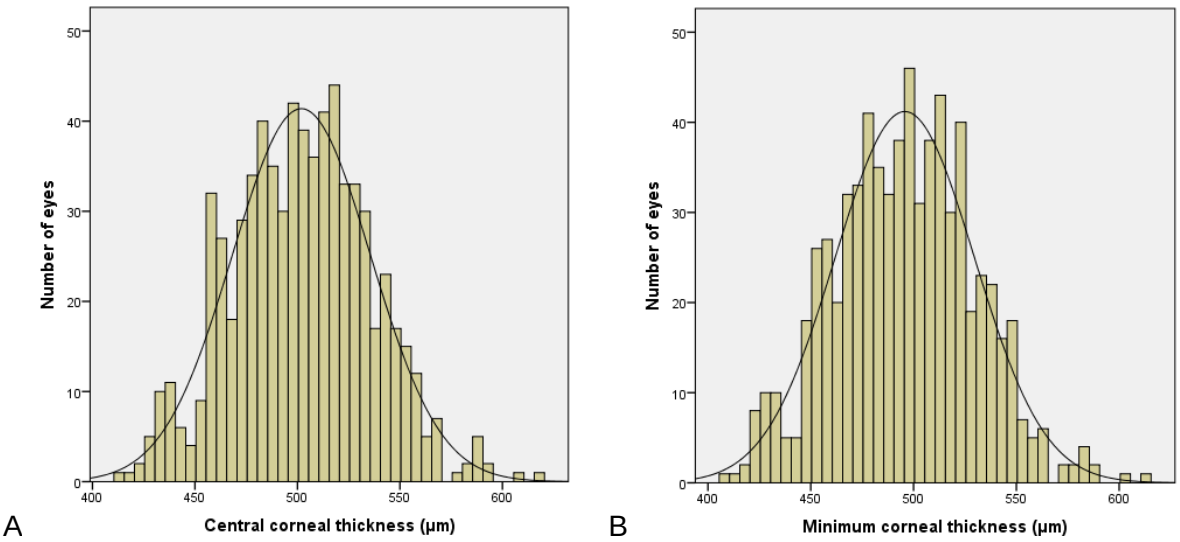


Figure 6.3: Distribution of thinnest corneal point location in the right eye

According to the Shapiro-Wilk's test (Table 6.5), corneal thickness measurements were normally distributed in all zones ($p \geq 0.095$). Histograms showing the distribution of CCT and minimum corneal thickness (Figure 6.4) as well as the four paracentral (Figure 6.5) and peripheral (Figure 6.6) quadrants resembled Gaussian curves (kurtosis range, –0.01 to –0.12; skewness range, 0.07 to 0.15).



A B

Figure 6.4: Distribution of CCT (A) and minimum corneal thickness (B) (µm) in the right eyes of young adults

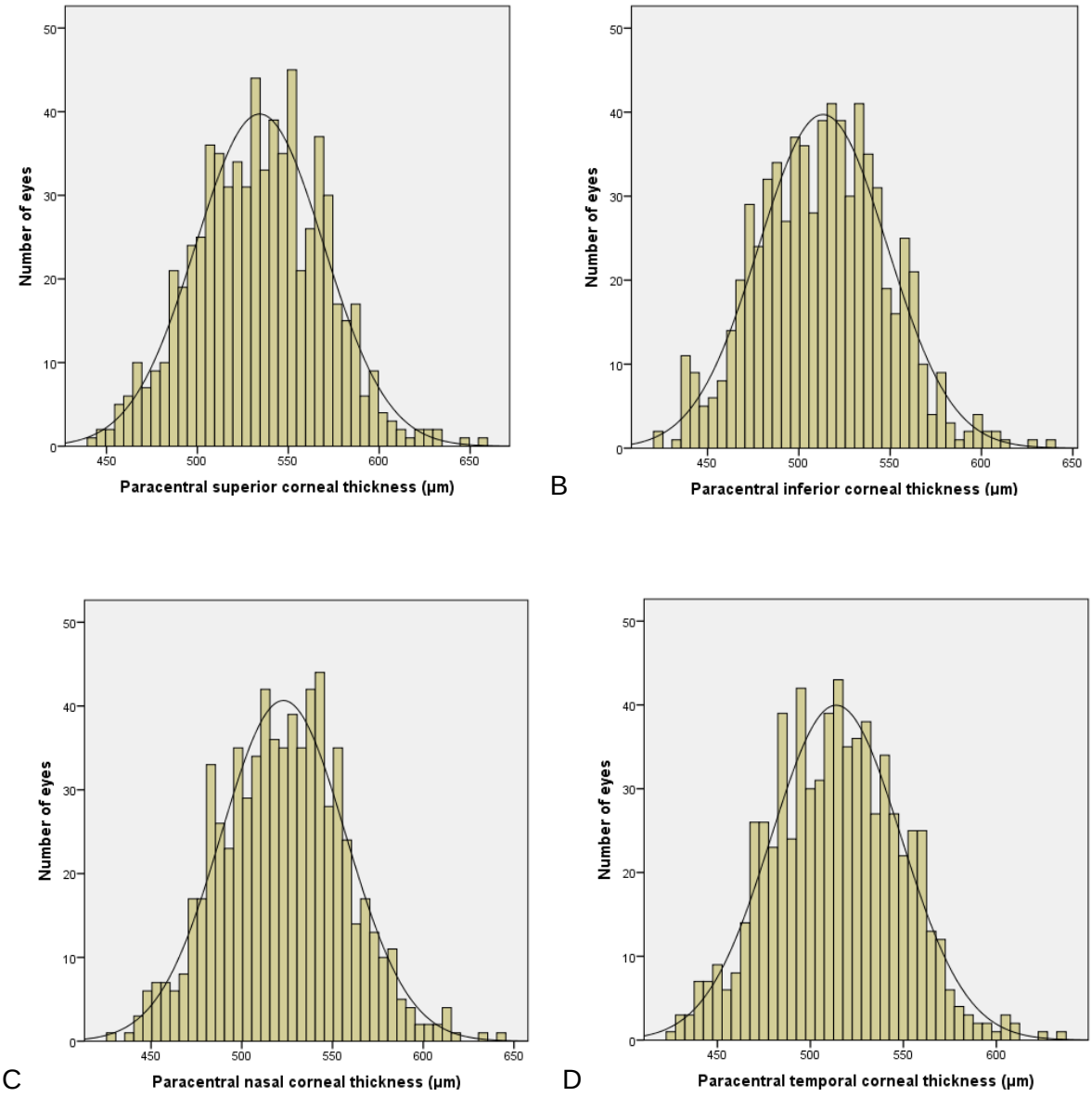


Figure 6.5: Distribution of paracentral superior (A), inferior (B), nasal (C) and temporal (D) corneal thickness (µm) in the right eyes of young adults

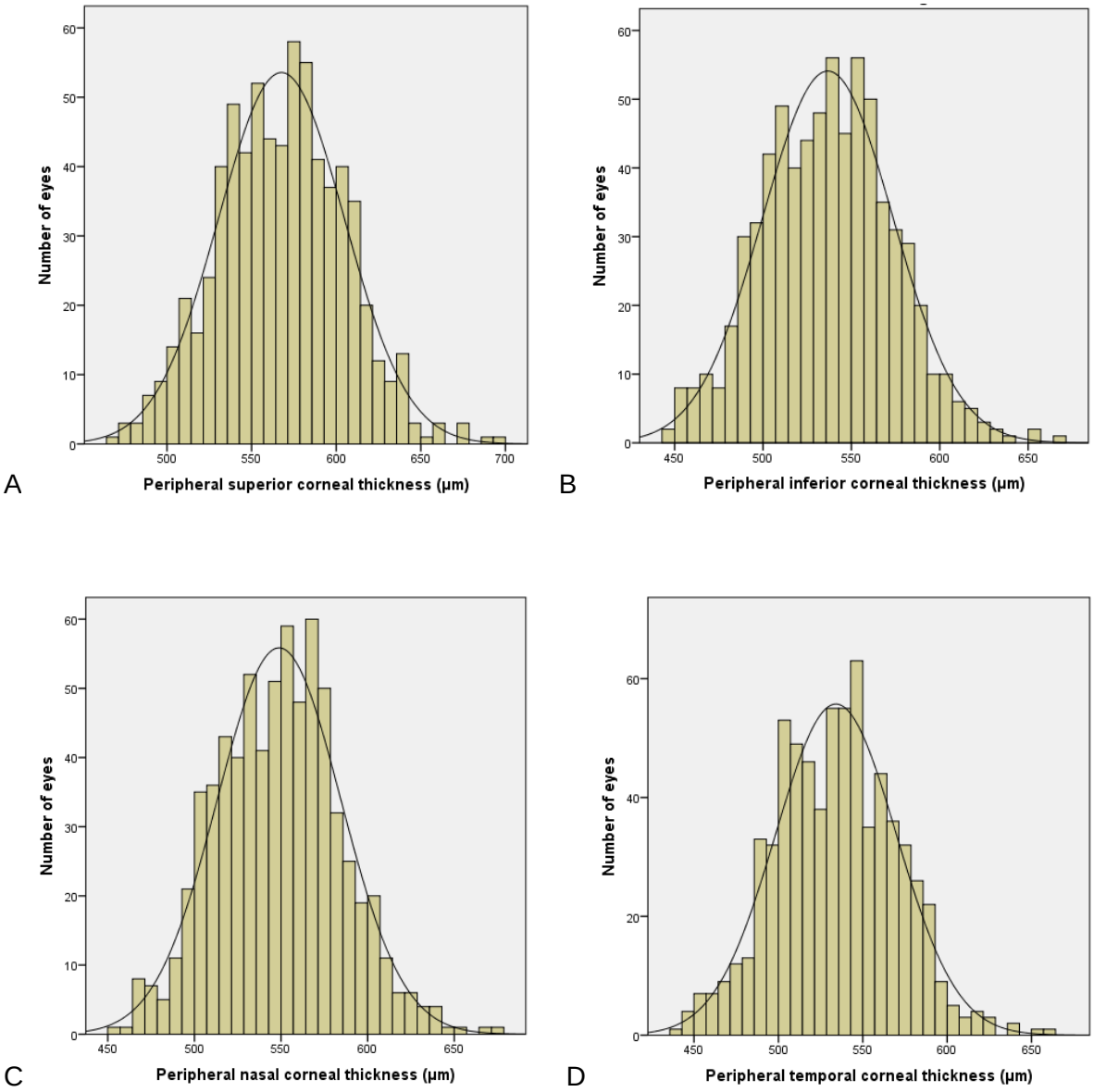


Figure 6.6: Distribution of peripheral superior (A), inferior (B), nasal (C) and temporal (D) corneal thickness (µm) in the right eyes of young adults

Table 6.6 shows the distribution of the measurements for the ACA width variables (AOD500 and TIA) in the nasal and temporal ACAs of the right eye (n = 697). The mean nasal and temporal AOD500 measurements in this study were 551.93 µm and 553.09 µm respectively. The mean nasal AOD500 measurements ranged between 280 µm and 1150 µm whereas the mean temporal AOD500 measurements ranged between 242 µm and 1210 µm. A mean AOD500 measurement of less than 300 µm was noted in only a few participants (n = 3 for the nasal ACA and n = 5 for the temporal ACA). The majority of participants had mean

AOD500 measurements of 500 µm or greater for the nasal (n = 473, 67.9%) and temporal (n = 468, 67.1%) ACAs. The average width of the AveAOD500 measurement was 552.51 ± 110.68 µm.

The mean measurement for the nasal TIA (36.58°) was almost identical to the mean measurement for the temporal TIA (36.77°). Overall, the mean TIA measurements ranged between 22.17° and 53.94° for the nasal ACA and 20.53° and 55.33° for the temporal ACA. None of the participants had mean TIA measurements of 20° or lower for either the nasal or the temporal ACAs. Most of the participants had mean TIA measurements of 30° or more in the nasal (n = 666, 95.6%) and temporal (n = 661, 94.8%) ACAs. The average width of the AveTIA measurement was 36.68 ± 4.65°. On average, the temporal AOD500 and TIA measurements were slightly wider than the nasal AOD500 and TIA measurements.

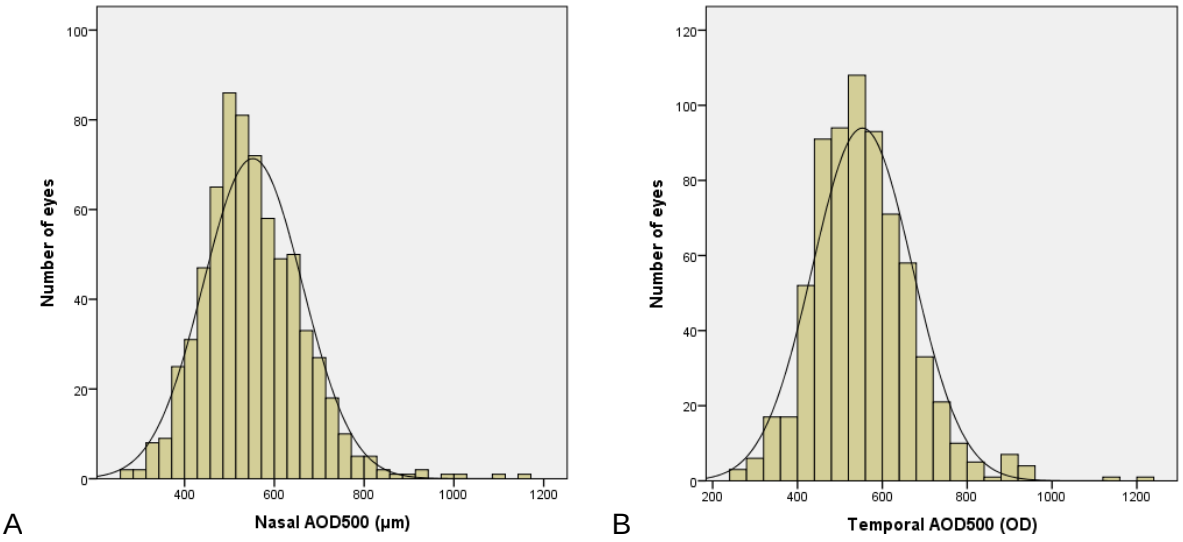
Table 6.6 Distribution of anterior chamber angle variables in the right eye of the sample

Anterior chamber angle variable	Mean ± SD	Median	CI (95% of mean)	Range	Kurtosis	Skewness	S-W
Nasal AOD500 (µm)	551.93 ± 110.68	539	543.68 to 560.19	280 to 1150	2.51	0.86	<0.001
Nasal TIA (°)	36.58 ± 4.58	35.62	36.24 to 36.92	22.17 to 53.94	0.03	0.36	<0.001
Temporal AOD500 (µm)	553.09 ± 117.71	542	544.31 to 561.87	242 to 1210	2.49	0.83	<0.001
Temporal TIA (°)	36.77 ± 4.87	35.94	36.41 to 37.14	20.53 to 55.33	0.40	0.36	<0.001

AOD500 = angle-opening distance taken at 500 µm
TIA = trabecular-iris angle
SD = standard deviation
CI = confidence interval
S-W = Shapiro-Wilk's test for normality p-value

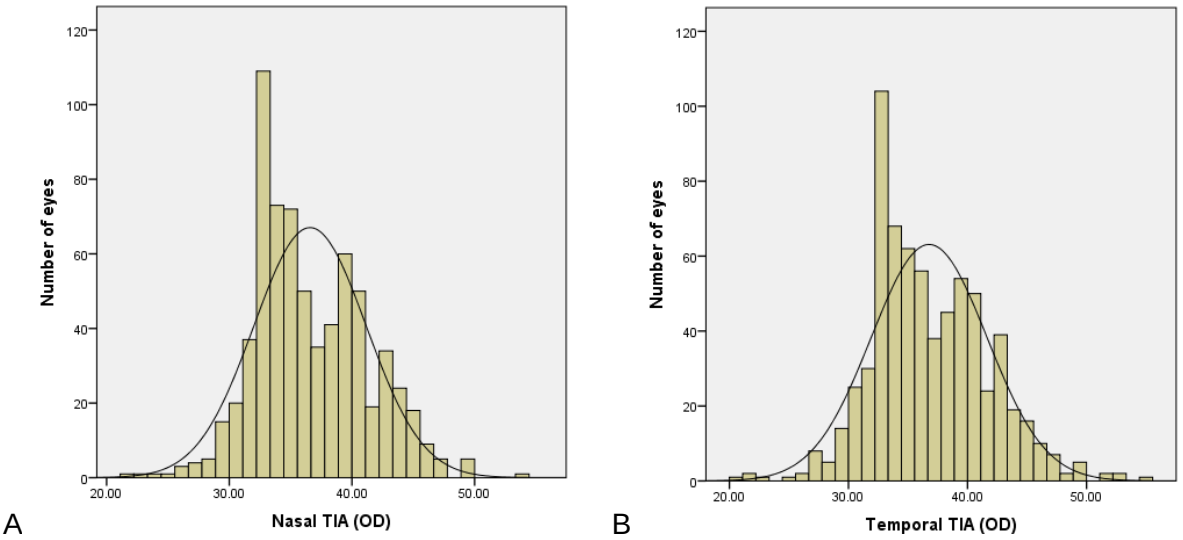
According to the Shapiro-Wilk's test (Table 6.6), both the AOD500 and TIA measurements for the nasal and temporal ACAs were not normally distributed ($p < 0.001$). Histograms for the distribution of nasal and temporal AOD500 and TIA measurements are shown in Figures 6.7 and 6.8 respectively. Both the nasal and temporal AOD500 distributions were positively skewed (moderate) with the right tail of the distributions being slightly longer than the left tail (skewness range, 0.83 to 0.86). In addition, the distributions for the nasal and temporal

AOD500 measurements (Figure 6.7) were leptokurtic implying a central peak which is higher and narrower together with tails that are longer and fatter (that is heavier) compared with a normal distribution (kurtosis range, 2.49 to 2.51).



A B

Figure 6.7: Distribution of nasal (A) and temporal (B) AOD500 measurements (µm) in the right eyes of young adults



A B

Figure 6.8: Distribution of nasal (A) and temporal (B) TIA measurements (°) in the right eyes of young adults

6.5 OBJECTIVE 3: RACIAL VARIATIONS IN ANTERIOR SEGMENT VARIABLES MEASURED USING OCT

The means, standard deviations and confidence intervals for corneal thickness measurements in the different zones for Black (n = 350) and Indian (n = 350) participants are shown in Table 6.7. Indian participants had significantly higher corneal thickness measurements than Black participants for each zone ($p < 0.001$). This corneal thickness difference was greatest in the inferior peripheral quadrant (36.38 µm) and least in the nasal paracentral quadrant (29.10 µm) (Figure 6.9). The mean CCT measurement in Indian participants was 516.60 µm compared with 487.21 µm in Black participants ($p < 0.001$). The difference in CCT measurement between these two race groups is further demonstrated by a 31 µm disparity for the median CCT measurement (485 µm and 516 µm in Black and Indian participants respectively). Approximately two-thirds of Black participants (n = 229, 65.4%) had mean CCT measurements less than 500 µm. In contrast, only 27.7% (n = 97) of the Indian participants showed the same trend of mean CCT measurements less than 500 µm.

The Indian participants had greater paracentral corneal thickness measurements than Black participants in all four quadrants (Table 6.7). This thickness difference in the paracentral cornea ranged between 29.10 µm (nasal) and 32.43 µm (inferior) and was statistically significant ($p < 0.001$) (Figure 6.9). In both Black and Indian participants, the superior paracentral quadrant was thickest followed by the nasal, temporal and inferior quadrants (Table 6.7). The CCT measurement was significantly thinner compared with all quadrants of the paracentral cornea in both Black and Indian participants ($p < 0.001$). The AveParaCT in Black and Indian participants was 505.44 µm and 536.68 µm respectively ($p < 0.001$). This implies that the CCT measurement was 18.23 µm and 20.08 µm thinner than the AveParaCT for Black and Indian participants respectively ($p < 0.001$).

The same trend was observed in the peripheral cornea where Indian participants had significantly higher (thickness difference range, 31.05 µm to 36.38 µm) corneal thickness measurements than the Black participants for all quadrants ($p < 0.001$). This thickness difference in the peripheral cornea ranged between 31.05 µm (nasal) and 36.38 µm (inferior) and was statistically significant ($p < 0.001$) (Figure 6.9). For both Black and Indian participants, the superior peripheral quadrant was the thickest followed by the nasal, inferior and temporal quadrants (Table 6.7). The CCT measurement was significantly thinner compared with all quadrants of the peripheral cornea in both Black and Indian participants ($p < 0.001$). The AvePeriCT was higher in Indian participants (563.62 µm) compared with Black participants (530.01 µm) ($p < 0.001$). Furthermore, the difference in corneal thickness between the mean CCT and AvePeriCT was statistically significant for the Indian (47.02 µm, $p < 0.001$) and Black (42.80 µm, $p < 0.001$) participants.

Table 6.7: Corneal thickness (µm) variations in Black and Indian participants indicated with means, standard deviations and confidence intervals

Cornea variable (µm)	Black (n = 350)		Indian (n = 350)		p-value†
	Mean ± SD	CI (95% of mean)	Mean ± SD	CI (95% of mean)	
CCT	487.21 ± 31.39	483.91 to 490.51	516.60 ± 29.34	513.52 to 519.69	<0.001*
Minimum	480.85 ± 31.30	477.56 to 484.14	510.61 ± 29.61	507.50 to 513.72	<0.001*
Paracentral superior	518.74 ± 32.64	515.31 to 522.17	549.75 ± 30.45	546.54 to 552.95	<0.001*
Paracentral inferior	497.00 ± 31.62	493.67 to 500.32	529.43 ± 30.79	526.19 to 532.67	<0.001*
Paracentral nasal	508.37 ± 31.70	505.04 to 511.71	537.47 ±30.54	534.26 to 540.68	<0.001*
Paracentral temporal	497.64 ± 31.89	494.29 to 500.99	530.06 ± 30.02	526.90 to 533.22	<0.001*
Peripheral superior	551.14 ± 34.41	547.53 to 554.76	584.13 ± 32.37	580.73 to 587.53	<0.001*
Peripheral inferior	518.47 ± 32.63	515.08 to 521.86	554.85 ± 31.91	551.50 to 558.21	<0.001*
Peripheral nasal	533.34 ± 32.47	529.92 to 536.75	564.39 ± 31.87	561.04 to 567.74	<0.001*
Peripheral temporal	517.11 ± 32.12	513.73 to 520.49	551.09 ± 30.91	547.84 to 554.34	<0.001*

CCT = central corneal thickness
SD = standard deviation
CI = confidence interval
† = Independent sample *t*-test
* = statistically significant

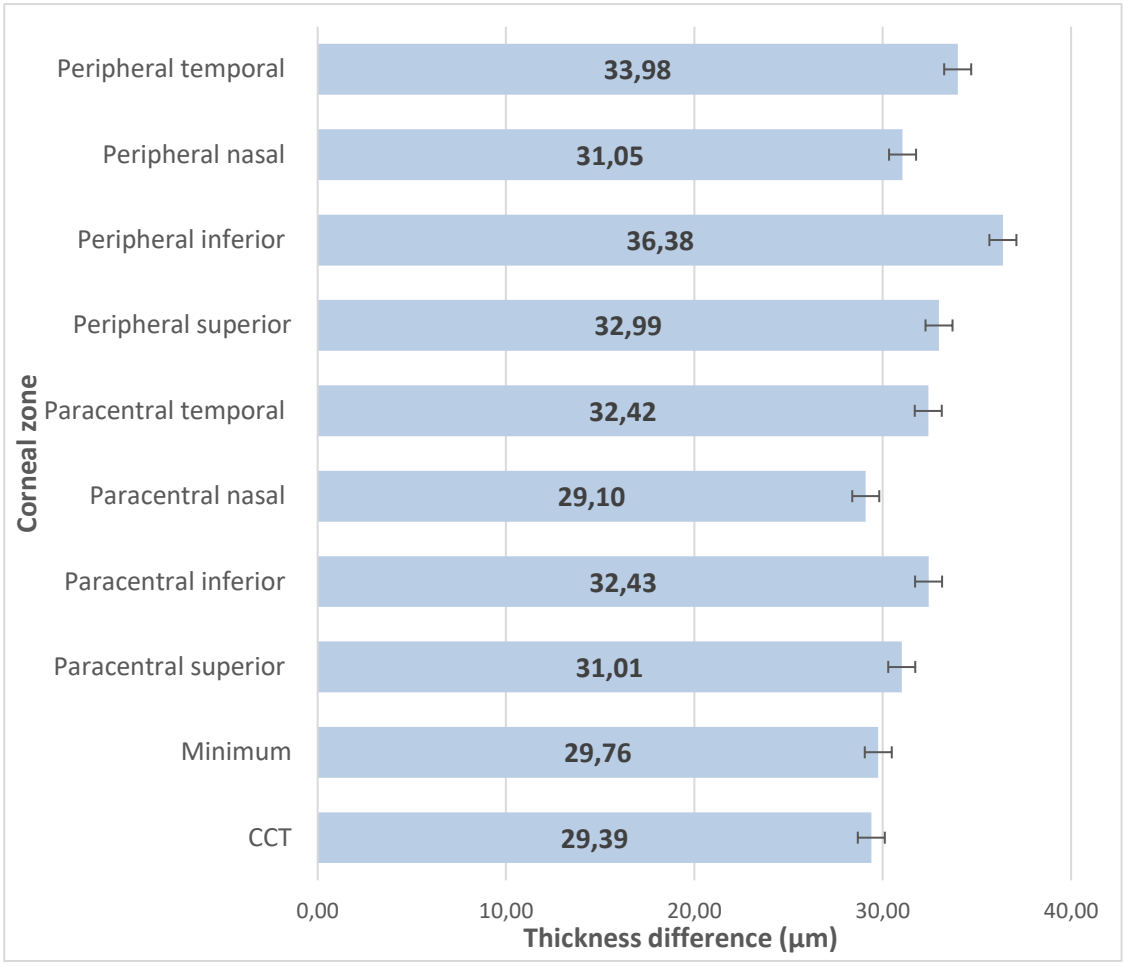


Figure 6.9: Corneal thickness mean differences (µm) for each zone between Black and Indian participants

Similar to the trend for the CCT, paracentral and peripheral corneal thickness measurements, ~30 µm lower minimum corneal thickness measurements (480.85 µm versus 510.61 µm, $p < 0.001$) were noted in Black than in Indian participants (Table 6.7). A small yet significant difference between CCT and minimum corneal thickness was found for both Black (6.36 µm, range between 2 µm and 19 µm) and Indian (5.99 µm, range between 3 µm and 31 µm) participants ($p < 0.001$). The thickness difference between these two points was 9 µm or lower in 93.4% (n = 327) of Black and 97.0% (n = 341) of Indian participants. In Black participants, the thinnest corneal point was most often central (n = 326, 93.1%) and then in the inferotemporal, temporal and inferior quadrants with frequency rates of 4.3%

(n = 15), 1.7% (n = 6) and 0.9% (n = 3) respectively (Figure 6.10). In Indian participants, the location of the thinnest corneal point was most often central (n = 333, 95.1%), followed by the inferotemporal (n = 14, 4.0%) and inferior (n = 3, 0.9%) quadrants (Figure 6.10).

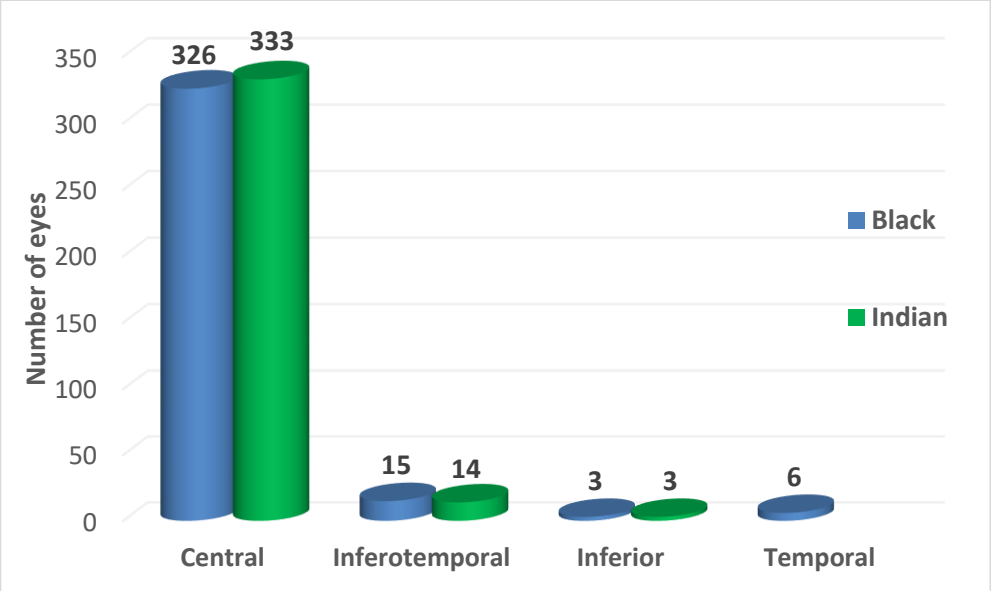


Figure 6.10: Distribution of thinnest corneal point in Black and Indian participants

Table 6.8 presents the medians, interquartile ranges and means for nasal and temporal ACA width variable measurements stratified for race. The median AOD500 measurements were smaller in Black than in Indian participants for both the nasal (534 µm versus 544 µm, p = 0.186) and temporal (536 µm versus 558 µm, p = 0.031) ACAs. The average difference by race for the median AOD500 measurement was ~16 µm (10 µm in the nasal ACA and 22 µm in the temporal ACA). Overall, the median temporal AOD500 measurements were slightly wider than the nasal AOD500 measurements in both Black and Indian participants. A mean AOD500 measurement of less than 300 µm was noted in a few more Indian than Black participants for the nasal (n = 2, 0.6% versus n = 1, 0.3%) and the temporal (n = 4, 1.1% versus n = 1, 0.3%) ACAs. In both races, the majority of participants had mean AOD500 measurements greater than 500 µm for both the nasal (236 Black participants and 237 Indian participants) and temporal (225 Black participants and 243 Indian participants) ACAs.

The median TIA measurements were slightly higher in Black than in Indian participants. The nasal TIA was 0.71° lower in Indian participants than in Black participants (p = 0.068). The temporal median TIA measurement in Black participants (36.01°) was almost identical to that obtained in Indian participants (35.92°) (p = 0.437). On average, the median temporal TIA measurement was slightly wider than the nasal TIA measurement in Indian participants. In Black participants, the nasal and temporal median TIA measurements were relatively similar with a difference of only 0.06°. None of the Black or Indian participants presented with mean TIA measurements of 20° or lower for either the nasal or the temporal ACAs. In both races, the majority of participants had mean TIA measurements of 30° or more for both the nasal (341 Black participants and 325 Indian participants) and temporal (340 Black participants and 321 Indian participants) ACAs.

Table 6.8: Anterior chamber angle variables in Black and Indian participants indicated with medians, interquartile ranges and means

Anterior chamber angle variable	Black (n = 349)			Indian (n = 348)			p-value†
	Median	IQR	Mean	Median	IQR	Mean	
Nasal AOD500 (µm)	534	119	544.54	544	160	561.56	0.186
Nasal TIA (°)	36.07	7.07	36.99	35.36	6.06	36.24	0.068
Temporal AOD500 (µm)	536	140	542.82	558	165	563.29	0.031*
Temporal TIA (°)	36.01	7.31	37.05	35.92	6.58	36.52	0.437

AOD500 = angle-opening distance taken at 500 µm
TIA = trabecular-iris angle
IQR = interquartile range
† = Mann-Whitney U test
* = statistically significant

Figures 6.11 and 6.12 show the nasal and temporal AOD500 and TIA measurement differences in Black and Indian participants respectively. Overall, the mean AOD500 and TIA measurements differed by less than 21 µm and 1º respectively in the two race groups.

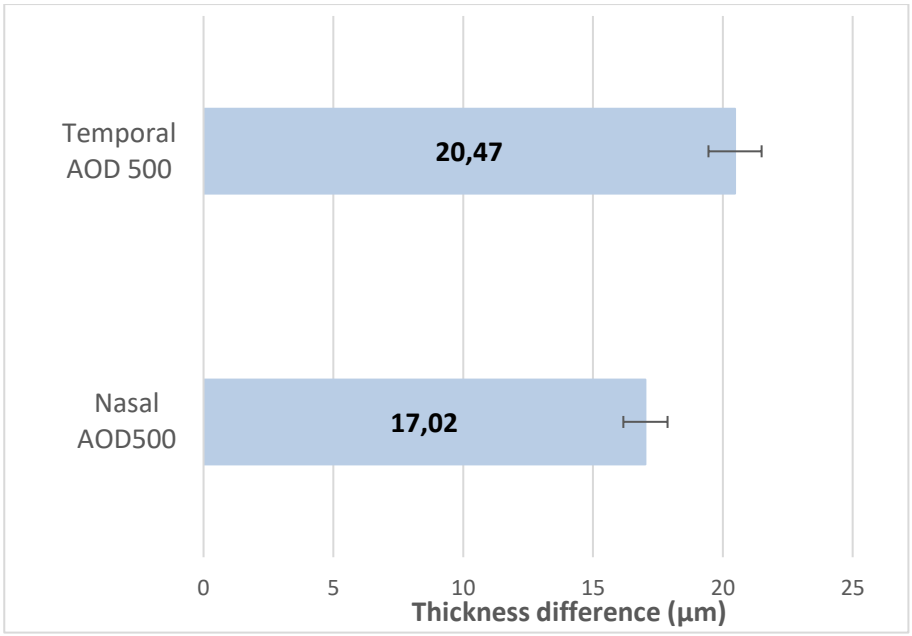


Figure 6.11: Nasal and temporal AOD500 thickness mean differences (µm) between Black and Indian participants

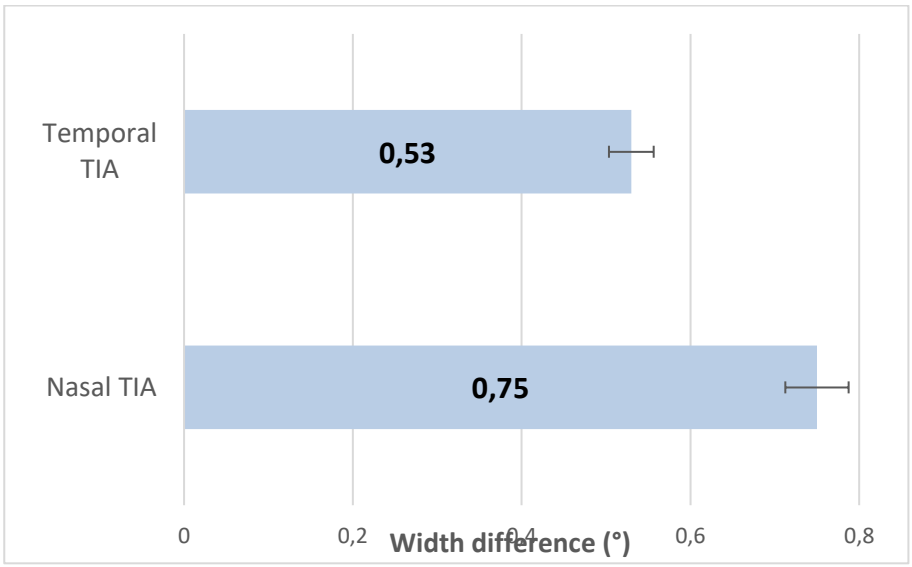


Figure 6.12: Nasal and temporal TIA width mean differences (º) between Black and Indian participants

6.6 OBJECTIVE 4: GENDER VARIATIONS IN ANTERIOR SEGMENT VARIABLES MEASURED USING OCT

The means, standard deviations and confidence intervals for corneal thickness measurements in the different zones for the two gender groups are shown in Table 6.9. For each zone, the mean corneal thickness was greater (range from 0.35 µm to 3.93 µm) in males than females (Figure 6.13). However, these gender differences were not statistically significant ($p \geq 0.137$) (Table 6.9). The mean CCT in female participants was ~3.50 µm thinner than that of male participants (500.14 µm versus 503.67 µm, $p = 0.166$). The gender difference in mean corneal thickness measurements for the paracentral cornea ranged between 1.70 µm and 3.93 µm and for the peripheral cornea between 0.35 µm and 2.87 µm (Figure 6.13). In both male and female participants, the superior quadrant was the thickest followed by the nasal, temporal and inferior quadrants in the paracentral cornea. In the peripheral cornea, the superior and temporal quadrants were the thickest and thinnest respectively for both male and female participants (Table 6.9).

Table 6.9: Corneal thickness (µm) variations in male and female participants indicated with means, standard deviations and confidence intervals

Cornea variable (µm)	Male (n = 350)		Female (n = 350)		p-value†
	Mean ± SD	CI (95% of mean)	Mean ± SD	CI (95% of mean)	
CCT	503.67 ± 34.58	500.04 to 507.31	500.14 ± 32.83	496.69 to 503.59	0.166
Minimum	497.45 ± 34.76	493.79 to 501.10	494.01 ± 32.96	490.54 to 497.47	0.180
Paracentral superior	535.55 ± 35.86	531.78 to 539.32	532.94 ± 34.43	529.32 to 536.56	0.327
Paracentral inferior	514.75 ± 36.06	510.96 to 518.54	511.68 ± 34.21	508.08 to 515.28	0.248
Paracentral nasal	523.77 ± 35.20	520.07 to 527.47	522.07 ± 33.49	518.55 to 525.59	0.512
Paracentral temporal	515.82 ± 35.58	512.08 to 519.56	511.89 ± 34.22	508.29 to 515.48	0.137
Peripheral superior	567.91 ± 37.75	563.94 to 571.87	567.37 ± 36.77	563.50 to 571.23	0.849
Peripheral inferior	537.88 ± 37.50	533.94 to 541.82	535.44 ± 36.24	531.63 to 539.25	0.382
Peripheral nasal	549.04 ± 36.28	545.22 to 552.85	548.69 ± 35.17	544.99 to 552.39	0.898
Peripheral temporal	535.54 ± 36.23	531.73 to 539.35	532.67 ± 35.35	528.95 to 536.38	0.289

CCT = central corneal thickness
SD = standard deviation
CI = confidence interval
† = Independent sample *t*-test

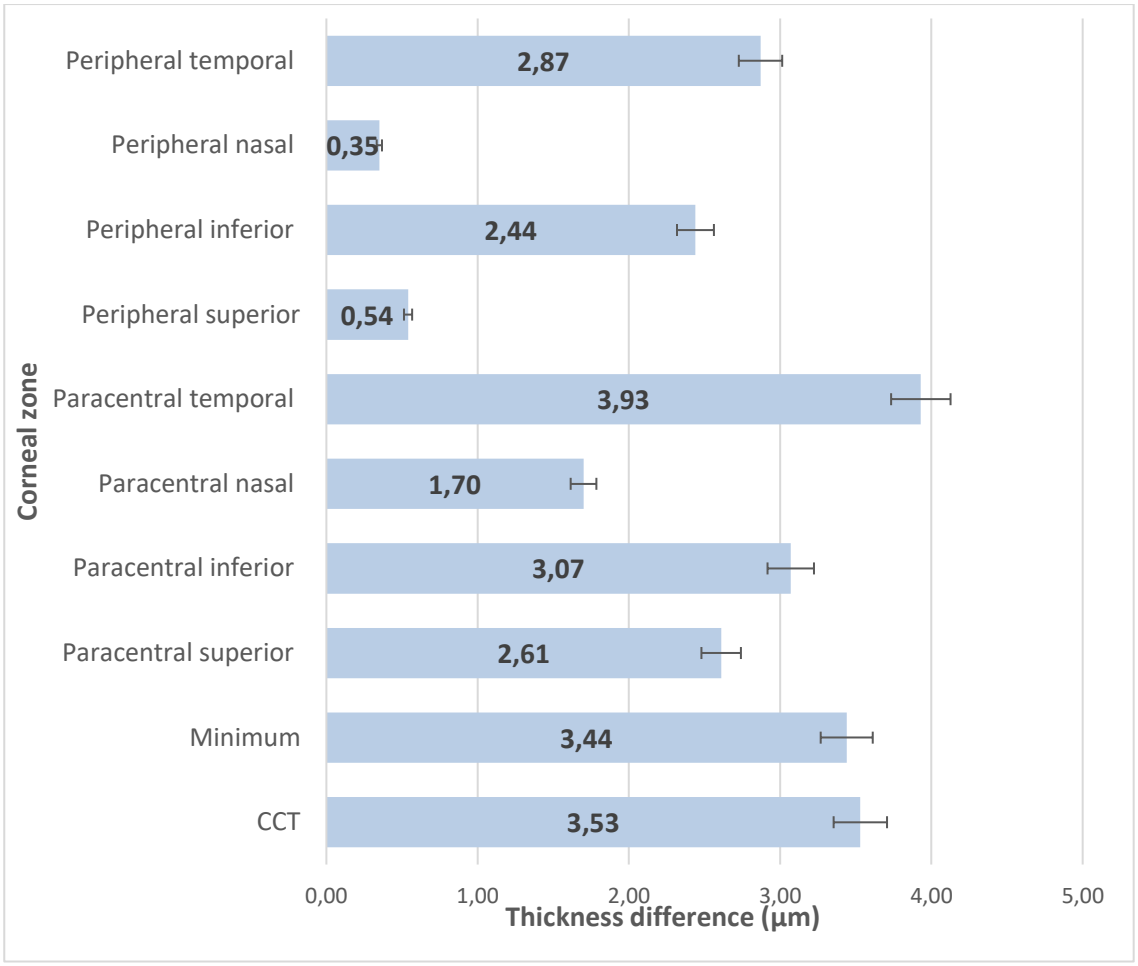


Figure 6.13: Corneal thickness mean differences (µm) for each zone between male and female participants

Similar to the trend for the CCT measurement, ~3.50 µm lower minimum corneal thickness measurements (497.45 µm versus 494.01 µm, p = 0.180) were noted in female than in male participants (Table 6.9). A small yet statistically significant difference between CCT and minimum corneal thickness was found for male (6.22 µm, range between 2 µm and 31 µm) and female (6.13 µm, range between 3 µm and 19 µm) participants (p < 0.001). The thickness difference between these two points was 9 µm or lower in the majority of both male (n = 330, 94.3%) and female (n = 338, 96.6%) participants. In male participants, the thinnest corneal point was most often central (n = 332, 94.9%), followed by the inferotemporal (n = 13, 3.7%), temporal (n = 3, 0.9%) and inferior (n = 2, 0.6%) quadrants (Figure 6.14). In female participants, the thinnest corneal point was also most often central

(n = 327, 93.4%) and then in the inferotemporal, inferior and temporal quadrants with frequency rates of 4.6% (n = 16), 1.1% (n = 4) and 0.9% (n = 3) respectively (Figure 6.14).

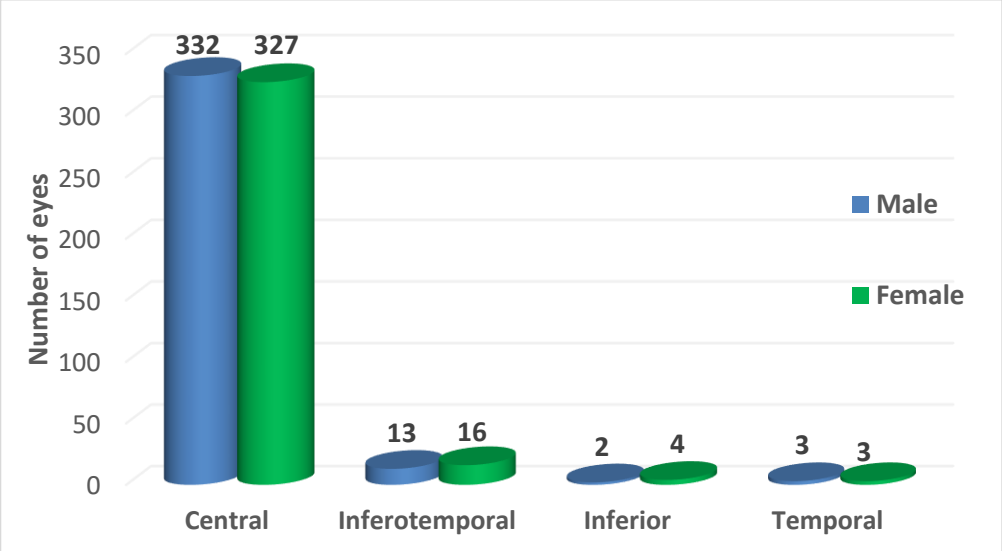


Figure 6.14: Distribution of thinnest corneal point in male and female participants

Table 6.10 shows the medians, interquartile ranges and means for nasal and temporal ACA width variable measurements stratified for gender. Female participants had higher median AOD500 measurements for both the nasal (543.00 µm versus 532.50 µm) and temporal (546.00 µm versus 537.50 µm) ACAs. Although these gender differences were 10.50 µm and 8.50 µm for the nasal and temporal ACAs respectively, they were not statistically significant ($p \geq 0.600$). Overall, the median temporal AOD500 measurement was higher than the median nasal AOD500 measurement in both male and female participants (Table 6.10). For the nasal ACA, a mean AOD500 measurement of less than 300 µm was noted in only a few male (n = 1, 0.3%) and female (n = 2, 0.6%) participants. A similar trend was observed for the temporal ACA where a mean AOD500 measurement of less than 300 µm was noted in only three (0.9%) male and two (0.6%) female participants. In both males and females, the majority of participants had mean AOD500 measurements of 500 µm or greater for both the nasal (239 male and 234 female participants) and temporal (233 male and 235 female participants) ACAs.

On average, the TIA measurements were slightly higher in the female than male participants for both the nasal and temporal ACAs (Table 6.10). The median TIA measurement for the nasal ACA was 35.27° and 36.58° in male and female participants respectively. The median TIA measurement for the temporal ACA was 35.46º and 36.80º in male and female participants respectively. Despite reaching statistical significance (p = 0.029), the average difference for the median temporal TIA measurement was less than 1.5°, which may be considered marginal. Overall, the temporal TIA measurement was slightly wider than the nasal TIA measurement in both male and female participants. None of the male or female participants presented with mean TIA measurements of less than 20° for either the nasal or the temporal ACAs. In both genders, the majority of participants had mean TIA measurements of 30° or more for both the nasal (335 male and 331 female participants) and temporal (330 male and 331 female participants) ACAs.

Table 6.10: Anterior chamber angle variables in male and female participants indicated with medians, interquartile ranges and means

Anterior chamber angle variable	Male (n = 350)			Female (n = 347)			p-value†
	Median	IQR	Mean	Median	IQR	Mean	
Nasal AOD500 (µm)	532.50	133	554.59	543.00	147	551.47	0.959
Nasal TIA (°)	35.27	6.11	36.27	36.58	7.25	36.95	0.078
Temporal AOD500 (µm)	537.50	144	552.61	546.00	149	553.41	0.600
Temporal TIA (°)	35.46	6.41	36.36	36.80	7.49	37.21	0.029*

AOD500 = angle-opening distance taken at 500 µm
TIA = trabecular-iris angle
IQR = interquartile range
† = Mann-Whitney U test
* = statistically significant

Figures 6.15 and 6.16 show the nasal and temporal AOD500 and TIA measurement differences in the two gender groups. Overall, the mean AOD500 and TIA measurements differed by less than 3.5 µm and 1º respectively in the two gender groups.

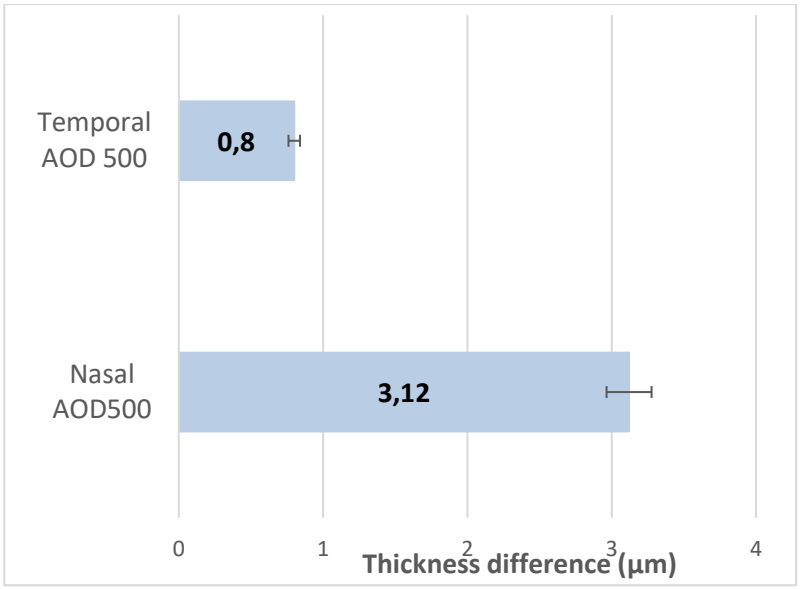


Figure 6.15: Nasal and temporal AOD500 thickness mean differences (µm) between male and female participants

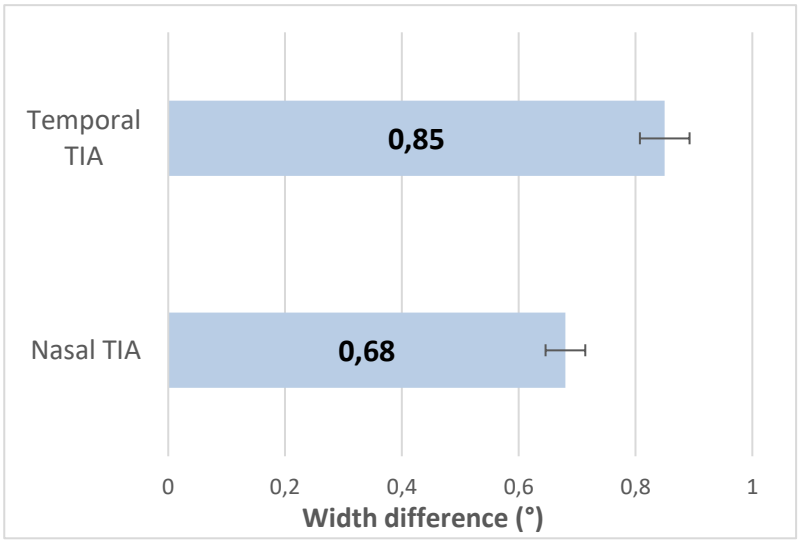


Figure 6.16: Nasal and temporal TIA width mean differences (º) between male and female participants

Overall, a similar pattern of gender differences for the anterior segment variables was noted when stratified for race. Male participants had greater corneal thickness measurements than female participants in the Black (range, 1.09 µm to 5.18 µm with $p \geq 0.129$) and Indian (range, 0.01 µm to 2.68 µm with $p \geq 0.404$) race groups although these gender differences

were insignificant. For the AOD500 measurements in the nasal and temporal ACAs, females had insignificantly higher median measurements than males in the Black (range, 0.50 µm to 4 µm with $p \geq 0.299$) and Indian (range, 20 µm to 21 µm with $p \geq 0.176$) race groups. In Black participants, the median nasal and temporal TIA measurements were slightly higher in females (range, 0.24º to 0.45º) although these gender differences were not statistically significant ($p \geq 0.810$). Indian females had higher median TIA measurements in the nasal (36.83º versus 34.74º $p = 0.007$) and temporal (37.42º versus 35.18º, $p = 0.001$) ACAs. Despite reaching statistical significance, the low magnitude of these gender differences for the median TIA measurements being less than 3º suggests that they may be considered marginal in Indian participants.

6.7 OBJECTIVE 5: EFFECT OF SPHERICAL EQUIVALENT REFRACTION ON ANTERIOR SEGMENT VARIABLES MEASURED USING OCT

Table 6.11 summarises the corneal thickness measurements in the three refractive error groups (emmetropes, myopes and hyperopes). Overall, hyperopes had on average 36 µm and 25 µm higher corneal thickness measurements than emmetropes and myopes respectively. There were statistically significant differences in corneal thickness measurements for all zones among the three refractive error groups ($p \leq 0.001$) (Table 6.11). A post-hoc analysis (Gabriel) revealed that corneal thickness measurements were significantly thinner in the emmetropes compared with myopes for all zones ($p \leq 0.002$). Furthermore, there were statistically significant differences in corneal thickness measurements between the emmetropes and hyperopes for all zones ($p \leq 0.027$) except the inferior quadrant of the paracentral and peripheral cornea ($p \geq 0.051$). Moreover, the myopes also showed thinner corneal thickness measurements in all zones compared with the hyperopes although these differences were not statistically significant ($p \geq 0.115$). It is important to note that as the sample included very few hyperopes ($n = 4$), one should be cautious with interpretation of the results relating to the sample of hyperopes in this study.

Table 6.11: Corneal thickness (µm) variations in the refractive error groups indicated with means and standard deviations

Cornea variable (µm)	Emmetropes (n = 490)	Myopes (n = 206)	Hyperopes (n = 4)	p-value†	F
CCT	498.89 ± 33.13	508.44 ± 33.40	535.25 ± 64.12	<0.001*	7.937
Minimum	492.79 ± 33.15	502.11 ± 33.96	527.25 ± 64.59	0.001*	7.354
Paracentral superior	530.77 ± 34.41	541.84 ± 34.69	568.75 ± 71.97	<0.001*	9.349
Paracentral inferior	509.95 ± 34.35	520.43 ± 35.04	542.00 ± 72.40	<0.001*	7.949
Paracentral nasal	519.85 ± 33.62	529.55 ± 34.09	557.75 ± 70.36	<0.001*	8.018
Paracentral temporal	510.36 ± 34.19	521.54 ± 34.60	546.00 ± 68.54	<0.001*	9.349
Peripheral superior	564.13 ± 36.47	575.32 ± 36.83	601.25 ± 77.75	<0.001*	8.357
Peripheral inferior	532.91 ± 36.18	545.10 ± 36.19	561.50 ± 76.51	<0.001*	9.044
Peripheral nasal	545.49 ± 34.94	556.22 ± 35.40	583.75 ± 72.68	<0.001*	8.664
Peripheral temporal	530.21 ± 34.93	542.72 ± 35.33	567.50 ± 72.92	<0.001*	10.912

CCT = central corneal thickness
† = one-way ANOVA
* = statistically significant
F = F statistic in one-way ANOVA test

Table 6.12 shows the nasal and temporal ACA width variable measurements in the three refractive error groups. There were statistically significant differences for all the ACA width variable measurements among the three refractive error groups ($p < 0.001$) (Table 6.12). A post-hoc analysis showed significantly lower nasal and temporal AOD500 and TIA measurements in the hyperopes compared with both the emmetropes ($p \leq 0.047$) and myopes ($p \leq 0.013$). Furthermore, the myopes had significantly higher nasal and temporal AOD500 and TIA measurements compared with emmetropes ($p < 0.001$). As the sample consisted of few hyperopes (n = 4), one should be cautious with interpretation of the results relating to the sample of hyperopes in this study.

Table 6.12: Anterior chamber angle variables in the refractive error groups indicated with medians and means

Anterior chamber angle variable	Emmetropia (n = 489)		Myopia (n = 204)		Hyperopia (n = 4)		p-value†	x^2
	Median	Mean	Median	Mean	Median	Mean		
Nasal AOD500 (µm)	525.50	537.53	582.00	592.87	384.00	403.50	<0.001*	41.997
Nasal TIA (°)	35.05	36.26	36.90	37.57	32.80	30.51	<0.001*	17.555
Temporal AOD500 (µm)	532.00	537.80	584.50	593.26	373.00	380.50	<0.001*	42.084
Temporal TIA (°)	35.56	36.44	36.92	37.76	31.82	29.57	<0.001*	19.803

AOD500 = angle-opening distance taken at 500 µm
TIA = trabecular-iris angle
† = Kruskal-Wallis test
* = statistically significant
x^2 = chi-square statistic in Kruskal-Wallis test

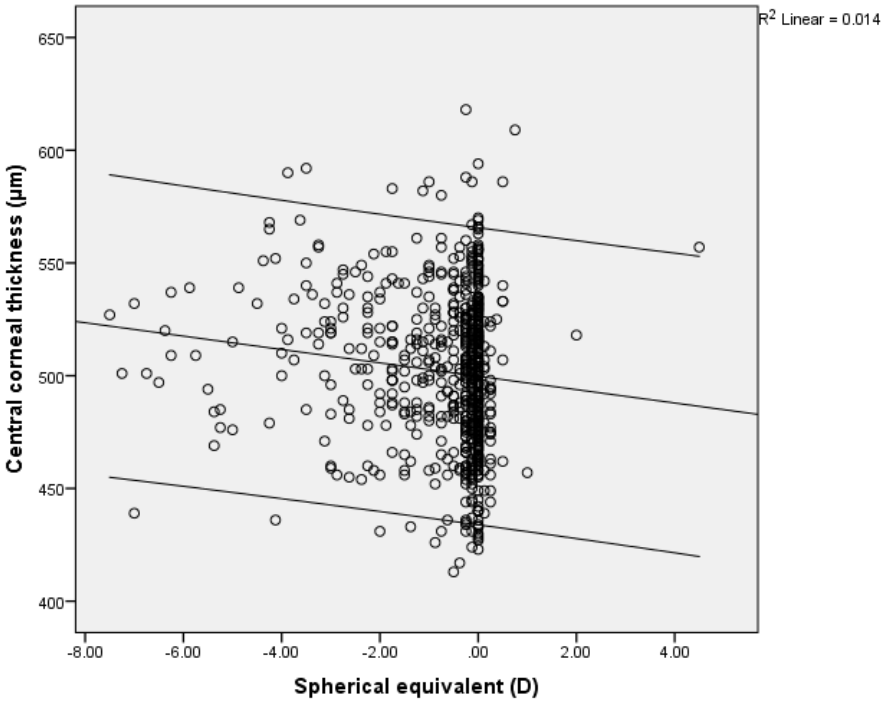
There were significant negative correlations between the anterior segment variables and spherical equivalent refraction (Table 6.13). However, the correlations for the ACA width variables (r_s between –0.125 and –0.222, $p \leq 0.001$) were marginally better than the correlations for the corneal thickness variables (r between –0.111 and –0.149, $p \leq 0.003$). The spherical equivalent refraction was also negatively associated with the AveAOD500 measurement ($r_s = –0.209$, $p < 0.001$) and the AveTIA measurement ($r_s = –0.125$, $p = 0.001$).

Table 6.13: Correlation analyses between anterior segment variables and spherical equivalent refraction

Anterior segment variable	r/r_s value	p-value
CCT	–0.118	0.002†
Minimum	–0.120	0.002†
Paracentral superior	–0.121	0.001†
Paracentral inferior	–0.128	0.001†
Paracentral nasal	–0.111	0.003†
Paracentral temporal	–0.137	<0.001†
Peripheral superior	–0.116	0.002†
Peripheral inferior	–0.139	<0.001†
Peripheral nasal	–0.115	0.002†
Peripheral temporal	–0.149	<0.001†
Nasal AOD500	–0.222	<0.001‡
Nasal TIA	–0.125	0.001‡
Temporal AOD500	–0.201	<0.001‡
Temporal TIA	–0.128	0.001‡

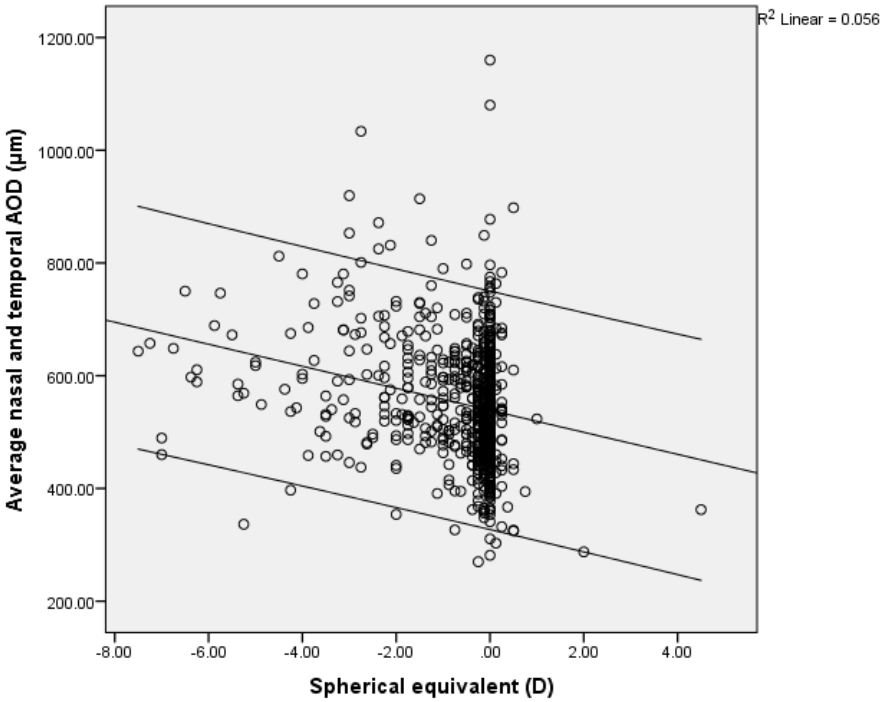
CCT = central corneal thickness
AOD500 = angle-opening distance taken at 500 µm
TIA = trabecular-iris angle
† = statistically significant p-value (Pearson correlation)
‡ = statistically significant p-value (Spearman correlation)

A scatterplot (Figure 6.17) shows the relationship between CCT and spherical equivalent refraction. From the regression line equation for the total sample, for every 1 D change in spherical equivalent, the CCT will change by 2.97 µm. Figure 6.18 shows the relationship between the spherical equivalent refraction and the AveAOD500 measurement wherein the latter will change by 19.53 µm for every 1 D change in spherical equivalent. Figure 6.19 shows the relationship between spherical equivalent refraction and the AveTIA measurement. From the regression line equation for the total sample, for every 1 D change in spherical equivalent, the AveTIA will change by 0.45°.



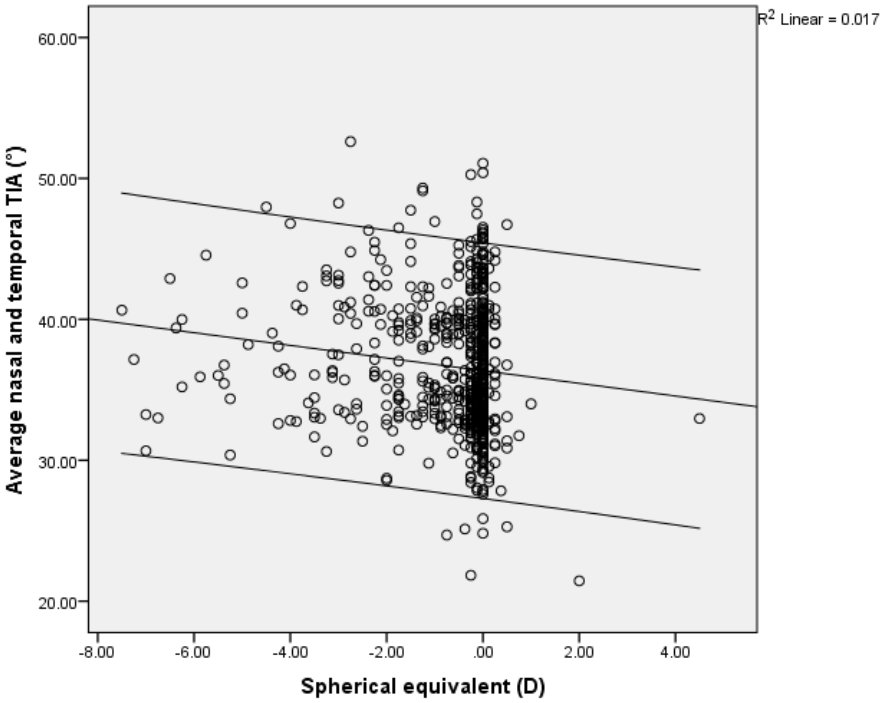
Note: The regression line shows CCT = 499.78 – 2.97 (spherical equivalent)

Figure 6.17: Scatterplot showing the relationship of spherical equivalent and CCT with 95% confidence interval of the regression line (R^2 = 0.014, r = –0.118, p = 0.002)



Note: The regression line shows average nasal and temporal AOD500 = 538.64 – 19.53 (spherical equivalent)

Figure 6.18: Scatterplot showing the relationship of spherical equivalent and AveAOD500 with 95% confidence interval of the regression line (R^2 = 0.056, r = –0.236 and r_s = –0.209, p < 0.001)



Note: The regression line shows average nasal and temporal TIA = 36.36 – 0.45 (spherical equivalent)

Figure 6.19: Scatterplot showing the relationship of spherical equivalent and AveTIA with 95% confidence interval of the regression line (R^2 = 0.017, r = –0.129 and r_s = –0.125, p < 0.001)

6.8 OBJECTIVE 6: REGRESSION TREE MODEL FOR THE INFLUENCE OF ANTERIOR SEGMENT VARIABLES ON IOP

Figures 6.20 and 6.21 show the unpruned and pruned regression tree models respectively. These regression tree models, which were generated automatically by the CART method, are shown with their respective decision rules. The first box in both regression tree models (Figures 6.20 and 6.21) is the root node which contains the total number of participants (n = 700) and displays the mean IOP (dependent variable) of 14.6 mmHg. The successive boxes in grey show the internal nodes which contain the different independent variables and their respective cut-off values (condition). Within the regression tree models, each independent variable occupies a level with each preceding level being more important than the following level. For example, the independent variable at level one is more important than the independent variable at level two and so on. For each internal node at every level,

if the condition (independent variable and its respective cut-off value) is satisfied, the regression tree is followed along the left branch (shown as **YES** in the regression tree models). However, if the condition (independent variable and its respective cut-off value) is not satisfied, the regression tree is followed along the right branch (shown as NO in the regression tree models).

Figure 6.20 shows that only four of the independent variables were selected for inclusion in the unpruned regression tree model. The selected variables were, in order of decreasing importance, CCT, AvePeriCT, axial ACD and AveParaCT (Figure 6.20). There were seven terminal branches in the unpruned regression tree model. Central corneal thickness was the most important variable, at level one, with a cut-off value of 527 µm. At level two, the AvePeriCT was selected as the next most important variable. The cut-off values for the AvePeriCT were 527 µm and 625 µm for CCT values that were less than 527 µm and 527 µm or greater respectively. The highest IOP of 19.4 mmHg was found in 11 participants who had CCT measurements of 527 µm or greater together with AvePeriCT measurements of 625 µm or greater. The lowest predicted IOP of 12.9 mmHg was found in 119 participants who had both CCT and AvePeriCT measurements of less than 527 µm together with an AveParaCT measurement of less than 488 µm. The majority of participants (n = 313, 44.7%) were found in a terminal branch that showed an IOP of 14.6 mmHg in which the CCT measurement was less than 527 µm but the AvePeriCT measurement was 527 µm or greater.

In participants (n = 155, 22.1%) with CCT measurements of 527 µm or greater together with AvePeriCT measurements of less than 625 µm, the predicted IOP differed by 1.1 mmHg depending on whether the axial ACD (level three) was less than 3.6 mm or 3.6 mm and greater. For participants (n = 102, 14.6%) with CCT and AvePeriCT measurements less than 527 µm and AveParaCT measurements of 488 µm or greater, the predicted IOP differed by 1.5 mmHg depending on whether the AvePeriCT was less than 516 µm or

516 µm and greater. On average, the IOP was less than 15 mmHg in participants with CCT measurements that were less than 527 µm and greater than 15 mmHg in participants with CCT measurements that were 527 µm or greater (Figure 6.20).

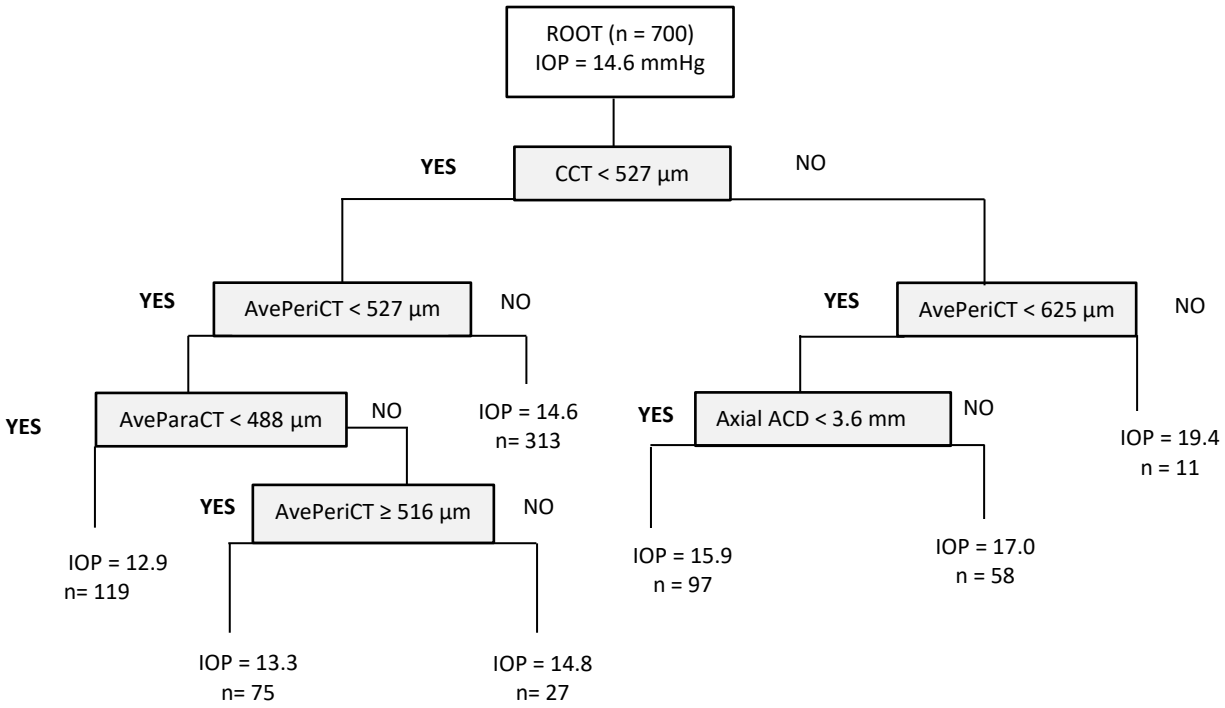


Figure 6.20: Unpruned regression tree model automatically generated by the CART method

Cross-validation was then used to prune this regression tree model to automatically generate an optimal sized regression tree model as indicated in Figure 6.21. The pruned regression tree model (Figure 6.21) consisted of only three independent variables (CCT, AvePeriCT and axial ACD) omitting the AveParaCT from the unpruned regression tree model (Figure 6.20). There were five terminal branches in the pruned regression tree model and any further splitting of the data did not show significant improvement in the regression tree model.

Similar to the unpruned regression tree model, at level one, CCT was the most important independent variable with a cut-off value of 527 µm. The terminal branch with the highest IOP (19.4 mmHg) remained the same and was found in the few participants (n = 11, 1.6%) who had CCT measurements of 527 µm or greater together with AvePeriCT measurements of 625 µm or greater. In the pruned regression tree model (Figure 6.21), the majority of participants (n = 534, 76.3%) had CCT measurements of less than 527 µm and IOP measurements that were less than 15 mmHg. The IOP was 13.2 mmHg in participants (n = 221, 31.6%) with both CCT and AvePeriCT measurements that were less than 527 µm. However, the IOP was 14.6 mmHg in participants (n = 313, 44.7%) who had CCT measurements of less than 527 µm but AvePeriCT measurements of 527 µm or greater.

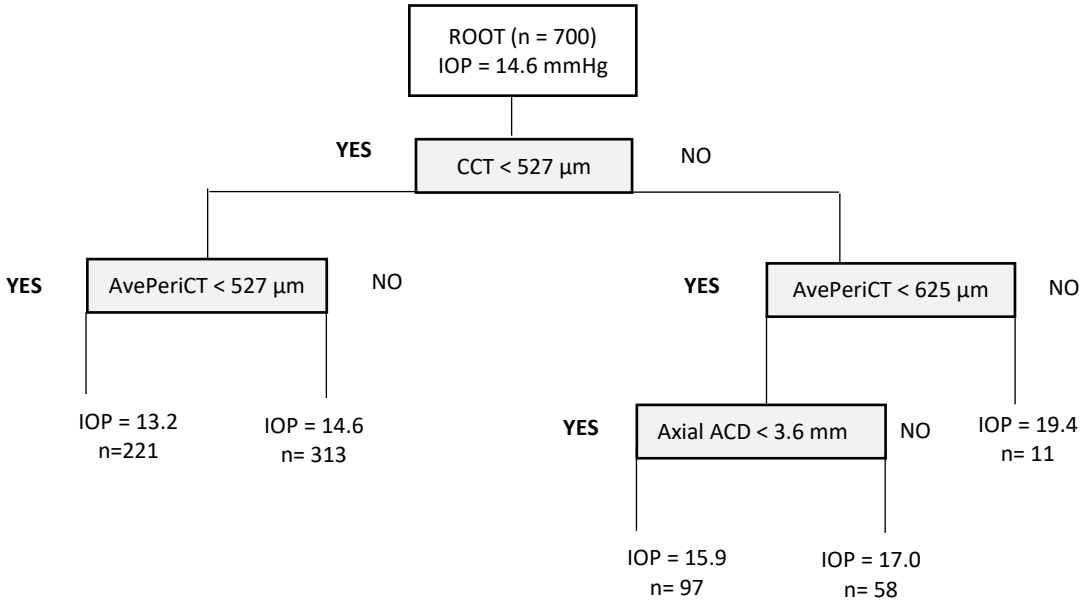


Figure 6.21: Pruned regression tree model automatically generated by the CART method

6.9 CONCLUSION TO THE CHAPTER

This chapter presented the results of phase one of this study. Phase one outlined the clinical description of anterior segment variables, measured using OCT, in a South African young adult population.

CHAPTER 7: DISCUSSION

7.1 INTRODUCTION TO THE CHAPTER

This chapter discusses the results presented in the previous chapter. Initially the demographic and ocular characteristics of the sample are briefly discussed. Thereafter, the discussion for phase one of the study, which consisted of the first six study objectives (1, 2, 3, 4, 5 and 6), is presented. This involves discussing the key findings of phase one of the study within the context of the literature and theoretical framework outlined in the preceding chapters. Moreover, the implications of the key findings are highlighted from a clinical perspective. The discussion from phase one of the study is presented according to the six study objectives.

7.2 DEMOGRAPHIC AND OCULAR CHARACTERISTICS

The age distribution of participants indicates that the study sample consisted of young adults with the majority of participants being younger than 22 years. This finding may be attributed to the study sample being drawn from a university population. In South Africa, as may be the trend globally, the majority of students that register and attend university consist of post secondary school individuals aged between 18 years and 24 years (Council on Higher Education 2013; Spaull 2013). The mean age of participants in this study (20.4 ± 1.8 years) is consistent with other studies that reported on anterior segment ocular biometry variable measurements for samples that were recruited from university populations (Mohd-Ali, Ching & Latif 2009; Sardiwalla et al. 2012). For example, Sardiwalla et al. (2012) reported a mean age of 20.1 ± 1.6 years for participants recruited from a South African university population. In another study, Mohd-Ali, Ching and Latif (2009) recruited participants from a Malaysian university population and reported a mean age of 21.4 ± 1.5 years.

Demographic variables such as age, race and gender are considered to have an effect on anterior segment ocular biometry variable measurements (Faragher et al. 1997; Doughty & Zaman 2000; Friedman et al. 2008; Dimasi, Burdon & Craig 2010). Some studies have reported a decrease in corneal thickness measurements (Su et al. 2009; Yuen et al. 2010; Hashemi et al. 2011) and ACA width variables (Cheon et al. 2010; Qin et al. 2011; Sun et al. 2012a) with increasing age. Consequently, this study consisted of a relatively young adult sample to minimise the effect of age on the anterior segment variable measurements. Moreover, this study included a sample of South African young adults who have been underrepresented in previous studies that have investigated and reported on anterior segment ocular biometry variables. There was an equal distribution of participants in the two race and gender groups to facilitate comparisons between and within the groups with maximal study power (Cohen 1962).

The sample consisted of participants across the different academic levels of study with the majority being students in their first year of study. Individuals at their fourth year or higher comprised the least number of participants. This may be related to the increased levels of academic workload demands and possibly less amounts of free time for students at academic levels beyond the first year (Willcoxson, Cotter & Joy 2011; Scott & Cashmore 2012). The profile of the sample in terms of their hometown reflects the diversity of students that attend university in South Africa, as may be the trend globally, with the number of students from urban areas exceeding those from rural and/or township (semi-urban) areas (Tumbo, Couper & Hugo 2009; Li et al. 2011; Wang 2011).

It is encouraging to note that approximately two-thirds of the sample reported having had a previous eye examination. Moreover, the most recent eye examination was conducted within two years of the study for more than 80% of the participants (n = 437) that reported positively for a previous eye examination. Studies have reported a positive association between education level and utilisation of eye care services (Vela et al. 2012; Olusanya et

al. 2016; Park et al. 2017). Consequently this sample of young adults, in the process of advancing their educational levels, may have been more knowledgeable about the importance of regular eye examinations as well as good eye health and were thus more likely to seek eye care services. Moreover university students, who presumably engage in long hours of detailed work at near and/or intermediate distances, may be more likely to seek eye care services as they have a high prevalence of ocular symptoms and are more sensitive to changes in their vision (Shantakumari et al. 2014; Olusanya et al. 2016; Mowatt et al. 2018). The finding that females were more likely to have been for a previous eye examination is consistent with reports from the literature regarding gender and the utilisation of eye care services (Vela et al. 2012; Park et al. 2017). Overall, the use of spectacles and/or contact lenses was relatively low in this sample. Just under three and one out of every ten participants reported positively for the use of spectacles and contact lenses respectively. The use of spectacles and/or contact lenses was more common in females than males which corroborates the findings from previous studies involving South African school children (Congdon et al. 2008), young adults (Moodley 2009) and middle-aged to elderly adults (Naidoo et al. 2013).

In this study, the mean measurements for ocular variables including corneal diameter, average corneal curvature, corneal astigmatism, axial length, axial ACD and IOP were almost identical in the right and left eyes. This finding is not surprising as the ocular variable measurements for the right and left eyes of the same individual are related when there are no ocular anomalies (Glynn & Rosner 2012; Karakosta et al. 2012; Armstrong 2013). Consequently, the lack of clinically significant interocular differences for the ocular variables may be accounted for by the sample comprising of normal healthy participants without any ocular diseases and/or anomalies. This explanation is reasonable as other studies, which included participants free from ocular diseases and/or anomalies, have also reported similar interocular measurements for anterior and posterior segment ocular variables as well as IOP measurements (Budenz 2008; Falavarjani et al. 2010; Li & Bao 2014; Durr et al. 2015).

An alternative explanation for the almost identical interocular measurements may be related to the inherent structural similarities of the two eyes (Prakash et al. 2010; Li & Bao 2014).

Similar to the other ocular variables, the mean spherical equivalent refraction was almost identical in the right and left eyes. Seven out of every ten participants presented with spherical equivalent refractions that were classified as emmetropia (between +0.50 D and –0.50 D) which is in agreement with the findings of a study involving young adults from a Serbian university population (Risovic et al. 2008). The high prevalence of emmetropia (~70%) in this study may explain why the mean spherical equivalent refraction was relatively low (less than 1 D). It is well known that the prevalence of myopia varies with geographic location (Foster & Jiang 2014; Rudnicka et al. 2016) and is reported to be low in Africa (Sun et al. 2012b; Rudnicka et al. 2016). Slightly less than one-third of the sample presented with myopia which is much lower than the prevalence of myopia reported in other studies involving predominantly Asian university samples (Sun et al. 2012b; Wang et al. 2017) but similar to a study reporting on the refractive errors in a Turkish university sample (Onal et al. 2007). Overall, the prevalence of hyperopia was low which agrees with other studies that have used the same definition of hyperopia as the present study (spherical equivalent refraction more than +0.50 D) and also included young adults from university populations (Blanco, Ferńandez & Sanz 2008; Hashemi et al. 2014; Yekta et al. 2017). Less than half of the sample had astigmatism and in accordance with other studies, WTR astigmatism was most common followed by oblique and ATR astigmatism (Fan et al. 2004; Koh et al. 2014).

7.3 OBJECTIVE 1: INTEROCULAR DIFFERENCES IN ANTERIOR SEGMENT VARIABLES MEASURED USING OCT

Considering that the eyes are one of the paired organs in the human body, the extent of interocular symmetry, or lack thereof, can be useful to evaluate the accuracy of ocular variable measurements as well as to detect ocular diseases and/or anomalies (Myrowitz, Kouzis & O'brien 2005; Falavarjani et al. 2010; Li & Bao 2014). The measures of interocular

symmetry included the ICC and Bland Altman analysis with the latter comprising of the mean interocular difference and LoAs as they are not influenced by paired measurements from the two eyes (McAlinden, Khadka & Pesudovs 2011; Armstrong 2013). Overall, the anterior segment variables of the right and left eyes showed high levels of symmetry as the ICCs were higher than 0.81 which suggests good to excellent degrees of agreement (Landis & Koch 1977; Budenz 2008). Moreover, the mean interocular differences for the corneal thickness and ACA width variable measurements were marginal and thus unlikely to be clinically important.

In this study, corneal thickness measurements of the right and left eyes were almost identical and showed almost perfect levels of interocular agreement as the ICCs were greater than 0.974 and the mean interocular differences were less than 6.5 µm. These results are in agreement with other studies that have reported high correlations between the two eyes for both central and peripheral corneal thickness measurements in population-based (Zheng et al. 2008; Hashemi et al. 2011) and clinic-based (Módis, Langenbucher & Seitz 2004; Rüfer et al. 2007) studies. The mean interocular difference for the CCT measurement was only 0.23 µm. Previous studies have reported on interocular differences for CCT measurements (Hahn et al. 2003; Prakash et al. 2010; Li & Bao 2014). For example, Hahn et al. (2003) reported a mean CCT interocular difference of 7.7 µm for 1578 participants aged 40 years and older. In a more recent study, Li and Bao (2014) reported high levels of interocular symmetry and a mean interocular difference of 0.51 µm for CCT measurements. In their study, Li and Bao (2014) evaluated 397 participants with a mean age of 23.81 years. Prakash et al. (2010) noted an interocular difference of 0.68 µm for CCT measurements in 100 participants aged between 23 years and 32 years.

It is possible that the smaller and relatively similar (less than 1 µm) interocular difference for the CCT measurement observed in this study and that by Li and Bao (2014) as well as Prakash et al. (2010) may be related to the age of the study participants. It is likely that

younger adult participants are able to fixate better, than older adult participants, thus resulting in the lower mean interocular CCT differences. It is well established that there are structural and physiological changes in the eye with increasing age (Owsley 2011), yet little is known about the levels of interocular symmetry due to ageing. However, it is possible that age may play a part in fixation as recent studies have reported age related changes in oculomotor function (Warren et al. 2013; Dowiasch et al. 2015) and an earlier study reported that older individuals showed more fixation inconsistencies along the horizontal meridian than vertical meridian when compared with younger individuals (Kosnik, Fikre & Sekuler 1986). In terms of the Bland Altman analysis, 95% of the interocular differences for the mean CCT measurements ranged between –11.53 µm and 11.07 µm. This implies that 95% of the mean CCT measurements for the right and left eyes differed by less than ± 12 µm which is approximately two times smaller than the 24.9 µm noted as the upper limit for the CCT interocular difference in a previous study (Hahn et al. 2003).

In this study, the minimum corneal thickness measurement showed the highest ICC of 0.994 and an interocular difference of just less than 0.50 µm. These findings are in agreement with a recent study (Durr et al. 2015) which also reported high levels of interocular symmetry for minimum corneal thickness measurements. In their study, Durr et al. (2015) reported an ICC of 0.984 and an interocular difference of 0.28 µm. In contrast, other studies have reported higher interocular differences for minimum corneal thickness measurements (Myrowitz, Kouzis & O'brien 2005; Falavarjani et al. 2010). Myrowitz, Kouzis and O'brien (2005) reported that the minimum corneal thickness measurements between the two eyes were highly correlated with an interocular difference of 8 µm. Falavarjani et al. (2010) reported an interocular difference of 8.42 µm when only a single measurement was taken for the minimum corneal thickness in each eye. The 275 participants in the study by Falavarjani et al. (2010) were older (mean age of 29.1 ± 7.7 years with a wider age range of 18 years to 56 years) which may explain the larger interocular differences compared with the present study.

For the paracentral and peripheral corneal thickness measurements, the nasal and temporal quadrants showed the lowest ICCs which ranged from 0.975 to 0.983. Despite being the lowest, these ICCs were still higher than 0.81 indicating good to excellent degrees of agreement (Landis & Koch 1977; Budenz 2008). Moreover the interocular differences for the nasal and temporal quadrants, although being the largest, were less than 6.5 µm and can be considered as relatively small. The explanation for the nasal and temporal quadrants consistently showing the lowest ICCs and largest interocular differences is unknown. However, it may be related to the way in which non-contact devices measure corneal thicknesses beyond the central cornea as studies have reported more variability for repeated corneal thickness measurements in the nasal and temporal quadrants when measured with Scheimpflug photography (Milla et al. 2011) and OCT (Rampersad & Hansraj 2016; Mansoori & Balakrishna 2017) devices.

The identification of the scleral spur is necessary for measurement of the ACA width variables (Radhakrishnan et al. 2007; Narayanaswamy et al. 2010). Studies have noted that visualisation and identification of the scleral spur are more difficult when vertical ACAs are imaged, individuals are older, the quality and resolution of the ACA images are poor and/or the ACA width is narrow (Radhakrishnan et al. 2007; Sakata et al. 2008; Liu et al. 2010; Seager et al. 2014). Previous studies, using time-domain OCT devices to image the nasal and temporal ACAs, have reported poor visibility of the scleral spur in the ACA images of 25% to 27% of study participants (Sakata et al. 2008; Narayanaswamy et al. 2010; Wang et al. 2011). The researchers attributed the relatively high number of participants that had to be excluded from the analysis, as the scleral spur could not be identified in the ACA images, to the low resolution capability of the OCT device being used to image the ACA (Sakata et al. 2008; Narayanaswamy et al. 2010). Despite also using a time-domain OCT device to image the ACA in a sample of middle-aged Indian adults, Sihota et al. (2012) reported that the scleral spur was visible in all the ACA images. In their study, Sihota et al. (2012) imaged the right eye of participants three times using the enhanced scan protocol which processes

and averages four images of the ACA to create one ACA image with improved contrast. Consequently, Sihota et al. (2012) explained that the discrepancies regarding the visualisation of the scleral spur in the ACA images in their study, compared with other studies, may be accounted for by the enhanced ACA images that they were able to acquire and analyse.

Previous studies have also used Fourier-domain OCT devices to image the nasal and temporal ACAs (Cheung et al. 2011; Grewal et al. 2011; Quek et al. 2012; Qin et al. 2013). Overall, these studies have reported better visibility rates of the scleral spur with the latter being identified in 81% to 88% of the ACA images of study participants (Cheung et al. 2011; Grewal et al. 2011; Quek et al. 2012; Qin et al. 2013). A study by McKee et al. (2013) imaged the ACAs in both the vertical and horizontal meridians, using a Fourier-domain OCT device, in one eye of 30 normal healthy Asian participants. In their study, McKee et al. (2013) reported that the scleral spur was visible in 97% to 100% of the horizontal ACA images. In the present study, the scleral spur could not be identified in only three and two participants for the right and left eyes respectively. This implies that the scleral spur was not identified in the ACA images of just under 1% of the study sample which is comparable with the findings of McKee et al. (2013).

The lower rates of poor visibility of the scleral spur noted in the present study and others (Cheung et al. 2011; Grewal et al. 2011; Quek et al. 2012; McKee et al. 2013; Qin et al. 2013) may be explained by the use of Fourier-domain OCT devices to image the ACA. Compared with time-domain OCT devices, Fourier-domain OCT devices use broader bandwidths and shorter wavelengths that allow for more than three times better axial and transverse resolutions which may explain the lower number of ACA images with poor visibility of the scleral spur (Schuman 2008; Li et al. 2010; Wojtkowski 2010). Moreover, Fourier-domain OCT devices are capable of generating more axial scans in shorter acquisition times as they have scanning speeds that are approximately 10 to 110 times

faster than time-domain OCT devices (Christopoulos et al. 2007; Schuman 2008; Wojtkowski 2010). Consequently, the effect of eye movements and/or motion artifacts are also minimised which may further account for the higher visibility rates of the scleral spur in the ACA images obtained using Fourier-domain OCT devices (Li et al. 2010; Bald, Li & Huang 2012).

Even though several studies have reported on ACA width variable measurements in the literature, the way in which the results have been presented in relation to the right and left eyes is inconsistent. The majority of studies have reported on the ACA width variable measurements of only one eye (Li et al. 2007; Ramani et al. 2007; Friedman et al. 2008; Leung et al. 2008; Xu et al. 2008; Leung et al. 2010; Grewal et al. 2011; Liu et al. 2011; Shimizu et al. 2017). In contrast, some studies have imaged both the right and left eyes of participants but grouped the measurements and reported on the average ACA width variables (Pekmezci, Porco & Lin 2009; Cheon et al. 2010) whereas other studies have reported on the ACA width variable measurements for both the right and left eyes (Yi et al. 2008; Rüfer et al. 2010; Kim et al. 2011; Fernández-Vigo et al. 2016).

In this study, the ACA width variable measurements of the right and left eyes were almost identical and showed high levels of interocular agreement as the ICCs were greater than 0.933. This finding is in agreement with other clinic-based studies that also noted similar measurements for ACA width variables in the right and left eyes (Yi et al. 2008; Rüfer et al. 2010; Kim et al. 2011; Fernández-Vigo et al. 2016). The mean interocular differences for the nasal and temporal AOD500 measurements were less than 2.5 µm and are unlikely to be clinically important. This result is consistent with that of Kim et al. (2011) who noted similar mean nasal and temporal AOD500 measurements for the two eyes with no statistically significant interocular differences. The mean interocular differences for the nasal and temporal TIA measurements were marginal (≤ 0.10°) and unlikely to be clinically important. This finding is consistent with other studies that have also reported small

interocular differences, which were less than 2°, for the nasal and temporal mean TIA measurements (Yi et al. 2008; Rüfer et al. 2010; Fernández-Vigo et al. 2016). The lack of clinically significant interocular differences in the ACA width variables may be due to the use of a non-contact imaging device, which uses near infrared light, with an inbuilt external fixation target that minimised that influence of pupil size on the ACA width variables (Li et al. 2007). There is limited information on the Bland Altman interocular LoAs for ACA width variables which limits the comparison of the upper and lower LoAs observed in the present study to other findings.

Taken together, the anterior segment variables of the two eyes showed high levels of interocular symmetry and marginal mean interocular differences. This suggests that in the absence of ocular diseases and/or anomalies, similar anterior segment variable measurements should be expected in the right and left eyes of normal healthy individuals when using an OCT device. Consequently, significant interocular differences in anterior segment variable measurements can be an indicator of ocular pathology and/or inaccuracies in the measuring device. The findings also suggest that measuring the anterior segment variables in both the right and left eyes may be unnecessary in normal healthy individuals. Considering the high levels of interocular symmetry in the present study, data from only the right eyes were analysed and presented for the remaining study objectives as has been done in previous studies that have reported on anterior and posterior segment ocular variables (Huynh et al. 2006; Zheng et al. 2008; Su et al. 2009; Hashemi et al. 2011; Wagner-Schuman et al. 2011; Mostafa 2014). This is aligned to the recommendation of using data from only one eye when there are high levels of interocular symmetry for the data from the two eyes (McAlinden, Khadka & Pesudovs 2011; Armstrong 2013).

7.4 OBJECTIVE 2: DISTRIBUTION OF ANTERIOR SEGMENT VARIABLES MEASURED USING OCT

In this study, a mean CCT measurement of ~502 µm was found using a Fourier-domain OCT device. Other studies involving South African young adult samples, with similar demographic characteristics, have reported mean CCT measurements of ~519 µm (Rampersad, Mashige & Jhetam 2011; Sardiwalla et al. 2012). This suggests that the mean CCT found in this study is thinner than that reported in studies involving similar South African samples. Differences in study methodologies, particularly concerning the device used to measure corneal thickness, may account for the variation in mean CCT measurements observed in these studies. The higher CCT measurements in the two studies, involving South African young adult samples, were obtained using Scheimpflug photography devices (Rampersad, Mashige & Jhetam 2011; Sardiwalla et al. 2012). Previous studies have reported higher mean CCT measurements with Scheimpflug photography devices than OCT devices when corneal thickness measurements were compared in the same study sample (Ho et al. 2007; Doors et al. 2009; Randleman et al. 2015). Consequently, the higher CCT measurements in the other studies involving South African samples (Rampersad, Mashige & Jhetam 2011; Sardiwalla et al. 2012) may be accounted for by the use of a Scheimpflug photography device.

The mean CCT measurement found in the present study is considerably lower than the mean CCT measurements reported in previous studies involving various sub-populations globally. Studies involving Caucasian and Asian sub-populations have reported mean CCT measurements that ranged from 527 µm to 554 µm and 511 µm to 575 µm respectively (Cho & Lam 1999; Doughty et al. 2002; Sanchis-Gimeno et al. 2004a; Vijaya et al. 2010). With the exception of the two studies involving the South African samples mentioned above, the mean CCT measurements for other African sub-populations ranged from 519 µm to 550 µm (Gelaw et al. 2010; Iyamu & Eze 2011). The mean CCT measurement in the present study is also lower than the normal expected CCT measurement of 535 µm reported in the meta-

analysis by Doughty and Zaman (2000). The discrepancy in mean CCT measurement found in this study versus other studies involving Caucasian, Asian and African sub-populations may be the result of various factors including differences in sample size, study design, gender as well as age distribution of participants and ethnicity (Doughty & Zaman 2000; Aghaian et al. 2004; Mohan et al. 2007).

The device used to measure the CCT is also an important consideration as different pachymeters may result in varying CCT measurements (Doughty & Zaman 2000). Studies have reported that corneal pachymetry devices based on the principles of ultrasound, slit-scanning topography, Scheimpflug photography and OCT are reliable for repeated measurements of CCT (Doors et al. 2009; Huang et al. 2010; Li et al. 2010; Milla et al. 2011; Mansoori & Balakrishna 2017). In spite of this, several studies caution against comparing CCT measurements across studies as well as using pachymetry devices interchangeably as these devices are based on different operating principles that are likely to contribute to varying CCT measurements (Doors et al. 2009; Su et al. 2009; Li et al. 2010; Ishibazawa et al. 2011; Tai et al. 2013). Consequently, the difference in mean CCT measurement observed in this study compared with previous studies involving African, Caucasian and Asian sub-populations globally may also be explained by the use of varying corneal pachymetry devices.

Studies that used ultrasound pachymetry devices reported mean CCT measurements that ranged from 519 µm to 550 µm, 527 µm to 548 µm and 511 µm to 575 µm in African, Caucasian and Asian sub-populations respectively (Cho & Lam 1999; Doughty et al. 2002; Gelaw et al. 2010; Vijaya et al. 2010; Gros-Otero, Arruabarrena-Sánchez & Teus 2011; Iyamu & Eze 2011). Accordingly the mean CCT measurement of ~502 µm in the present study, obtained using a light-based pachymetry device, is lower than the mean CCT measurements reported in studies that used sound-based pachymetry devices. It is likely that the thinner CCT measurement observed in this study is due to the differing operating

principles of light-based and sound-based corneal pachymetry devices as studies have observed that CCT measurements are lower with OCT devices compared with ultrasound pachymetry devices when taken on the same study sample (Ho et al. 2007; Chen et al. 2012).

As a result of its ultrahigh resolution together with fast scanning speeds and non-contact nature, OCT devices are being widely used for clinical, research and surgical applications of the cornea (Simpson & Fonn 2008; Sandali et al. 2013). The comparison of the mean CCT measurement found in the present study to previous studies, involving predominantly Asian sub-populations, which used OCT devices to measure the CCT reveals interesting trends. In most of the studies involving Asian sub-populations (Zhang et al. 2008; Yuen et al. 2010; Ang et al. 2012), the mean CCT measurements were greater than 555 µm which implies that the mean CCT in the present study is ~53 µm thinner. The studies involving the Asian sub-populations consisted of middle-aged to elderly adult participants with mean ages older than 56 years which could underlie the variation observed. Other studies that used OCT devices to measure the CCT in samples consisting of younger adults, with mean ages less than 36 years, have reported mean CCT measurements of 533 µm to 537 µm (Keech, Simpson & Jones 2010; Huang et al. 2014). This suggests that differences in mean CCT measurements are apparent even when devices based on the same operating principles are used. This further adds to the argument that comparisons of mean CCT measurements across studies must be interpreted with caution as various factors including age, sample size, gender distribution of participants, study criteria, anthropometic measurements, corneal curvature, refractive error and type of pachymetry device can influence the CCT measurements (Cho & Lam 1999; Doughty & Zaman 2000; Nemesure et al. 2003; Su et al. 2009; Hashemi et al. 2011; Iyamu & Osuobeni 2012).

Knowledge of the mean CCT measurement is necessary for interpreting the IOP measurements (Mohan et al. 2007). The clinical gold standard for IOP measurements is

Goldmann applanation tonometry (Schneider & Grehn 2006; Avitabile et al. 2010) which is calibrated on a theoretical assumption of a CCT measurement of 520 µm (Whitacre, Stein & Hassanein 1993). In an early study, Ehlers (1970) concluded that IOP measurements may be altered by 5 mmHg for any deviation of 70 µm on either side of 520 µm. The association between IOP and CCT is well known with several studies having reported that the IOP is underestimated in thinner corneas and overestimated in thicker corneas (Suzuki et al. 2005; Nangia et al. 2010; Vijaya et al. 2010). The mean CCT measurement of ~502 µm found in the present study is lower than the theoretical assumption of Goldmann applanation tonometry. This implies that the IOP measurements in the present study, with Goldmann applanation tonometry, may have been underestimated in this sample of South African young adults.

The CCT measurement is also necessary for making decisions regarding corneal surgeries and/or selecting individuals for laser in situ keratomileusis (Mohan et al. 2007; Nakhjavanpour et al. 2016). Thinner corneas with preoperative CCT measurements lower than 500 µm are considered at risk for developing keratectasia post laser in situ keratomileusis (Randleman et al. 2008; Tatar et al. 2014). Consequently, laser in situ keratomileusis is usually not performed in individuals with corneas that have CCT measurements lower than 500 µm (Khairat et al. 2013). In this study, approximately 47% of the sample had mean CCT measurements that were less than 500 µm. Nevertheless, the finding that slightly less than half of the sample had mean CCT measurements lower than 500 µm may not have any implications for laser in situ keratomileusis considering that the majority of participants presented with emmetropia. However, the percentage of participants with mean CCT measurements lower than 500 µm in the present study is more than two times higher than a previous study which reported that 21.4% of participants had mean CCT measurements lower than 500 µm (Hashemi et al. 2011).

Doughty and Zaman (2000) concluded that CCT measurements greater than 600 µm are observed in less than 5% of a normal population. In this study, just under 1% of the sample (n = 2) presented with mean CCT measurements that were greater than 600 µm. This finding is consistent with other studies that have also reported small proportions of their samples, consisting of healthy non-glaucomatous participants, with mean CCT measurements greater than 600 µm. For example, Eballe et al. (2010) and Durkin et al. (2007) reported that 3.09% and 2.65% of their study participants respectively had mean CCT measurements greater than 600 µm. As expected, the percentage of participants with mean CCT measurements greater than 600 µm in the present study is considerably lower compared with studies that included participants with ocular hypertension and corneal anomalies. For example, approximately one out of every four participants in the OHTS had mean CCT measurements greater than 600 µm (Brandt et al. 2001), which is not surprising, considering that the OHTS only included participants with ocular hypertension. Aghaian et al. (2004) reported that 7.2% of their participants had mean CCT measurements greater than or equal to 600 µm. This percentage, which is lower than the 24% reported in the OHTS but higher than that found in the present study, may be owing to Aghaian et al. (2004) including both normal participants and participants with various glaucoma disorders (primary open-angle, chronic angle-closure, normal tension, ocular hypertension and pseudoexfoliation) in their study sample.

In this study, the standard deviation for the CCT measurement was 33.74 µm which is comparable with the findings of other studies that have measured and reported on CCT measurements using non-contact (Keech, Simpson & Jones 2010; Hashemi et al. 2011; Fares et al. 2012) and contact (Hahn et al. 2003; Casson et al. 2008; Thapa et al. 2012) pachymetry devices. Moreover, the standard deviation for the CCT measurement was lower than the standard deviation for all the corneal thickness measurements beyond the central cornea as has been the trend in several other studies (Zheng et al. 2008; Mohd-Ali, Ching & Latif 2009; Hashemi et al. 2011; Huang et al. 2014; Ortiz et al. 2014). This implies that the

CCT measurement had the least variability, because of the lowest standard deviation, compared with all the paracentral and peripheral corneal thickness measurements. This finding may be accounted for by the corneal optical zone, corresponding to the CCT measurement, being perpendicular to the OCT light beam when fixating on the internal fixation target (Muscat et al. 2002; Mansoori & Balakrishna 2017). Moreover, the corneal optical zone has a relatively uniform spherical curvature and is more compact with lower mean collagen inter-fibrillar separations compared with the corneal periphery (Boote et al. 2003; Queirós et al. 2007; Gupta & Krishna 2009). Consequently, the topographical and structural anatomical differences between the central and peripheral cornea could also account for the larger variability of the corneal thickness measurements beyond the central corneal zone.

Corneal thickness measurements beyond the central cornea are important for diagnosing and monitoring keratoconus and pellucid marginal degeneration as well as for ocular surgeries including intrastromal corneal ring insertion, radial keratotomy and refractive surgery for hyperopia (Rah, Deng & Jackson 2006; Doors et al. 2010; Brautaset et al. 2013). Knowledge of the corneal thickness measurements beyond the central cornea is also essential to achieve a better match between the host and donor corneas in penetrating keratoplasty (Rüfer et al. 2007). In this study, there were variations of the corneal thickness measurements in the different quadrants beyond the central corneal zone. This finding compares favourably with studies that have also noted the same trend of varying corneal thickness measurements beyond the central cornea (Rüfer et al. 2007; Zheng et al. 2008; Huang et al. 2014; Randleman et al. 2015). For both the paracentral and peripheral cornea, the superior and nasal quadrants were thicker than the inferior and temporal quadrants respectively which is consistent with reports from other studies (Rüfer et al. 2007; Hashemi et al. 2009; Hashemi et al. 2011; Fares et al. 2012; Ortiz et al. 2014). Accordingly, the findings of this study also showed that corneal thickness measurements beyond the central cornea are asymmetric which is in agreement with the literature on peripheral corneal

thickness measurements (Doughty & Zaman 2000; Rüfer et al. 2007; Rüfer et al. 2009; Lee, Kim & Park 2011; Tao et al. 2011).

In this study, corneal thickness was greatest in the superior quadrant for both the paracentral and peripheral cornea. This finding is in agreement with other studies that have also highlighted the tendency for the superior cornea to be thickest when peripheral corneal thickness measurements were obtained with various non-contact devices based on the principles of OCT (Keech, Simpson & Jones 2010; Huang et al. 2014; Randleman et al. 2015), Scheimpflug photography (Zheng et al. 2008; Hashemi et al. 2011; Fares et al. 2012) and slit-scanning topography (Liu, Huang & Pflugfelder 1999; Hashemi et al. 2009; Ortiz et al. 2014). It is speculated that the superior cornea has the greatest thickness as a result of chronic hypoxia that is induced by the upper eyelid that partially covers the superior cornea (Erickson, Comstock & Zantos 2002).

Different from the results of this study, some studies (Módis, Langenbucher & Seitz 2004; Rüfer et al. 2007; Mohd-Ali, Ching & Latif 2009) have reported that corneal thickness in the nasal quadrant was thickest. Further analysis of the results in these studies revealed that the difference in mean thickness between the superior and nasal quadrants was less than 2 µm in the two studies that used slit-scanning topography devices (Módis, Langenbucher & Seitz 2004; Rüfer et al. 2007). In the other study that used ultrasound pachymetry, a mean thickness difference of ~29 µm was apparent between the superior and nasal quadrants (Mohd-Ali, Ching & Latif 2009). The large difference noted in the latter study (Mohd-Ali, Ching & Latif 2009) could be related to the lack of standardised fixation targets and inaccuracies in applying the probe over the same corneal point with ultrasound pachymetry (Liu, Huang & Pflugfelder 1999; Fares et al. 2012).

For the paracentral cornea, similar corneal thickness measurements of ~513 µm were observed in the temporal and inferior quadrants. Moreover, the corneal thickness

measurements in these two quadrants were the lowest. Studies, which also used OCT devices, have reported similar corneal thickness measurements for the temporal and inferior quadrants with mean thickness differences ranging between 0.2 µm and 3.1 µm (Keech, Simpson & Jones 2010; Huang et al. 2014; Randleman et al. 2015). For the peripheral cornea, corneal thickness was lowest in the temporal quadrant. This implies that in the present study, the corneal thickness measurements beyond the central cornea were thinnest in the temporal quadrant as has been reported consistently in the literature (Liu, Huang & Pflugfelder 1999; Módis, Langenbucher & Seitz 2004; Khoramnia, Rabsilber & Auffarth 2007; Rüfer et al. 2007; Zheng et al. 2008; Mohd-Ali, Ching & Latif 2009; Keech, Simpson & Jones 2010; Huang et al. 2014; Randleman et al. 2015). For the peripheral cornea, the order of the quadrants representative of decreasing corneal thickness were superior, nasal, inferior and temporal which agrees well with the findings of other studies (Hashemi et al. 2009; Keech, Simpson & Jones 2010; Hashemi et al. 2011; Fares et al. 2012; Ortiz et al. 2014).

In this study, the CCT was significantly thinner than both the AveParaCT and AvePeriCT with thickness differences of 19.15 µm and 44.91 µm respectively. This finding is expected considering that the mean corneal thickness for each quadrant in the paracentral and peripheral cornea was significantly thicker than the mean CCT as has been the trend in other studies (Módis, Langenbucher & Seitz 2004; Sanchis-Gimeno et al. 2004a; Lee, Kim & Park 2011). It is well recognised that there is an increase in corneal thickness measurements from the centre towards the periphery in healthy eyes free from ocular diseases and/or anomalies (Sanchis-Gimeno et al. 2004a). Consequently, the findings of the present study are not surprising and relate to the overall increase in corneal thickness away from the centre as observed in studies that measured central and peripheral corneal thicknesses in children (Hussein et al. 2004), young adults (Sanchis-Gimeno et al. 2004a; Mohd-Ali, Ching & Latif 2009) and middle-aged to elderly adults (Módis, Langenbucher & Seitz 2004; Hashemi et al. 2009; Hashemi et al. 2011). It is speculated that the increase in

corneal thickness away from the corneal centre is due to the higher number of collagen fibrils in the peripheral stroma compared with the central stroma (Henriksson, Bron & Bergmanson 2012). Apart from the stroma, the increase in thickness of Bowman's layer away from the centre could also explain the normal thickening of the cornea towards the periphery (Kobayashi, Yokogawa & Sugiyama 2006; Tao et al. 2011).

Previously the CCT measurement, especially with ultrasound pachymetry, was considered as the thinnest point on the cornea (Ashwin et al. 2009; Keech, Simpson & Jones 2010). However, with the advent of newer non-contact pachymetry mapping systems capable of mapping corneal thickness over a larger corneal area simultaneously, it is now being recognised that the thinnest point on the cornea is a distinct point that most often lies inferior-temporal to the CCT (Liu, Huang & Pflugfelder 1999; Khoramnia, Rabsilber & Auffarth 2007; Hashemi et al. 2009). It is postulated that the location of the thinnest point on the cornea, being situated inferior-temporal to the CCT, could explain the displacement of the corneal apex in keratoconus and the position of ectasia post laser in situ keratomileusis (Demirbas & Pflugfelder 1998; Malecaze et al. 2006). This may be the case as clinically the identification of the thinnest point on the cornea, corresponding to the minimum corneal thickness measurement, has implications for diagnosing the early stages of keratoconus and for estimating the residual stromal bed thickness in laser in situ keratomileusis as well as photorefractive keratectomy (Li et al. 2008; Zheng et al. 2008).

In the present study, the location of the thinnest point on the cornea was most often central which corresponds to a circular area, of 2 mm diameter, centred on the corneal centre. This finding agrees with Sanchis-Gimeno et al. (2004b) who reported that the thinnest point on the cornea was consistently central. In contrast, other studies have reported that the location of the thinnest point on the cornea was positioned in the inferotemporal quadrant (Liu, Huang & Pflugfelder 1999; Zheng et al. 2008; Hashemi et al. 2009; Rüfer et al. 2009; Hashemi et al. 2011; Saenz-Frances et al. 2014). However, further analysis of the actual

vector location of the thinnest point in these studies reveals interesting results. For example, Rüfer et al. (2009) reported that the thinnest point was located 0.56 mm and 0.69 mm from the corneal centre for the right and left eyes respectively. Some studies (Zheng et al. 2008; Hashemi et al. 2009; Hashemi et al. 2011) have reported mean distances of 0.52 mm to 0.57 mm between the thinnest point on the cornea and the corneal centre whereas other studies (Liu, Huang & Pflugfelder 1999; Keech, Simpson & Jones 2010; Saenz-Frances et al. 2014) have noted slightly higher mean distances of 0.90 mm to 1.01 mm between these two points. This suggests that although the thinnest point was reported to be situated in the inferotemporal quadrant in these studies, this point was still located within a 2 mm circular area of the corneal centre which is consistent with the results of the present study. This observation further supports the argument that there are inconsistencies in the location of the thinnest point on the cornea (Fam, Lim & Reinstein 2005). It is speculated that these inconsistencies are because of the rate of thickness changes across the cornea coupled with the thinnest point being identified as a single distinct point rather than an average of multiple points (Fam, Lim & Reinstein 2005; Keech, Simpson & Jones 2010).

Overall, there is a wide distribution of minimum corneal thickness measurements in the literature wherein mean values ranging between 526 µm and 578 µm have been reported (Módis, Langenbucher & Seitz 2004; Hashemi et al. 2011). The minimum corneal thickness measurement of ~496 µm in the present study, which was recorded at the thinnest point, is considerably lower when compared with previous studies that have reported on the minimum corneal thickness measurement in Iranian (Hashemi et al. 2009; Hashemi et al. 2011), Chinese (Zheng et al. 2008; Huang et al. 2014), German (Módis, Langenbucher & Seitz 2004; Khoramnia, Rabsilber & Auffarth 2007; Rüfer et al. 2009) and American (Randleman et al. 2015) samples. Despite the mean minimum corneal thickness measurement being lower, the standard deviation of 33.89 µm associated with this measurement is similar to that reported in previous studies (Khoramnia, Rabsilber & Auffarth 2007; Keech, Simpson & Jones 2010; Fares et al. 2012).

As expected, the minimum corneal thickness measurement was the lowest compared with all other corneal thickness measurements including the CCT and thickness for each quadrant in the paracentral and peripheral cornea. Overall, the minimum corneal thickness was 6.18 µm thinner than the CCT measurement. The thickness differences between the minimum corneal thickness and the CCT measurements ranged from 2 µm to 31 µm. Other studies have also reported on the thickness differences between the minimum corneal thickness and CCT measurements (Zheng et al. 2008; Ashwin et al. 2009; Hashemi et al. 2011; Randleman et al. 2015). In contrast to the findings of this study, Hashemi et al. (2011) and Zheng et al. (2008) reported lower thickness differences of 3.23 µm and 3.24 µm respectively between these two points although their range of differences, being 0 µm to 105 µm and 0 µm to 66 µm respectively, were much wider than that found in the present study. In the other studies, Ashwin et al. (2009) and Randleman et al. (2015) reported thickness differences of 6 µm (range, 0 µm to 16 µm) and 7.8 µm (range, 0 µm to 23 µm) respectively which are comparable with the findings of the present study. Considering that the thickness difference between these two points was relatively small in the present study, it is possible that this thickness difference may have little clinical relevance despite reaching statistical significance as noted in a previous study (Hashemi et al. 2011).

In the present study, an equivalent thickness difference of 1.23% was observed between the minimum corneal thickness and CCT measurements. This finding is supported by other studies that have reported percentage thickness differences between these two points of 0.78% to 2.80% (Khoramnia, Rabsilber & Auffarth 2007; Rüfer et al. 2009; Keech, Simpson & Jones 2010). Moreover it was observed that for more than 95% of participants, the thickness difference between the minimum corneal thickness and CCT measurements was 9 µm or lower. This small difference may be due to the inclusion of only normal healthy participants, in the study sample, specifically those without any corneal anomalies. Consequently, the lack of clinically significant thickness differences between the minimum corneal thickness and CCT measurements implies that although these points are important

for research and analysis, the difference in their thicknesses and location may not be relevant in planning refractive surgery in normal healthy individuals (Fares et al. 2012).

The distribution of corneal thickness measurements has been investigated in several studies with particular emphasis on the CCT measurement (Wolfs et al. 1997; Eysteinsson et al. 2002; Nemesure et al. 2003; Hashemi et al. 2009; Nangia et al. 2010). In the present study, the CCT measurements were normally distributed with the corresponding histogram showing a Gaussian curve. This finding is in agreement with other population-based (Zheng et al. 2008; Su et al. 2009; Hashemi et al. 2011) and clinic-based (Sardiwalla et al. 2012) studies that also reported normal distributions for the CCT measurements. In the present study, all the corneal thickness measurements beyond the central cornea were also normally distributed which is consistent with the reports of previous studies (Zheng et al. 2008; Hashemi et al. 2011). It is postulated that the normal distribution of corneal thickness measurements is not unexpected as these are quantitative biological characteristics and most biological variables are normally distributed (Bland & Altman 1996; Dimasi, Burdon & Craig 2010; Bland 2015a).

In this study, mean nasal and temporal AOD500 measurements of ~552 µm and ~553 µm respectively were found when using an OCT device to image the ACA. Overall, the mean nasal and temporal AOD500 measurements in the present study are different from the results of other studies wherein mean AOD500 measurements ranging between 267 µm and 490 µm have been reported in Indian (Ramani et al. 2007; Grewal et al. 2011), Singaporean (Amerasinghe et al. 2009; Narayanaswamy et al. 2010; Sakata et al. 2010), Polish (Wylęgała et al. 2009) and American (Radhakrishnan et al. 2005) samples. The mean nasal and temporal AOD500 measurements in the present study seem to have inconsistent patterns when compared with studies involving Korean and Chinese samples. For example, the mean values for the nasal and temporal AOD500 measurements in the present study compare favourably with the measurements reported in studies by Leung et al. (2008) and

Cheon et al. (2010) that also imaged the ACA using OCT devices. In contrast, Liu et al. (2011) and Kim et al. (2011) reported mean AOD500 measurements that were lower than 508 µm and greater than 650 µm respectively. This implies that the results of the present study are different from the latter studies involving Korean and Chinese samples despite these studies also having used OCT devices to image the ACA and included young adult participants (Kim et al. 2011; Liu et al. 2011). Overall, the mean AOD500 measurements for both ACAs ranged from 242 µm to 1210 µm which is different from the range of 204 µm to 484 µm and 15 µm to 1755 µm reported by Müller et al. (2006) and Fernández-Vigo et al. (2016) respectively. It is likely that differences related to the study participants and devices used to image the ACA may explain the varying ranges observed in these studies.

Grewal et al. (2011) compared the nasal and temporal ACA width variables, which were measured using an OCT device, between individuals with open non-occludable ACAs and narrow occludable ACAs (defined as a Shaffer grade of ≤ 1 in all four quadrants with gonioscopy). Based on this comparison, it was proposed that a mean AOD500 measurement of less than 300 µm is characteristic of individuals with narrow occludable ACAs (Campa et al. 2011; Grewal et al. 2011). In the present study, less than 1.5% of the sample may be classified with narrow occludable ACAs if the proposed criterion of an AOD500 measurement of less than 300 µm is used. In general, the mean AOD500 measurement is 500 µm or greater in individuals with open non-occludable ACAs (Campa et al. 2011; Grewal et al. 2011). This implies that more than two-thirds of the sample may be classified as having open non-occludable ACAs. Overall these findings suggest that for the majority of study participants, the mean nasal and temporal AOD500 measurements were not abnormal and did not show any risk for angle closure. This observation may be influenced by the sample consisting of young adult participants as previous studies have reported narrower AOD500 measurements in older individuals (Cheon et al. 2010; Maruyama et al. 2014; Shimizu et al. 2017). This concurs with the observation of primary angle closure and primary angle-closure glaucoma usually being associated with older

individuals which may be a consequence of increasing lens thickness and shallowing of the anterior chamber with increasing age (Congdon et al. 2002; Aung et al. 2005; Friedman & He 2008; Kanski 2008).

In this study, the mean nasal and temporal TIA measurements were 36.58° and 36.77° respectively. The values for the mean nasal and temporal TIA measurements in the present study compare favourably with the measurements reported for studies involving Polish (Wylęgała et al. 2009) and German (Müller et al. 2006; Rabsilber, Khoramnia & Auffarth 2006) samples. With the exception of one study (Hosseini, Abolbashari & Mohidin 2013), all studies involving Indian samples reported lower mean TIA measurements that ranged between 22.28° and 32.09° (Dada et al. 2007; Ramani et al. 2007; Dacosta et al. 2008; Sihota et al. 2012). Even though it was not specified which ACA was measured, the study by Hosseini, Abolbashari and Mohidin (2013) reported a mean TIA measurement of 39.36° which is higher than the measurements observed in the present study and the other studies involving Indian samples. The sample used by Hosseini, Abolbashari and Mohidin (2013) were younger (25.93 years) compared with the other Indian samples and a Scheimpflug photography device was use to image the ACA which may explain this discrepancy.

The comparison of the mean TIA measurements observed in the present study with previous studies involving Asian samples reveals interesting findings. With the exception of Liu et al. (2011), all studies involving adult Asian samples reported mean TIA measurements ranging between 38.10° and 47.32° which are higher than the mean nasal and temporal TIA measurements found in the present study (Li et al. 2007; Leung et al. 2008; Xu et al. 2008; Yi et al. 2008). The study by Liu et al. (2011) reported mean nasal and temporal TIA measurements of ~33° and ~35° respectively which are lower than the measurements observed in the present study and those involving other Asian samples. It is likely that this difference in mean TIA measurements may be due to the mean age of participants being

older in the study by Liu et al. (2011) when compared with the mean age of participants in the present study and the majority of studies involving Asian samples.

Overall, the mean TIA measurements in the present study ranged from 20.53° to 55.33°. Other studies have also reported on the range of mean TIA measurements (Müller et al. 2006; Rabsilber, Khoramnia & Auffarth 2006). For example, Müller et al. (2006) reported a range of 24° to 46° for the mean TIA measurements which were determined using an anterior segment OCT device. Another study, which imaged the ACA using a Pentacam device, reported a range of 21.17° to 44.37° for the mean TIA measurements (Rabsilber, Khoramnia & Auffarth 2006). This implies that the lower limit (minimum value) for the range of mean TIA measurements in the present study is comparable with the lower limit of the ranges reported in other studies (Müller et al. 2006; Rabsilber, Khoramnia & Auffarth 2006). In contrast, the upper limit (maximum value) for the range of mean TIA measurements in the present study is much higher than that reported in other studies and may be explained by the inclusion of middle-aged to elderly adult participants, who were likely to have had physiological age related ACA changes, in those studies (Müller et al. 2006; Rabsilber, Khoramnia & Auffarth 2006). The difference between the mean nasal and temporal TIA measurements in the present study was only 0.19° which is almost identical to the difference of 0.26° reported in a sample of young (median age of 21 years) Chinese adults (Lam & Tse 2013).

The literature suggests that angular measurements of the ACA that are 20° or less are indicative of narrow occludable ACAs at risk for angle closure (Campa et al. 2011; Sihota et al. 2012; Cheng et al. 2014). In the present study, none of the participants presented with mean nasal or temporal TIA measurements that were 20° or less. This finding is in contrast with Sihota et al. (2012), who reported that 39% of their sample showed mean ACA measurements that were lower than 20°. This discrepancy may be accounted for by the inclusion of older individuals in the study by Sihota et al. (2012) wherein the mean age of

their sample (51.49 ± 5.41 years) was more than two times higher than that of participants in the present study.

The normal TIA measurement is approximately 30° in normal healthy individuals with open non-occludable ACAs (Pavlin, Harasiewicz & Foster 1992; Wirbelauer et al. 2005; Campa et al. 2011). In the present study, ~95% of participants presented with mean TIA measurements that were 30° or more in the nasal and temporal ACAs. In contrast, Sihota et al. (2012) reported that only 23% of their sample showed mean ACA measurements that were greater than 30° and the inclusion of individuals aged 40 years or older in their sample may possibly underlie this discrepancy. The finding that the majority of participants in this study may be classified with open non-occludable ACAs is not surprising as overall there is a low prevalence of angle-closure glaucoma in Africa (Quigley & Broman 2006) and specifically among South African adults (Salmon et al. 1993; Rotchford & Johnson 2002; Rotchford et al. 2003). Moreover, the sample consisted of normal healthy young adults which may further account for the high number of participants classified with open non-occuldable ACAs.

In this study the other characteristics of the ACA width variable measurements, apart from the mean values and ranges discussed above, have revealed interesting results. Consistent with the results of previous studies involving normal healthy participants, the mean AOD500 and TIA measurements were slightly higher in the temporal ACA than the nasal ACA (Leung et al. 2008; Yi et al. 2008; Wylęgała et al. 2009; Kim et al. 2011; Liu et al. 2011; Maruyama et al. 2014). The trend of higher ACA width variable measurements in the temporal ACA than in the nasal ACA has also been observed in individuals with glaucoma disorders (Mansouri, Sommerhalder & Shaarawy 2010; Kim et al. 2011; Maruyama et al. 2014). The exact reason for the wider temporal ACA compared with the nasal ACA is not readily explained. Differences have been documented between the vertical (superior and inferior) and horizontal (nasal and temporal) ACA width variable measurements when the ACA is

imaged with individuals in a seated position (Friedman et al. 2008; Mansouri, Sommerhalder & Shaarawy 2010; Liu et al. 2011). It has been suggested that differences in the vertical and horizontal ACA width variable measurements exist because of the influence of gravity (Friedman et al. 2008; Dorairaj, Liebmann & Ritch 2007). However, it is unlikely that the nasal and temporal ACAs may be differently affected by gravity as they are theoretically located on the same horizontal plane within the eye.

In the present study, the AveAOD500 measurement was 552.51 µm which is much higher than the average AOD500 values reported by Müller et al. (2006) and Kobayashi et al. (1999) of 316 µm and 350 µm respectively. In contrast, the AveAOD500 measurement in the present study is comparable with the calculated average AOD500 measurements of 555.50 µm (Cheon et al. 2010) and 549.50 µm (Leung et al. 2008) observed for two Asian sub-populations. In the present study, an AveTIA of 36.68° was found. This value is comparable with the average TIA measurements of 35.90° and 38.31° reported by Müller et al. (2006) and Xu et al. (2008) respectively who also evaluated the ACA using OCT devices. In contrast, the AveTIA measurement in the present study is much higher than the average TIA measurements of 23.24° and 28.74° reported by Sihota et al. (2012) and Kobayashi et al. (1999) respectively. Sihota et al. (2012) used a time-domain OCT device and Kobayashi et al. (1999) used an ultrasound biomicroscopy device as well as assessed a paediatric sample which may be the possible reasons for this discrepancy.

In general, few studies have evaluated and reported on the distribution of ACA width variable measurements. Some studies have presented histograms illustrating the distribution of ACA width variable measurements but have omitted to comment on the normality, or lack thereof, of these distributions (Sihota et al. 2012; Schuster et al. 2016). Overall, knowledge of the distribution of ACA width variable measurements is inconsistent as contradictory results have been reported in literature. Some studies have reported that ACA width variable measurements are normally distributed (Henzan et al. 2010; Fernández-Vigo et al. 2016)

whereas other studies have noted that ACA width variable measurements do not follow Gaussian distributions (Grewal et al. 2011; Jin et al. 2016). The present study is in agreement with the latter group of studies as both the AOD500 and TIA measurements were asymmetrically distributed with the corresponding histograms resembling non-Gaussian curves. Despite most naturally occurring biological variables being normally distributed (Bland 2015a), the inclusion of young adult participants with a small age range in the present study is likely to account for the non-Gaussian distributions. In this study, the age range of participants was 14 years. The influence of the age range of participants on the distribution of ACA width variable measurements is a plausible reason as studies that reported normal distributions consisted of participants with much wider age ranges including 51 years (Henzan et al. 2010) and 68 years (Fernández-Vigo et al. 2016).

Taken together, the distribution of anterior segment variables in this study were comparable with the results of some studies while at the same time different from the results of other studies. Overall, the findings in this South African young adult sample suggest that anterior segment variable measurements, particularly corneal thicknesses and AOD500 measurements are different compared with the values reported in other sub-populations globally. However, when considering the anterior segment variables in the present study and the results from previous studies, it is important to interpret any comparison with caution as it is well recognised that methodological differences between studies limit the direct comparison of results across studies (Doughty & Zaman 2000; Aghaian et al. 2004). Most studies performed to date have investigated anterior segment variable measurements in Asian and Caucasian sub-populations. Consequently, there is limited knowledge and data related to the anterior segment variables, particularly of the ACA, in South African individuals. Accordingly, the present study provides useful information related to the distribution of anterior segment variables in a healthy South African young adult population.

7.5 OBJECTIVE 3: RACIAL VARIATIONS IN ANTERIOR SEGMENT VARIABLES MEASURED USING OCT

Previous studies (Shimmyo et al. 2003; Aghaian et al. 2004; Lifshitz et al. 2006; Landers et al. 2007; Leung et al. 2010; Wang et al. 2011; Sardiwalla et al. 2012) have investigated and reported on racial variations in anterior segment variables. Despite such studies appearing in the literature, there are some limitations associated with these studies that influence the interpretation and generalisation of their results and conclusions. Firstly, the majority of studies (Shimmyo et al. 2003; Aghaian et al. 2004; Torres et al. 2008; Leung et al. 2010; Wang et al. 2011) have compared anterior segment variables among Caucasian, African-American and Asian sub-populations with limited attention to the South African Black and Indian populations. This implies that there is limited information on the racial variations in anterior segment variables in a South African population. Knowledge concerning the normative data and associated racial variations in anterior segment variables for the South African Black and Indian populations may provide a necessary baseline for future research involving these South African populations.

Other limitations of previous studies investigating racial variations in anterior segment variables relate to the measuring devices used, variables measured, sample sizes and age range of participants. For example, several studies (Aghaian et al. 2004; Lifshitz et al. 2006; Durkin et al. 2007; Landers et al. 2007; Mohd-Ali, Ching & Latif 2009) have relied exclusively on ultrasound pachymetry devices to measure corneal thickness. Despite the usefulness of ultrasound pachymetry, there are several disadvantages associated with this technique particularly its contact nature, lack of fixation targets and need for corneal anaesthesia (Mohan et al. 2007). Moreover, the majority of studies have compared predominantly CCT measurements among the different race groups (Durkin et al. 2007; Mohd-Ali, Ching & Latif 2009; Sardiwalla et al. 2012; Lazreg et al. 2013) with limited attention to corneal thickness measurements beyond the central cornea and ACA width variables. The few studies (Leung et al. 2010; Wang et al. 2011) that did report on racial variations in ACA width variable

measurements used OCT devices with lower resolutions and scanning speeds compared with the newer Fourier-domain OCT devices. In addition, some studies consisted of relatively small sample sizes with the number of participants in each race group ranging between 26 and 125 individuals (Aghaian et al. 2004; Lifshitz et al. 2006; Landers et al. 2007; Mohd-Ali, Ching & Latif 2009; Leung et al. 2010; Wang et al. 2011). This implies that in some studies, the number of participants in each race group may have been too small to detect differences in the anterior segment variables. Finally, it is well recognised that age has an influence on the anterior segment variables (Doughty & Zaman 2000; Friedman et al. 2008; Cheon et al. 2010). Consequently, the studies (Durkin et al. 2007; Torres et al. 2008; Wang et al. 2011) that included participants with wide age ranges may have influenced the results and conclusions.

Overall, the Indian participants had thicker corneal thickness measurements than Black participants in all zones. Moreover these corneal thickness differences, which ranged from 29.10 µm to 36.38 µm, were found to be significant in all zones. These findings are consistent with previous studies that also noted significant racial variations in corneal thickness measurements, specifically for CCT measurements (Lifshitz et al. 2006; Sardiwalla et al. 2012; Lazreg et al. 2013). Despite several studies reporting racial variations in mean CCT measurements between different race groups, the exact reason for this difference is not clearly explained. It has been hypothesised that structural and thickness variations in the corneal stroma may account for the variation in corneal thickness measurements observed in the different race groups (Ehlers & Hjortdal 2004; Dimasi, Burdon & Craig 2010). However, future studies focused specifically on the thickness and histological evaluation of the corneal stroma are needed to validate this explanation and confirm precisely which corneal layers and/or the characteristics therein are responsible for the racial variations in corneal thickness measurements. An alternative explanation, for the racial variations in CCT measurements, may be genetic factors as CCT measurements are influenced by genetics (Toh et al. 2005; Dimasi et al. 2011). Consequently the racial

variations in corneal thickness measurements, between the South African Black and Indian individuals, may be explained by the high levels of genetic variation observed among individuals of the same population (Edgar & Hunley 2009; Fujimura et al. 2014). Genetic variations are reported to be highest among individuals from the African continent (Petersen et al. 2013) which may further account for the differing corneal thickness measurements between these two South African samples.

Studies, which reported on the racial variations in CCT measurements, involving African samples from within and outside the African continent have shown interesting trends. Sardiwalla et al. (2012) reported significantly lower mean CCT measurements in South African Black (512.4 µm) than in South African Indian (526.5 µm) participants which is consistent with the results of the present study. Lazreg et al. (2013) reported a similar trend of significantly lower mean CCT measurements in North African (518 µm) than in French (553 µm) participants. These results are in agreement with the findings of Lifshitz et al. (2006) who showed significantly thinner mean CCT measurements in North African individuals compared with individuals from other origins, including Israel and Europe for both the right (518.9 µm versus 545.4 µm) and left (518.4 µm versus 546.3 µm) eyes. Other studies involving African samples from outside the African continent have also reported similar findings wherein significantly lower mean CCT measurements have been observed for African-American individuals compared with Caucasian, Asian and Hispanic individuals (La Rosa, Gross & Orengo-Nania 2001; Shimmyo et al. 2003; Aghaian et al. 2004; Torres et al. 2008).

In this study, the mean CCT was higher in Indian (516.60 µm) than in Black (487.21 µm) participants. This implies that a mean CCT difference of ~29 µm was observed between these two South African samples. The variation in CCT measurement, between these two South African samples, is further demonstrated with a 31 µm difference for the median CCT measurement. This variation in mean CCT measurement is likely to influence the

interpretation of IOP measurements which has consequences for screening, diagnosing and monitoring glaucoma. Considering that Goldman applanation tonometry is based on a theoretical assumption of a 520 µm CCT measurement, these findings suggest that IOP measurements in South African Black individuals may be underestimated on the basis of their lower CCT measurements. Thinner CCT measurements are considered as a risk factor for the development and progression of open-angle glaucoma (Gordon et al. 2002; Leske et al. 2003; Herndon, Weizer & Stinnett 2004; Kim & Chen 2004). This implies that the South African Black population may have greater susceptibility to open-angle glaucoma than the South African Indian population. Moreover, primary open-angle glaucoma is more prevalent in Black populations globally wherein the condition also presents earlier in life and is more aggressive (Brandt et al. 2001; Kyari et al. 2013). Although studies have reported a low prevalence of glaucoma (4.50% to 5.30%) and specifically primary open-angle glaucoma (1.52% to 2.90%) in the South African population, these studies were undertaken 16 to 25 years ago and may not accurately reflect the current prevalence of glaucoma disorders in this population (Salmon et al. 1993; Rotchford & Johnson 2002; Rotchford et al. 2003).

Apart from its importance in glaucoma, the CCT measurement is also a necessary consideration in corneal refractive surgeries (Mohan et al. 2007). In this study, a mean CCT measurement of less than 500 µm was observed in approximately two-thirds and one-third of the Black and Indian participants respectively. This finding suggests that South African Black young individuals may not be suitable for corneal refractive surgery, particularly laser in situ keratomileusis, if a cut-off mean CCT measurement of 500 µm is used to determine eligibility (Khairat et al. 2013). The finding of more Black participants having mean CCT measurements of less than 500 µm is consistent with a previous clinic-based study (Lazreg et al. 2013). In their study, Lazreg et al. (2013) reported that mean CCT measurements lower than 500 µm were more commonly observed in North African (n = 478) than in French (n = 17) participants.

In the present study, the mean CCT of the Black participants was ~487 µm which is considerably lower than the mean values reported for other Black samples both within and outside the African continent. In South Africa, mean CCT measurements of 512 µm have been reported for South African Black participants (Sardiwalla et al. 2012; Bonnemaijer et al. 2017). Within Africa, higher mean CCT measurements have been reported such as 535 µm to 550 µm in Nigerian (Mercieca et al. 2007; Iyamu & Eze 2011), 529 µm in Cameroonian (Eballe et al. 2010), 519 µm in Ethiopian (Gelaw et al. 2010), 530 µm in Sudanese (Mohamed et al. 2009) and 531 µm in Ghanaian (Ntim-Amponsah et al. 2012) samples. This implies that South African Black individuals may have thinner CCT measurements than other Black populations from within the African continent. It is possible that the significant genetic and environmental heterogeneity among the different African sub-populations may account for the varying CCT measurements (Rotchford et al. 2003; Petersen et al. 2013). Moreover, this finding suggests that CCT measurements specific to one African sub-population may not necessarily be similar and/or extrapolated to other sub-populations within Africa. Previous studies involving African-American samples, which used ultrasound pachymetry, reported mean CCT measurements ranging between 525 µm and 535 µm (La Rosa, Gross & Orengo-Nania 2001; Shimmyo et al. 2003; Aghaian et al. 2004; Torres et al. 2008). Although this finding suggests that the mean CCT measurement in South African Black individuals may also be thinner when compared with African-American populations, caution should be exercised with this comparison as different pachymetry devices could account for the variations observed (Doughty & Zaman 2000).

In this study, the mean CCT of the Indian participants was ~517 µm. This measurement is comparable with the mean CCT measurements in other population-based (Nangia et al. 2010; Vijaya et al. 2010) and clinic-based (Ramesh, Jha & Srikanth 2017) studies conducted in India involving Indian participants (511 µm to 516 µm) as well as the study (Sardiwalla et al. 2012) involving South African Indian participants (527 µm). One study from India (Malik et al. 2010) reported a mean CCT of ~545 µm which is different from the mean CCT

measurement in the present study and that reported in other studies involving Indian samples. The sample in the study by Malik et al. (2010) was considerably smaller (n =150), compared with the present study and other studies involving Indian participants which may explain this discrepancy. Moreover, the mean CCT measurement for the South African Indian participants in the present study is comparable with the measurements reported in some Asian sub-populations. For example, mean CCT measurements of ~522 µm and 518 µm to 521 µm have been reported for Myanmarese (Casson et al. 2008) and Japanese (Suzuki et al. 2005; Kawase et al. 2008) samples respectively. This implies that South African Indian individuals may have similar mean CCT measurements when compared with other Indian and Asian sub-populations.

Overall, these findings suggest that the mean CCT measurements for the two South African samples in the present study are different from the values reported in other African and Indian populations although the mean CCT value for the Black participants showed greater discrepancies. The mean CCT measurement in Caucasian individuals, using various pachymetry devices, ranges between 527 µm and 563 µm (Doughty et al. 2002; Aghaian et al. 2004). This implies that, on average, the mean CCT measurements in the South African samples are thinner than the average CCT measurements reported in Caucasian samples. Despite the methodological differences between the present and other studies involving Caucasian samples, it is possible that skin colour may account for the variation in mean CCT measurements as thinner CCT measurements have been associated with darker skin colour in both human and strains of inbred mice samples (Dimasi et al. 2011).

For both Black and Indian participants, the CCT measurement was thinnest followed by the AveParaCT and AvePeriCT measurements. This finding is not unexpected as it aligns with the general observation of increasing corneal thickness measurements away from the corneal centre towards the periphery (Tao et al. 2011; Fares et al. 2012). In the present study, the variation of the corneal thickness measurements with the superior and nasal

quadrants showing greater measurements than the inferior and temporal quadrants respectively is in agreement with previous studies (Zheng et al. 2008; Huang et al. 2014; Randleman et al. 2015). In both Black and Indian participants, the superior quadrant of the paracentral and peripheral cornea was the thickest as has been noted previously (Hashemi et al. 2009; Fares et al. 2012; Ortiz et al. 2014). In both Black and Indian participants, the inferior and temporal quadrants for the paracentral and peripheral cornea respectively were thinnest. The corneal thickness differences between the inferior and temporal quadrants, for these two South African samples, in the paracentral and peripheral cornea did not exceed 4 µm. This suggests that corneal thickness measurements in the inferior and temporal quadrants were relatively similar in these two South African samples. Consequently, the lowest corneal thickness measurements were observed in the inferior and temporal quadrants which concurs with reports from previous studies for the inferotemporal quadrant consistently showing the thinnest corneal thickness measurements (Rüfer et al. 2009; Hashemi et al. 2011; Saenz-Frances et al. 2014).

In this study, the minimum corneal thickness measurement for Black and Indian participants was ~481 µm and ~511 µm respectively. This implies that the minimum corneal thickness measurement differed by 30 µm which is consistent with the corneal thickness differences, between these two South African samples, that have been observed and discussed above. Despite this racial variation, the mean values for the minimum corneal thickness measurement in both Black and Indian participants are considerably lower than the mean values reported in other studies involving Caucasian (526 µm to 578 µm), Chinese (528 µm to 533 µm) and Iranian (526 µm to 551 µm) samples (Módis, Langenbucher & Seitz 2004; Zheng et al. 2008; Hashemi et al. 2009; Keech, Simpson & Jones 2010; Hashemi et al. 2011; Huang et al. 2014). Moreover, the minimum corneal thickness measurements in paediatric Chinese (548 µm) and adolescent Iranian (571 µm) samples are also higher than the values found for the two South African samples in the present study (Zheng et al. 2008; Hashemi et al. 2009).

For more than 93% of the Black and Indian participants, the location of the thinnest point on the cornea was central which is in agreement with a previous study that measured the minimum corneal thickness using a slit-scanning topography device (Sanchis-Gimeno et al. 2004b). The thinnest point was located in the temporal quadrant in only Black participants although the small number of participants (n = 6) limits the clinical significance of this finding. When the thinnest point was not central or temporal in both Black and Indian participants, there was an almost equal distribution in either the inferotemporal or inferior quadrants. Overall, the findings related to the minimum corneal thickness in these two South African samples suggest that while there are racial variations in the mean corneal thickness measurement, there are no major differences in the location of this point on the cornea. This implies that, even though there are varying corneal thickness measurements, the corneal architectural structure and pachymetry profile are relatively similar in South African Black and Indian individuals. This may be a consequence of the sample consisting of normal healthy South African Black and Indian participants as the corneal architectural structure and pachymetry profile are usually altered in conditions such as keratoconus (Ambrósio et al. 2006; Saad & Gatinel 2010).

Overall, the ACA width variable measurements have revealed interesting results regarding the racial variations in the two South African samples. Indian participants had higher AOD500 measurements than Black participants for both the nasal and temporal ACAs. Moreover, the racial variation for only the temporal AOD500 measurement reached statistical significance with a 22 µm and ~20 µm difference for the median and mean measurements respectively. The TIA measurements were marginally higher in Black than Indian participants for both the nasal and temporal ACAs. Moreover, the racial differences for the median and mean TIA measurements in both the nasal and temporal ACAs were less than 1°. These findings suggest that the ACA width variable measurements in South African Black and Indian young individuals are similar even though the difference in the temporal AOD500 measurement was statistically significant. These results are consistent

with previous studies that also noted clinically insignificant racial variations in ACA width variable measurements among normal healthy Caucasian, African-American and Asian individuals when assessed using gonioscopy (Oh et al. 1994; Congdon et al. 2002) and OCT devices (Leung et al. 2010; Wang et al. 2011).

It is well recognised that the prevalence of angle-closure glaucoma is higher in Asian sub-populations than European and/or African sub-populations (Quigley & Broman 2006; Tham et al. 2014). Consequently, the lack of clinically significant racial differences in ACA width variable measurements in previous studies (Leung et al. 2010; Wang et al. 2011) suggests that other anterior segment structures and mechanisms, in addition to the ACA width, may be implicated in the pathophysiology of angle-closure glaucoma. This is plausible as characteristics of the anterior segment such as a shallow anterior chamber depth, small corneal diameter, steep corneal curvature, anteriorly positioned lens and pronounced lens thickness are considered as risk factors for angle-closure glaucoma (Aung et al. 2005; Leung et al. 2010; Wright et al. 2016).

The width of the ACA is an important indicator for the risk of angle closure and can be expressed as a linear and/or angular measurement (Müller et al. 2006; Wang et al. 2011). Narrow ACAs at risk for angle closure are characterised by mean TIA measurements of 20° or less and mean AOD500 measurements that are less than 300 µm (Campa et al. 2011). Overall, none of the Black and Indian participants showed mean TIA measurements of 20° or less while a few participants ($n \leq 4$) showed mean AOD500 measurements that were less than 300 µm in either ACA. This aligns with the general observation that the majority of South African Black and Indian participants had open non-occludable ACAs that were characterised by mean AOD500 measurements greater than 500 µm and/or mean TIA measurements of 30º or more. This finding is not surprising as previous studies have shown low prevalence of primary angle-closure glaucoma (0.5% to 2.3%) among South African adults (Salmon et al. 1993; Rotchford & Johnson 2002; Rotchford et al. 2003).

In the present study, the ACA width variable measurements noted for Black participants are different compared with other studies. The mean AOD500 measurements were ~545 µm and ~543 µm in the nasal and temporal ACAs respectively. The mean TIA measurement was ~37º for both the nasal and temporal ACAs. This implies that the mean AOD500 measurements are higher than those reported for Caucasian (316 µm to 452 µm) and some Asian (266 µm to 507 µm) adult samples from China, Singapore and Japan (Kobayashi et al. 1999; Radhakrishnan et al. 2005; Müller et al. 2006; Amerasinghe et al. 2009; Wylęgała et al. 2009; Narayanaswamy et al. 2010; Sakata et al. 2010; Liu et al. 2011; Shimizu et al. 2017). In contrast, the mean AOD500 measurements (530 µm to 755 µm) in other Asian samples from Korea and Hong Kong are higher than the mean values found in the present study (Li et al. 2007; Cheon et al. 2010; Kim et al. 2011). A similar trend was observed for the TIA measurements wherein lower mean measurements (29º to 36º) were reported for Caucasian and some Asian samples from China and Japan (Kobayashi et al. 1999; Müller et al. 2006; Rabsilber, Khoramnia & Auffarth 2006; Wylęgała et al. 2009; Liu et al. 2011). There is limited information on the mean AOD500 and TIA measurements in African sub-populations, from within the African continent, which limits the comparison of the results observed in this study.

The ACA width variable measurements observed for Indian participants in the present study are different from other studies involving Indian samples. In the present study, the nasal and temporal mean AOD500 measurements were ~562 µm and ~563 µm respectively which are much higher than those reported in two other Indian samples (Ramani et al. 2007; Grewal et al. 2011). The two studies conducted by Ramani et al. (2007) and Grewal et al. (2011) reported mean AOD500 measurements that ranged between 320 µm to 490 µm. The mean age of the Indian participants in the latter two studies was more than two times the mean age of participants in the present study which may explain the variation observed. In the present study, the mean TIA measurement for the nasal and temporal ACAs was ~36°. This measurement is much higher than the mean measurements (~22° to ~32°) reported in other

studies involving Indian samples that used OCT and ultrasound biomicroscopy devices to image the ACA (Dada et al. 2007; Ramani et al. 2007; Dacosta et al. 2008; Sihota et al. 2012). In contrast, one study (Hosseini, Abolbashari & Mohidin 2013) assessed the ACA in 60 young Indian adults and reported a mean TIA measurement of ~39°. As the latter study used a different device (Scheimpflug photography) to assess the ACA, this may account for the higher mean TIA measurement compared with the present and other studies involving Indian samples. This explanation is reasonable because higher TIA measurements have been observed in individuals, both with open and narrow ACAs, when using a Scheimpflug photography device compared with an OCT device (Mou 2010).

Taken together, interesting results have been found for the racial variations in anterior segment variable measurements between these two South African samples. The corneal thickness measurements showed statistically significant differences that may also have important clinical implications based on the magnitude of the variations found. In contrast, the ACA width variables measurements were comparable which suggests that the ACA configurations are similar in these two South African samples. The exact reason for this discrepancy regarding the racial variations in anterior segment variable measurements is not readily explained. Even though the influence of genetic factors and the high levels of genetic variations among individuals from the African continent are possible reasons for this finding, they do not fully account for why significant differences were noted for only the corneal thickness measurements. Consequently, it is interesting to speculate that the association between skin colour and corneal thickness measurements may be a possible reason for the trend observed in the present study (Dimasi et al. 2011). However future research studies, which involve individuals from different race groups with standardised methodologies, investigating the influence of skin colour on anterior segment variable measurements are needed to validate this speculation.

7.6 OBJECTIVE 4: GENDER VARIATIONS IN ANTERIOR SEGMENT VARIABLES MEASURED USING OCT

The relationship between gender and anterior segment variables has been investigated and reported in studies involving African (Mercieca et al. 2007; Iyamu et al. 2010; Sardiwalla et al. 2012), Caucasian (Lleó et al. 2003; Sanchis-Gimeno et al. 2004a; Altinok et al. 2007) and Asian (Yuen et al. 2010; Ang et al. 2012; Thapa et al. 2012) samples. This may be the case as certain ocular diseases tend to suggest a gender predilection because of a higher prevalence in either males or females. For example, females are at a three times higher risk of developing primary angle-closure glaucoma (Quigley & Broman 2006; Cheng et al. 2014; Wright et al. 2016). Although it is understood that keratoconus affects both genders (Romero-Jimenez, Santodomingo-Rubido & Wolffsohn 2010), the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study reported gender differences between male and female individuals with keratoconus (Fink et al. 2005). Moreover, recent studies have reported a higher frequency of keratoconus in males (Barsam et al. 2015; Abdu et al. 2016). Consequently, knowledge concerning the influence of gender on the anterior segment variable measurements could help to enhance understanding of the possible mechanisms of certain ocular diseases in the two gender groups.

The relationship between gender and corneal thickness measurements is inconsistent as conflicting results have been reported in the literature. Some studies (Lleó et al. 2003; Hashemi et al. 2009; Gelaw et al. 2010; Ang et al. 2012) have reported that females have higher corneal thickness measurements whereas other studies (Sanchis-Gimeno et al. 2004a; Zhang et al. 2008; ul Hassan et al. 2010; Iyamu & Eze 2011) have reported higher measurements in males. The results of the present study are in agreement with the latter studies and found that corneal thickness measurements were greater in male than female participants. Moreover the gender related differences in corneal thickness measurements in the present study, which ranged from 0.35 µm to 3.93 µm, were statistically insignificant as

has been reported in previous studies (Rüfer et al. 2007; Chen et al. 2009; Hashemi et al. 2009; Lee, Kim & Park 2011; Iyamu & Osuobeni 2012).

In the present study, the male participants had slightly higher mean CCT measurements than the female participants. Overall, the gender difference for the CCT measurement was ~3.50 µm and failed to reach statistical significance which is in agreement with other studies that also used OCT devices to measure CCT in male and female participants (Dacosta et al. 2008; Yuen et al. 2010; Ang et al. 2012). Studies that used different pachymetry devices including slit-scanning topography (Hashemi et al. 2009; Lee, Kim & Park 2011), ultrasound pachymetry (Su et al. 2009; Eballe et al. 2010; Kadhim & Farhood 2016) and optical pachymetry (Herse & Yao 1993) have also reported insignificant gender differences for the CCT measurement.

In contrast with the results of the present study, some studies have found statistically significant gender differences for the mean CCT measurement (Hahn et al. 2003; Suzuki et al. 2005; Li et al. 2006; Mercieca et al. 2007; Nangia et al. 2010; Vijaya et al. 2010). A study by Mercieca et al. (2007), which used ultrasound pachymetry, reported a significant gender difference of 19 µm. The study by Mercieca et al. (2007) consisted of a relatively small sample size (n = 29) with an asymmetrical distribution of male (n = 17) and female (n = 12) participants therein which may explain the discrepancy to the present study. In the study by Hahn et al. (2003), a statistically significant gender difference of 4.6 µm was reported although the researchers concluded that this difference was not clinically significant due to its low magnitude (Hahn et al. 2003). Even though other studies have also reported statistically significant gender differences for the CCT measurement, the range of differences (5.8 µm to 7.6 µm) was only slightly higher than the result observed in the present study (Suzuki et al. 2005; Li et al. 2006; Nangia et al. 2010; Vijaya et al. 2010).

The findings related to the minimum corneal thickness measurement concerning its gender difference, location and relation to the CCT measurement in male and female participants revealed interesting results. The gender difference for the minimum corneal thickness measurement was almost identical to the gender difference for the CCT measurement in this South African sample. This finding is not surprising and may be owing to the location of the thinnest corneal point being central for the majority of participants in the two gender groups as has been found previously (Sanchis-Gimeno et al. 2004b). When the thinnest corneal point was not central, it was found to lie with similar frequencies in either the inferotemporal, inferior or temporal quadrants in the two gender groups. Despite the mean difference between the minimum corneal thickness and CCT measurements reaching statistical significance in the two gender groups, the relatively low magnitude of this difference (~6 µm) suggests that it is unlikely to be clinically important. Moreover, this finding concurs with Hashemi et al. (2011), who also reported small statistically significant differences (3 µm to 4 µm) between the minimum corneal thickness and CCT measurements in male and female participants. For both male and female participants, the superior and temporal quadrants in the peripheral cornea were thickest and thinnest respectively which is in agreement with the results of other studies (Hashemi et al. 2011; Huang et al. 2014; Randleman et al. 2015). Overall, these findings suggest that the corneal pachymetry profile and architectural structure are similar in South African young male and female adults that are free from ocular diseases and/or anomalies.

In this study, the median AOD500 measurements were slightly higher in female than male participants for both the nasal and temporal ACAs. Overall the gender difference for the median AOD500 measurements, which ranged from 8.50 µm to 10.50 µm, failed to reach statistical significance. This finding agrees with the study by Ramani et al. (2007), who noted 10 µm higher AOD500 measurements in Indian female participants that were also statistically insignificant. The results of the present study are in contrast with some studies that have reported significantly higher AOD500 measurements in males than females

(Friedman et al. 2008; Amerasinghe et al. 2009; Leung et al. 2010). In the latter group of studies, the gender difference for the AOD500 measurements were higher than that noted in the present study and ranged from 29 µm to 80 µm (Friedman et al. 2008; Leung et al. 2010). It is possible that this discrepancy could be related to a cohort effect as the studies that reported significant gender differences consisted of samples of primarily Asian individuals (Friedman et al. 2008; Amerasinghe et al. 2009; Leung et al. 2010). It is well known that Asian females are more likely to develop primary angle-closure glaucoma (Cheng et al. 2014; Wright et al. 2016). Moreover, Rüfer et al. (2010) reported that the reduction in ACA width is mainly influenced by female gender. Consequently, the significant gender differences in AOD500 measurements in these studies may be accounted for by these samples consisting of Asian male and female participants (Friedman et al. 2008; Amerasinghe et al. 2009; Leung et al. 2010).

In this study, the median and mean TIA measurements were comparable in male and female participants. Overall, the gender difference for the median TIA measurements were less than 1.50°. This implies that even though the gender difference for the temporal TIA measurement reached statistical significance, the low magnitude of this difference suggests that it is unlikely to be clinically important. This finding is in agreement with several studies that also reported marginal gender differences in TIA measurements that were less than 2° (Ramani et al. 2007; Dacosta et al. 2008; Friedman et al. 2008; Rüfer et al. 2010; Hosseini, Abolbashari & Mohidin 2013; Jin et al. 2016). In contrast, other studies have reported significant gender differences in TIA measurements (Oh et al. 1994; Leung et al. 2010; Fernández-Vigo et al. 2016). However, further analysis of the results reported in these studies showed that the gender differences ranged from 2.1° to 5.6° which is comparable with the findings of the present study (Oh et al. 1994; Leung et al. 2010; Fernández-Vigo et al. 2016). This implies that the TIA measurements in normal healthy South African male and female adults are similar which is consistent with the results for the two gender groups

outlined in previous studies worldwide (Ramani et al. 2007; Dacosta et al. 2008; Friedman et al. 2008; Hosseini, Abolbashari & Mohidin 2013).

Other characteristics associated with the ACA width variable measurements for the male and female participants showed interesting trends. For example, the majority of participants in the two gender groups had mean AOD500 and TIA measurements that were greater than 500 µm and 30° respectively for both the nasal and temporal ACAs. This implies that the majority of normal healthy South African young male and female adults have ACAs that may be classified as open and at low risk for angle closure. This finding is expected as overall there is a low prevalence of primary angle-closure glaucoma (0.5% to 2.3%) among South African normal healthy adult males and females (Salmon et al. 1993; Rotchford & Johnson 2002; Rotchford et al. 2003). For both male and female participants, the median AOD500 and TIA measurements were slightly wider in the temporal ACA than the nasal ACA. Even though other studies (Kim et al. 2011; Liu et al. 2011; Maruyama et al. 2014) have also reported this trend of the temporal ACA being wider than the nasal ACA, the exact reason for this finding is not readily explained.

Taken together, the results of this study suggest that there are no clinically significant gender differences in anterior segment variables in normal healthy South African young adults. The same pattern was also noted when gender differences were investigated in the Black and Indian race groups. This implies that the corneal thickness and ACA width variable measurements are comparable between South African males and females. Moreover, the gender related differences in the present study are in agreement with the findings of previous studies involving normal healthy individuals (Ramani et al. 2007; Dacosta et al. 2008; Friedman et al. 2008).

7.7 OBJECTIVE 5: EFFECT OF SPHERICAL EQUIVALENT REFRACTION ON ANTERIOR SEGMENT VARIABLES MEASURED USING OCT

In the present study, the anterior segment variable measurements differed significantly among the three refractive error groups. This observation is in agreement with the literature wherein significantly different corneal thicknesses, particularly the CCT measurement, as well as ACA width variable measurements have been reported for individuals with varying refractive errors (Cosar & Sener 2003; Dacosta et al. 2008; Mohamed et al. 2009; Nakhjavanpour et al. 2016). Overall, the corneal thickness measurements were thinnest in the emmetropes, followed by myopes and hyperopes for all zones. For the ACA width variables, the hyperopes showed the narrowest measurements followed by emmetropes and myopes.

In this study, the CCT measurement varied significantly among the three refractive error groups and was thinnest in the emmetropes (~499 µm), followed by myopes (~508 µm) and hyperopes (~535 µm). However, this comparison should be interpreted with caution as there were very few participants with hyperopia (n = 4). In the literature, there are inconsistent reports regarding the increasing order of CCT measurements among the different refractive error groups. For example, Mohamed et al. (2009) reported that mean CCT measurements were thinnest in myopes (~450 µm), followed by emmetropes (~543 µm) and hyperopes (~558 µm). Mostafa (2014) reported the same trend in a sample of adults younger than 20 years wherein the mean CCT measurements were thinnest in myopes (530 µm) compared with emmetropes (531 µm) and hyperopes (533 µm). In a more recent study, Kadhim and Farhood (2016) also noted that myopes had thinner mean CCT measurements (539 µm) when compared with emmetropes (550 µm) and hyperopes (551 µm). Cosar and Sener (2003) showed that mean CCT measurements in emmetropes (~514 µm) were thinner than myopes (~536 µm) and hyperopes (~551 µm). In contrast, Dacosta et al. (2008) reported that mean CCT measurements were thinnest in emmetropes (512 µm), followed by hyperopes (522 µm) and myopes (527 µm) in a sample of individuals aged 36.78 ± 14.46

years. More recently, Nakhjavanpour et al. (2016) reported the same trend with mean CCT measurements in emmetropes, hyperopes and myopes being 507 µm, 528 µm and 541 µm respectively.

This implies that there is little consensus in the literature in relation to whether the thinnest CCT measurements are found in emmetropes or myopes. Differences in study methodologies, specifically regarding the methods used to determine the refractive error and classify participants into the different refractive error groups, could compound comparisons across studies and account for the variation observed. Moreover, the influence of the refractive characteristics of the different study samples is likely to have an impact on the study results and conclusions. This is plausible as it has been suggested that thinner CCT measurements are observed in individuals with more myopic refractive errors because of changes in the anterior segment as a result of myopia progression and elongation of the eye (Chang et al. 2001; Nemesure et al. 2003; Uçakhan et al. 2008).

The majority of studies have reported that the mean CCT measurements in hyperopes are higher when compared with emmetropes and/or myopes (Cosar & Sener 2003; Uçakhan et al. 2008; Mohamed et al. 2009; Hashemi et al. 2011; Mostafa 2014). Consequently, the observation of the thickest mean CCT measurements in hyperopes in the present study, albeit the small number of participants (n = 4), concurs with reports in the literature (Cosar & Sener 2003; Uçakhan et al. 2008; Mohamed et al. 2009; Hashemi et al. 2011; Mostafa 2014). In contrast, some studies (Dacosta et al. 2008; Hashemi et al. 2009; Nakhjavanpour et al. 2016) have reported that hyperopes have thinner mean CCT measurements than emmetropes and/or myopes. Further analysis of the results reported in two of these studies revealed mean thickness differences of only 2 µm to 5 µm between the hyperopes as well as the emmetropes and/or myopes (Dacosta et al. 2008; Hashemi et al. 2009). In the study by Nakhjavanpour et al. (2016), hyperopes had mean CCT measurements that were 13 µm

thinner than the myopes which may be accounted for by the considerable differences in mean age between the hyperopes (44.88 years) and myopes (27.37 years).

In this study, the ACA width variable measurements varied significantly among the three refractive error groups and was found to be narrowest in hyperopes, followed by emmetropes and myopes. However, this comparison should be interpreted with caution as there were very few hyperopes (n = 4) in this study. Nevertheless, this observation is consistent with previous studies that have also reported significantly narrower ACA width variable measurements in hyperopes compared with emmetropes and myopes (Dacosta et al. 2008; Uçakhan et al. 2008; Xu et al. 2008). This implies that the results of the present study validates the influence of refractive error on the width of the ACA. This finding is not surprising as hyperopia is a well-known risk factor for the development of angle-closure glaucoma (Wright et al. 2016). Moreover, hyperopes are almost three times more likely than myopes to have narrow ACAs which is considered to be one of the anatomical mechanisms for angle-closure glaucoma (Li et al. 2014). The axial length accounts for the main structural difference between eyes with hyperopia and myopia wherein the latter is associated with longer axial lengths (Llorente et al. 2004; Blanco, Ferńandez & Sanz 2008; Chen et al. 2009; Jin et al. 2016). As a result, the narrower ACAs in hyperopes may be a consequence of the shorter axial lengths inherent in eyes with hyperopia. This is probable as it has been hypothesised that the longer axial lengths in myopes serve as a protective factor against developing angle closure (Li et al. 2014).

Various studies have reported on the correlations between anterior segment variables and spherical equivalent refraction (Xu et al. 2008; Chen et al. 2009; Su et al. 2009; Fernández-Vigo et al. 2016). In the present study, significant negative correlations were found between corneal thickness measurements in all zones and spherical equivalent refraction. However, these correlations may be considered inconsequential owing to the r values being lower than –0.150 implying that less than 3% of the variation in corneal thickness measurements may be accounted for by the spherical equivalent refraction. Even though several studies

have reported on the correlation between CCT and spherical equivalent refraction, there is little consensus on the association between these two variables. The majority of studies have reported no significant correlation between CCT and spherical equivalent refraction (Cho & Lam 1999; Fam et al. 2006; Zhang et al. 2008; Chen et al. 2009; Hashemi et al. 2009; Su et al. 2009; Mostafa 2014) whereas other studies reported significant correlations (Chang et al. 2001; Cosar & Sener 2003). Despite the low magnitude of the significant correlation between CCT and spherical equivalent refraction in the present study ($r = –0.118$, $p = 0.002$), this finding is consistent with earlier studies (Chang et al. 2001; Cosar & Sener 2003) that reported significant correlations where the magnitude of these associations were also weak (r between 0.06 and 0.16). In the present study, the spherical equivalent refraction was significantly correlated with the ACA width variables as has been reported in previous studies (Xu et al. 2008; Amerasinghe et al. 2009; Rüfer et al. 2010; Kim et al. 2011; Fernández-Vigo et al. 2016). For every 1 D change in spherical equivalent refraction, the CCT, AveAOD500 and AveTIA measurements will change by ~3 µm, ~20 µm and ~0.50° respectively.

Taken together, these results suggest that the anterior segment variables vary depending on the type of refractive error. The finding of lowest corneal thickness and ACA width variable measurements in emmetropes and hyperopes respectively is fairly consistent with the results in the literature. Overall, the anterior segment variables were significantly correlated with spherical equivalent refraction although the low magnitude of the correlations suggest that the influence of these associations may not be clinically significant.

7.8 OBJECTIVE 6: REGRESSION TREE MODEL FOR THE INFLUENCE OF ANTERIOR SEGMENT VARIABLES ON IOP

Glaucoma, which is an optic neuropathy, is the second most common cause of global blindness (Quigley & Broman 2006; Pascolini & Mariotti 2012). Overall, it is estimated that approximately 76 to 80 million people worldwide will be affected by this optic neuropathy

over the next two years (Quigley & Broman 2006; Tham et al. 2014). To compound this global epidemic, a recent meta-analysis concluded that the prevalence of glaucoma is projected to increase substantially and affect almost 112 million people by the year 2040 (Tham et al. 2014). After Asia, Africa has the second highest prevalence of glaucoma and accounts for 13% of the total number of people with the condition worldwide (Tham et al. 2014). Moreover, recent estimates suggest that the number of people with glaucoma in Africa is projected to increase by 130.8% with 19.14 million people being affected by the year 2040 (Tham et al. 2014). Consequently, it has been recommended that glaucoma screening procedures be incorporated into routine eye examinations (Cook 2009; Thomas 2012). Moreover, in Africa glaucoma blindness control initiatives have been implemented as the socio-economic impact of glaucoma is concerning as it can lead to irreversible visual impairment (Quigley et al. 2000; Kabiru et al. 2005; Damji et al. 2017).

The assessment of the IOP measurement is a fundamental clinical test that is used to screen, diagnose and monitor glaucoma (Hashemi et al. 2005; Kanski 2008). This may be the case as IOP is still regarded as an important recognised risk factor for the development of glaucoma (Hashemi et al. 2005; Kanski 2008; Cook & Foster 2012). Apart from the IOP measurement, studies have reported that other ocular variables, specifically from the anterior segment, may be useful in screening for individuals at risk for glaucoma (Devereux et al. 2000; Gordon et al. 2002; Nolan et al. 2003; Leske et al. 2007; Xu et al. 2008). For example, the importance of the CCT measurement in evaluating the risk for developing primary open-angle glaucoma was highlighted as a seminal finding in the OHTS (Gordon et al. 2002). Ocular variables associated with the anterior chamber, which include the ACD and ACA width, may also be useful in evaluating the risk for developing angle-closure glaucoma (Devereux et al. 2000; Nolan et al. 2003; Xu et al. 2008).

As a result, several population-based (Foster et al. 2003; Fukuoka et al. 2008; Tomoyose et al. 2010; Jonas et al. 2011) and clinic-based (Kohlhaas et al. 2006; Medeiros & Weinreb

2006; Iyamu & Memeh 2007) studies have investigated and reported on the relationship between IOP and anterior segment variables. Investigating the relationship between IOP and anterior segment variables may be useful to better understand the association between IOP and the different anterior segment variables (Hashemi et al. 2005). This knowledge may help in a clinical setting to identify patients with anterior segment ocular risk factors that are associated with elevated IOP measurements (Jonas et al. 2011).

Throughout the literature, the majority of studies have used traditional statistical methods, including correlation and regression analyses, to assess the relationship between IOP and anterior segment variables (Foster et al. 2003; Medeiros & Weinreb 2006; Fukuoka et al. 2008; Kawase et al. 2008; Tomoyose et al. 2010). Although correlation and regression analyses have been widely used for optometry and medical research, they may result in erroneous and spurious conclusions, especially when their inherent assumptions are misunderstood and/or the results are inaccurately interpreted (Armstrong, Eperjesi & Gilmartin 2005; Tu et al. 2005; Veličković 2015). Moreover, both correlation and linear regression analyses are used to determine if there is a linear relationship between two continuous variables and may omit the more complex relationships that exist when there are more than two variables of interest (Armstrong, Eperjesi & Gilmartin 2005; Mukaka 2012; Veličković 2015). Not surprisingly therefore, several researchers have cautioned against misinterpreting a large significant correlation between two variables as a causal relationship between the two variables of interest (Armstrong, Eperjesi & Gilmartin 2005; Mukaka 2012; Veličković 2015).

In the absence of any ocular anomalies, the ocular variable measurements in the right and left eyes of the same individual are inherently related (Glynn & Rosner 2012; Karakosta et al. 2012; Armstrong 2013). Moreover the different ocular variables, within the same eye, may also be inherently related and correlated. The related nature of clinical variables, from a particular biological system, is not exclusive to optometry and has also been shown in

dental and medical research (Bagley, White & Golomb 2001; Tu et al. 2005; Benndorf, Baltzer & Kaiser 2011). Multiple regression analysis is often used to make predictions and suggest explanations for a dependent variable when there are more than two independent variables (Bagley, White & Golomb 2001; Maree 2007). When clinical variables used in multiple regression analysis are highly correlated, it results in mathematical coupling and collinearity (Bagley, White & Golomb 2001; Næs & Mevik 2001; Tu, Clerehugh & Gilthorpe 2004). Collinearity can distort the relationship between two ocular variables, especially when both variables of interest are highly correlated with another ocular variable (Armstrong, Eperjesi & Gilmartin 2005). Therefore, a statistical method that overcomes some of these challenges is preferred for assessing the relationship between IOP and multiple anterior segment ocular variables.

Classification and regression tree is an analysis method that is able to detect which variables are important in a relationship or model (Breiman et al. 1984; Morgan 2014). This method is particularly useful for large data sets that contain multiple variables that may have non-linear relationships (De'ath & Fabricius 2000; Moisen 2008; Speybroeck 2012). The CART method has several advantages including that it can be used with skewed data, requires minimal input from the researcher because of an automatic independent variable selection process, is able to handle collinearity together with missing variables and displays information in a way that is simple to interpret even for individuals with limited statistical backgrounds (Lewis 2000; Timofeev 2004; Speybroeck 2012).

The CART method generates a regression tree model when a dependent variable is predicted based on multiple independent variables (Loh 2011). In a regression tree model, the dependent variable is continuous while the independent variables may be either continuous or categorical (Marshall 2001; De'ath 2002; Timofeev 2004; Speybroeck 2012). Moreover, regression tree models are simple to present and resemble the process used in clinical reasoning as they are generated based on a logical sequence of 'if then'

statements/decision rules (Loh 2011). For this reason, the CART method is said to have greater practical relevance in a clinical setting (Lewis 2000). To this end, several studies have produced regression trees, using the CART method, for clinical conditions including myocardial infarction (Kurt, Ture & Kurum 2008), dental caries (Ito et al. 2011), asthma (Sato et al. 2009), dry eye (Mathers & Choi 2004), vernal keratoconjunctivitis (Sacchetti et al. 2010), keratoconus (Smadja et al. 2013) and low vision rehabilitation (Fraser et al. 2015).

Graphically, regression tree models consist of a single node (call the root) and consecutive internal nodes that are defined by a characteristic independent variable and its respective cut-off value that splits the data into two sub-groups (Lewis 2000; Moisen 2008; Speybroeck 2012). At each internal node, the CART method iteratively evaluates all the independent variables and automatically selects the variable and its cut-off value that is most efficient in splitting the data into two sub-groups containing similar values for the dependent variable (Timofeev 2004; Strobl, Malley & Tutz 2009; Speybroeck 2012). Consequently, regression tree models are generated using binary recursive partitioning because of the two-way split at each internal node (Lewis 2000; Marshall 2001; Loh 2011). The process of splitting the sub-groups is continued until the data cannot be split any further resulting in terminal nodes (Moisen 2008). The root node contains all cases in the data while each terminal node depicts the number of cases (from the data) and the mean value of the dependent variable located within that branch (Marshall 2001; Moisen 2008).

Regression tree models that consist of too many branches are unnecessarily large and complex (Moisen 2008). Such a model is likely to ‘overfit’ the data resulting in poor generalisability to new data (Lewis 2000; Moisen 2008; Smadja et al. 2013). Thus, a pruning process is applied to the initial large regression tree model that removes internal nodes that are considered ‘noise’ and contribute no predictive power to the regression tree model (Strobl, Malley & Tutz 2009). Consequently, pruning often results in a smaller regression tree model (Moisen 2008). Furthermore, pruned regression trees have better predictive

accuracy because they go through a cross-validation procedure to select the optimal sized tree (De'ath 2002; Timofeev 2004).

In this study, the influence of 11 independent variables (assessed in the present study) on IOP measurements was investigated. This included eight anterior segment ocular variables and three demographic variables. Instead of using traditional statistical methods that require an a priori deliberate selection of which variables to analyse, by the researcher and/or statistician, the CART method was used. This method is often used in data mining as it makes no assumptions about the data and automatically selects the most important variables in a relationship or model (Breiman et al. 1984; Morgan 2014). The results showed that four anterior segment variables influenced IOP. Three of these variables were measures of corneal thickness (CCT, AvePeriCT and AveParaCT) while the other was the axial ACD.

Both regression tree models showed that CCT (at level one) was the most important anterior segment variable that influenced IOP. This finding is not surprising as several studies have reported strong associations between IOP and CCT in normal individuals (Suzuki et al. 2005; Mohamed et al. 2009; Nangia et al. 2010; Vijaya et al. 2010) and those with glaucoma (Gelaw 2012). Even though such associations have been reported in the literature, the exact reason for this association is unclear. However, it could be a consequence of both IOP and CCT being measured at the corneal optical zone as well as the characteristics therein. For example, the corneal optical zone, which has a diameter of 4 mm, is thought to have a uniform spherical curvature (Gupta & Krishna 2009). A regular corneal surface is important because applanation tonometry measurements are estimated based on the force needed to applanate a certain area (Fleming & Semes 2006).

A fixed area of flattening is especially important for Goldmann applanation tonometry because, at an applanation diameter of 3.06 mm, the opposing effects of corneal rigidity and

the surface tension of the tear film are cancelled out (Fleming & Semes 2006). Furthermore, the corneal optical zone has reduced thickness (Hashemi et al. 2011; Randleman et al. 2015), is more compact and has lower mean collagen inter-fibrillar separations (Boote et al. 2003) than the corneal periphery. These differences between the corneal optical zone and periphery could account for differences in resistance to applanation tonometry (Queirós et al. 2007). It is speculated that these anatomical, physiological and topographical differences may also account for the association between IOP and CCT at the corneal optical zone. This explanation is reasonable because it has been shown that corneal biomechanical properties influence IOP measurements (Liu & Roberts 2005; Medeiros & Weinreb 2006). Moreover, in this study the IOP measurements in the root node were split based on cut-off CCT value of 527 µm, which is similar to the theoretically calibrated CCT measurement of 520 µm for Goldmann applanation tonometry (Whitacre, Stein & Hassanein 1993).

After CCT, the next important anterior segment variables were AvePeriCT, AveParaCT and axial ACD. Corneal thickness beyond the corneal optical zone is not routinely measured in clinical practice. However, the results suggest that these corneal thicknesses may be important determinants of IOP measurements. No studies could be found that investigated the relationship of IOP and corneal thickness measurements beyond the corneal optical zone (peripheral corneal thickness). The paucity of literature regarding IOP together with peripheral corneal thicknesses may relate to the fact that IOP is also not usually measured beyond the corneal optical zone. However, such measurements may be useful estimates of IOP especially in instances of refractive surgeries, central corneal ulcers, epithelial oedema and high irregular astigmatism (Schipper et al. 2000; Queirós et al. 2007). Moreover, studies conducted on IOP measured at points beyond the corneal optical zone have reported reliable IOPs that are in agreement with IOPs measured at the corneal optical zone (Schipper et al. 2000; Garzozi et al. 2001; Queirós et al. 2007). The exact reason for the influence of peripheral corneal thicknesses on IOP is not readily explained. However, it may be related to the thinnest point on the cornea not being located at the corneal apex

(corresponding to the CCT measurement), as previously thought, but rather being inferior-temporal to the CCT measurement (Hashemi et al. 2009; Hashemi et al. 2011; Fares et al. 2012; Saenz-Frances et al. 2014). It is also likely that corneal rigidity will vary in relation to the different corneal thickness profiles and may also influence the IOP measurements (Liu & Roberts 2005; Medeiros & Weinreb 2006).

The normal axial ACD is approximately 3 mm with a wide range of 2.6 mm to 4.6 mm (Barrett & McGraw 1998). In the present study, the mean axial ACD (3.4 mm) and axial ACD cut-off value (3.6 mm) in the regression tree models were within this expected range. Surprisingly, participants with axial ACDs deeper than the cut-off value had slightly higher IOP measurements (1.1 mmHg). Tomoyose et al. (2010) theorised that higher IOP measurements may not necessarily be associated with narrow anterior chambers when the ACA is open in normal individuals. In this study, the axial ACD was selected as one of the important anterior segment ocular variables that influenced IOP. This finding is in contrast with previous studies that reported no association between IOP and ACD (Kawase et al. 2008; Tomoyose et al. 2010). This difference may be due to a cohort effect because studies that noted no association between IOP and ACD consisted of primarily older Japanese participants (Kawase et al. 2008; Tomoyose et al. 2010). It should be noted that Tomoyose et al. (2010) reported on the axial ACD whereas Kawase et al. (2008) reported on the limbal ACD measurements.

In this study, no ACA width variables were selected by the CART method to influence the IOP measurement. These results are in agreement with previous studies that also reported no meaningful association in normal healthy non-glaucomatous eyes between IOP and ACA width variables (Amerasinghe et al. 2009; Rüfer et al. 2010). However, other studies that used gonioscopy to evaluate the ACA width have reported that IOP and ACA width are related (Foster et al. 2003; Jonas et al. 2011). Both these studies however further commented that the associations found were marginal (Jonas et al. 2011) and would only

result in small changes in IOP (0.2 mmHg for every 10° change in ACA width) (Foster et al. 2003).

In this study, the other corneal variables (excluding the measures of corneal thickness discussed above) have revealed interesting results. Both corneal curvature and diameter were not selected by the CART method for inclusion in the regression tree models. This finding is consistent with the lack of strong associations noted between IOP and corneal curvature or diameter as has been reported in other studies (Eysteinsson et al. 2002; Kohlhaas et al. 2006; Özcura, Aydin & Uzgören 2008; Iyamu & Osuobeni 2012). The exact reason for the lack of association between IOP and corneal curvature as well as diameter is not readily explained.

Despite an equal distribution of males and females in the study sample, gender was not detected as an important factor in the regression tree models. This finding is consistent with some studies that also reported that IOP is not affected by gender (Hashemi et al. 2005; Iyamu & Memeh 2007; Casson et al. 2008; Su et al. 2009). Contradictory findings have been reported regarding IOP and age. Studies involving Asian individuals reported that IOP decreases with increasing age (Nomura et al. 2002; Fukuoka et al. 2008; Kawase et al. 2008; Tomoyose et al. 2010) whereas other studies reported that IOP increases with increasing age (Leske et al. 1997; Hashemi et al. 2005). In this study, IOP was not affected by age, which may be attributed to the small age range of participants this being in contrast to other studies that reported associations between IOP and age (Hashemi et al. 2005; Kawase et al. 2008; Tomoyose et al. 2010).

The mean IOP in the general population ranges between 11 mmHg and 21 mmHg (Kanski 2008). The mean IOP of 14.6 ± 2.4 mmHg in this study is almost identical to that reported by Sardiwalla et al. (2012). Despite using a non-contact tonometer, Sardiwalla et al. (2102) also measured IOP in a South African young adult sample and reported a mean IOP

measurement of 14.6 ± 2.8 mmHg. In contrast, the mean IOP measurements reported in several older South African samples (Rotchford & Johnson 2002; Rotchford et al. 2003) were smaller (13.7 mmHg to 13.9 mmHg) than that found in this study which may be attributed to the influence of age on IOP (Nomura et al. 2002; Tomoyose et al. 2010). This difference may also be related to differences in sample sizes wherein the studies with lower mean IOP measurements consisted of larger study samples (Rotchford & Johnson 2002; Rotchford et al. 2003). As this study only included participants with IOP measurements that were 21 mmHg or less, all sub-groups of participants shown in the terminal nodes of the regression tree models can be considered as variations of an essentially normal South African young adult population. Although some eyes with IOP measurements of 21 mmHg or less could have normal tension or low tension glaucoma, the age range of participants in this study (17 years to 30 years) probably excluded such instances. From the regression tree models, it can be seen that based on some anterior segment ocular variables, there is a wide range of normal IOP measurements (12.9 mmHg to 19.4 mmHg) in this South African young adult sample.

Taken together, these findings suggest that the regression tree models not only validate the profound influence that CCT has on the IOP measurements but also draws attention to the importance of corneal thickness measurements outside the corneal optical zone. There is a need to comprehend the important factors that influence IOP measurements in a ‘simple to understand’ way in the context of clinical values instead of solely relying on correlation coefficients and p-values of significance. Consequently, the regression tree models further provide eye care personnel with a realistic approximation of the IOP based on the measurements of other anterior segment ocular variables. This information may help practitioners to detect which patients require monitoring of IOP on the basis of other routinely measured anterior segment ocular variables.

7.9 CONCLUSION TO THE CHAPTER

This chapter presented the discussion related to the six objectives from phase one of this study which involved discussing the important results from phase one of the study in the context of the literature and highlighting the clinical implications of these findings.

CHAPTER 8: CLINICAL BIOMETRIC GUIDELINE

8.1 INTRODUCTION TO THE CHAPTER

Phase two of the study entailed developing a clinical biometric guideline and comparing the values therein to anterior segment variables currently available for other healthy African sub-populations. This chapter outlines phase two of the study which consisted of two study objectives (7 and 8). Study objective seven focuses on the development of a clinical biometric guideline with normal reference intervals for anterior segment variables measured using OCT. Study objective eight involves comparing the clinical biometric guideline to anterior segment variable measurements currently available for other healthy African sub-populations living within the African continent. The results from phase two of the study are presented according to the two study objectives.

8.2 OBJECTIVE 7: DEVELOP A CLINICAL BIOMETRIC GUIDELINE WITH NORMAL REFERENCE INTERVALS FOR ANTERIOR SEGMENT VARIABLES MEASURED USING OCT

This section focuses on the development of a clinical biometric guideline with normal reference intervals for anterior segment variables measured using OCT. The absence of such information makes it difficult to interpret anterior segment variable measurements, obtained using OCT, when examining patients in clinical and/or research settings. The section begins with an overview of the theory related to reference intervals. This is followed by an outline of the reference intervals for anterior segment variables, measured using OCT, which includes the presentation of the clinical biometric guideline with the normal reference intervals therein.

8.2.1 Theory related to reference intervals

The concept of reference values, first introduced in the late 1960s (Gräsbeck & Saris 1969), was proposed as an alternative to the more ambiguous concept of 'normal values' (Sunderman 1975). Some of the problems associated with the idea of 'normal' from the concept of 'normal values' include:

i. sylleptic ambiguity: where the clinical and statistical meaning of 'normal' are different wherein the former would imply healthy and the latter a Gaussian distribution (Sunderman 1975; Gräsbeck 2004; Bland 2015b). Furthermore, Gräsbeck (2004) asserts that the word 'normal' has multiple meanings that at times may be conflicting.

ii. emotional implications: where the idea that what is not 'normal' is 'abnormal' and thus requires correction (Sunderman 1975). According to Murphy (1966), the concept of 'normal' has insidious emotional implications particularly for those individuals identified as 'abnormal'.

iii. unclear scientific definition: where it is difficult to determine the precise scientific definition of the concept 'normal' (Murphy 1966; Siest et al. 2013). This further supports the idea that the concept of 'normal values' is imprecise and scientifically flawed (Gräsbeck 2004; Higgins 2012).

Consequently, it was suggested that the concepts of 'normal' and 'normal values' be abolished (Dybkær & Gräsbeck 1973) as they represent vestigial aspects of the medical field that have been inherited from the unscientific era of medicine (Murphy 1966). This led to considerable interest and expansion in the field of reference values, particularly in the 1980s, with the development of several approved recommendations from the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC-LM). Six approved recommendations were published by the IFCC-LM which focused on the theory, generation, application and presentation of reference values. The six approved recommendations were:

i. Part 1: The concept of reference values (Solberg 1987a).

ii. Part 2: Selection of individuals for the production of reference values (PetitClerc & Solberg 1987).

iii. Part 3: Preparation of individuals and collection of specimens for the production of reference values (Solberg & PetitClerc 1988).

iv. Part 4: Control of analytical variation in the production, transfer and application of reference values (Solberg & Stamm 1991).

v. Part 5: Statistical treatment of collected reference values. Determination of reference limits (Solberg 1987b).

vi. Part 6: Presentation of observed values related to reference values (Dybkær & Solberg 1987).

Despite the usefulness of these approved recommendations, they were subsequently revised by the CLSI which developed and published one guideline. The EP28-A3c guideline, formerly referred to as the C28-A3c guideline, outlines the specific terminology and procedures associated with the concept of reference intervals (CLSI 2008). To date, the EP28-A3c guideline represents a significant development in the field of reference intervals and is still being used (Ozarda 2016). Based on the EP28-A3c guideline (CLSI 2008), the terms and their respective descriptions relevant to the concept of reference intervals are briefly outlined below.

i. *Reference individual*: an individual selected for testing by predefined study (inclusion and exclusion) criteria. These reference individuals are assumed to be 'healthy' individuals. Bland (2015b) asserts that normal individuals refers to the apparently

healthy individuals in a local population. Considering that health is a relative concept that is difficult to define (Solberg 1987a; Horn et al. 2001; Gräsbeck 2004), these reference individuals are selected based on clearly defined study criteria that serve as an estimate of health.

ii. *Reference population*: the group of all possible reference individuals and usually consists of an unknown number of reference individuals (Solberg 1987a).

iii. *Reference sample group*: a subset of the reference population and should consist of an adequate number of reference individuals, selected using a random sampling approach, which are representative of the reference population.

iv. *Reference value*: the value or test result that is obtained through either observation or measurement on a reference individual. The reference value refers to only one value obtained on one reference individual which is different from a reference limit (defined below).

v. *Reference distribution*: the statistical distribution of reference values.

vi. *Reference limit*: the value that is derived from the reference distribution. There are usually two values that are representative of the lower and upper reference limits. The corresponding confidence interval for each reference limit is usually specified (Henny et al. 2000; Higgins 2012; Miller et al. 2016) which makes them descriptive of the reference values (CLSI 2008). Moreover, the reference limits define the reference interval (Solberg 1987a).

vii. *Reference interval*: the interval between, and including, the two reference limits which denotes the resulting interval that has been established after statistical

calculations have been performed on the reference distribution (Gräsbeck 2004). Usually, the reference interval describes a specific proportion of the reference values obtained on reference individuals. Most often, this proportion corresponds to 95% wherein a reference interval describes the central 95% of the distribution of reference values (Henny et al. 2000; Miller et al. 2016). This corresponds to the range between the 2.5 percentile and 97.5 percentile (Solberg 1987b; Higgins 2012; Bland 2015b). Consequently, 2.5% of the reference values lie below the lower reference limit and 2.5% of the reference values lie above the upper reference limit (Harris & Boyd 1995; Ceriotti & Henny 2008; Bland 2015b). This means that in 5% of healthy individuals, it is normal to observe measurements that are outside the range of the reference interval (Lumsden & Mullen 1978; Häggström 2014; Bland 2015b). Accordingly, a reference interval describes the usual range of measurements obtained on reference individuals (Sikaris 2014). Other terms used to denote the reference interval include the normal range, 95% reference range, 95% reference interval and physiological/biological reference interval (Ceriotti & Henny 2008; Häggström 2014; Bland 2015b). However, using the term 'range' to refer to the reference interval has been discouraged because in statistics, this term represents the difference between the highest and lowest numbers in a data set (Higgins 2012). Consequently, the term 'range' is rejected as the reference interval does not include the entire collection of reference values (Horn et al. 2001). The reference interval width may be determined as the difference between the lower and upper reference limits (Horn & Pesce 2003).

viii. *Observed value*: the value or test result that is obtained through either observation or measurement on an individual. An observed value can be compared to the reference values, reference distribution, reference limits and/or reference intervals.

Figure 8.1 describes the relationship between the terms relevant to the concept of reference intervals as specified in the EP28-A3c guideline (CLSI 2008). This guideline also highlights

issues related to the selection of reference individuals, minimum number of reference individuals needed in a reference sample group, various statistical methods that can be used to compute the reference interval and the presentation of reference intervals (CLSI 2008).

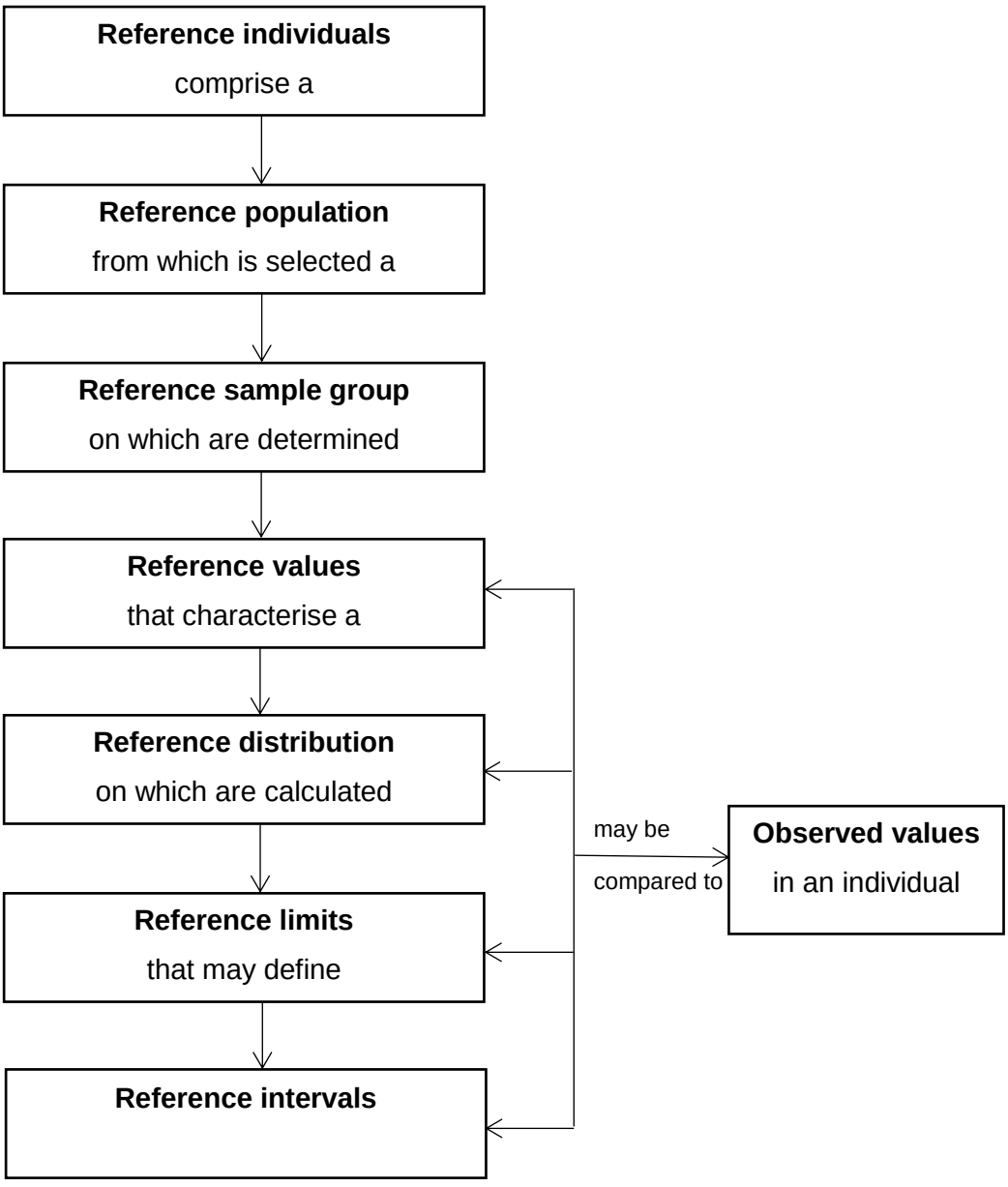


Figure 8.1: Relationship between the terms related to the concept of reference intervals according to the CLSI EP28-A3c guideline (CLSI 2008)

Reference intervals play an important role in clinical practice and have been used widely as clinical guidelines (Lumsden & Mullen 1978; Harris & Boyd 1995; Gräsbeck 2004; CLSI

2008; Friedrichs et al. 2012). In a clinical setting, the test results obtained on patients have limited meaning when considered in isolation (Higgins 2012). Reference intervals facilitate the process of transforming clinical test results into meaning as they allow for comparisons (Higgins 2012; Miller et al. 2016). By using an appropriate reference interval, clinicians can compare the test results obtained on patients to aid in clinical interpretation and decision-making (Aytekin & Emerk 2008; CLSI 2008; Jung & Adeli 2009; Pavlov, Wilson & Delgado 2012; Häggström 2014). Reference intervals account for physiological variations as they contain the range of possible test values, for a particular variable, in healthy individuals without disease (Harris & Boyd 1995; Gräsbeck 2004; CLSI 2008). This implies that, as part of the clinical decision-making process, a test result that falls outside the specified reference interval should be flagged for further attention (Harris & Boyd 1995; Jung & Adeli 2009; Miller et al. 2016). This is because there is a less than 2.5% probability that a test result that falls outside the specified reference interval could have occurred due to random variability in a healthy individual (Häggström 2014).

Since its inception, the field of reference intervals including the statistical methods used to compute the reference intervals have undergone considerable development (Harris & Boyd 1995). Statistical methods for computing reference intervals can be broadly classified into two categories namely parametric (Gaussian) and non-parametric (Lumsden & Mullen 1978; Harris & Boyd 1995). Early calculations of reference intervals used mainly parametric methods that assumed a Gaussian reference distribution of the clinical variable of interest. However with advancements in the field of reference intervals, it was established that not all clinical variables had Gaussian distributions and that such assumptions were therefore unnecessary (Lumsden & Mullen 1978; Jung & Adeli 2009; Ozarda 2016).

There is some debate regarding the ideal method to compute the reference interval (Friedrichs et al. 2012). To this extent, researchers have suggested that the optimal method to compute the reference interval should be guided by size of the reference sample group

together with the characteristics of the reference distribution (Ichihara & Boyd 2010; Friedrichs et al. 2012). Harris and Boyd (1995) cautioned that if the reference distribution is skewed (non-Gaussian) and the reference interval is computed using the parametric method, it would result in a biased inaccurate reference interval. Therefore, it is necessary to evaluate the reference distribution of the clinical variable of interest before computing the reference interval (Lumsden & Mullen 1978; Harris & Boyd 1995; CLSI 2008; Ichihara & Boyd 2010; Higgins 2012). Moreover, it is recommended that the non-parametric method be used to compute the reference interval if the assumption of a Gaussian distribution is violated (Lumsden & Mullen 1978; Harris & Boyd 1995; Ichihara & Boyd 2010; Higgins 2012).

The parametric method to compute the reference interval involves the use of the mean ($\bar{x}$), standard deviation (s) and variance (s^2) together with the assumption of a Gaussian distribution (Harris & Boyd 1995; Ozarda 2016). Using this method, the two reference limits (2.5 percentile and 97.5 percentile) are determined using the formula $\bar{x} \pm 2s$ or more accurately using the formula $\bar{x} \pm 1.96s$ (Lumsden & Mullen 1978; Ichihara & Boyd 2010; Pavlov, Wilson & Delgado 2012; Siest et al. 2013; Ozarda 2016). As the parametric method with its associated formula is based on the assumption of a Gaussian distribution, it may be used when the reference distribution resembles a Gaussian distribution (Harris & Boyd 1995; Geffré et al. 2009). However, researchers have cautioned against using the parametric method to compute the reference interval (Ichihara & Boyd 2010; Pavlov, Wilson & Delgado 2012). This is because the parametric method results in reference intervals that have strict distributions and wide confidence interval widths making it the least preferred method especially with small sample sizes (Solberg 1987b; Pavlov, Wilson & Delgado 2012).

In the event of a skewed reference distribution, the parametric method may be used after a transformation process to normalise the distribution (Ichihara & Boyd 2010; Friedrichs et al. 2012; Pavlov, Wilson & Delgado 2012). This process involves the mathematical logarithmic transformation of the skewed reference distribution to follow a Gaussian distribution (Harris & Boyd 1995; Geffré et al. 2009; Higgins 2012; Pavlov, Wilson & Delgado 2012; Ozarda 2016). However, the resulting transformed distribution, referred to as a log-Gaussian distribution, may not work all the time (Horn & Pesce 2003; Ichihara & Boyd 2010). Historically, the parametric method was most commonly used to compute the reference interval with early studies inappropriately using the parametric method even when the Gaussian assumption was violated (Horn & Pesce 2003). Horn et al. (2001) reported that reference values considered as extreme outliers have a negative impact on the reference interval computation specifically when the parametric method is used. Moreover, it has been shown that when the parametric method is used on data that either follows a Gaussian distribution or has been transformed to follow a Gaussian distribution, the resulting reference intervals may be erroneous (Ichihara & Boyd 2010). Therefore, it is recommended that the parametric method should not be used particularly if the reference distribution is skewed and normality cannot be achieved and that the non-parametric method should be used to compute the reference interval (CLSI 2008; Ichihara & Boyd 2010; Friedrichs et al. 2012).

The non-parametric method to compute the reference interval is easier to use especially as there are no assumptions made about the reference distribution (Solberg 1987b; Harris & Boyd 1995). Moreover, the non-parametric method is less reliant on statistical expertise for computing the reference interval (Horowitz 2008). The EP28-A3c guideline recommends the use of the non-parametric method to compute the reference interval particularly when the reference sample group consists of more than 120 reference individuals irrespective of the characteristics of the reference distribution (Aytekin & Emerk 2008; CLSI 2008; Horowitz 2008; Jung & Adeli 2009; Ichihara & Boyd 2010; Friedrichs et al. 2012; Pavlov, Wilson & Delgado 2012). Consequently, this method is frequently used as it is easy to apply and can

be used on all types of reference distributions (Harris & Boyd 1995; Horowitz 2008; Häggström 2014).

With the non-parametric method, the reference interval is computed by ordering the reference values according to magnitude from the smallest value to the largest value (Horowitz 2008). These ordered reference values are then assigned a rank (r) in sequence upward from 1. The 2.5 percentile corresponds to the reference value with the r equivalent to $0.025 \times (n + 1)$ (Harris & Boyd 1995; Horowitz 2008; Jung & Adeli 2009; Köseoğlu et al. 2010). The 97.5 percentile corresponds to the reference value with the r equivalent to $0.975 \times (n + 1)$ (Harris & Boyd 1995; Horowitz 2008; Jung & Adeli 2009; Köseoğlu et al. 2010). When the corresponding r is not an integer, the percentile value is determined by linear interpolation between the two ordered values (Harris & Boyd 1995; Köseoğlu et al. 2010). Considering that not all clinical variables display Gaussian distributions together with the possibility of the failure of a log-Gaussian distribution, the non-parametric method is recommended for computing reference intervals (CLSI 2008; Ichihara & Boyd 2010; Friedrichs et al. 2012).

It is also recommended that the confidence intervals should be included in the presentation of the reference interval (Solberg 1987b; CLSI 2008). The confidence interval estimate refers to a range of values computed from the data that includes the value of the parameter (which in this case are the two reference limits) being computed. As the confidence interval provides an indirect quantitative measure of the variability of the reference limits, it can be used as an indicator of the precision of the reference limits (Harris & Boyd 1995; CLSI 2008; Arseneau & Balion 2016).

Reference intervals may be separated or partitioned into sub-groups on the basis of demographic characteristics such as age, gender and race (Lahti, Petersen & Boyd 2002;

Lahti et al. 2002; Siest et al. 2013). In this way, a clinician may find it more useful to compare the clinical test result of a patient to a reference interval that matches the patient's demographic characteristics thereby improving the specificity of the reference interval (Harris & Boyd 1990; Lahti, Petersen & Boyd 2002). This is because reference intervals that are incorrectly matched for demographic characteristics may be suboptimal and clinically ineffective (Miller et al. 2016). Despite the partitioning of reference intervals having both theoretical and practical value, it is often observed that reference intervals are presented for an entire population without considering the various demographic characteristics. This observation may be attributed to the lack of agreement concerning the criteria that warrant partitioning of the reference intervals (Geffré et al. 2009; Siest et al. 2013).

Jung and Adeli (2009) cautioned that unnecessary partitioning of reference intervals can result in confusion. Therefore, it is recommended that reference intervals should only be partitioned when there is an important need for partitioned reference intervals based on demographic characteristics (Jung & Adeli 2009). Various methods have been proposed to determine if a reference interval should be partitioned (Sinton, Cowley & Bryant 1986; Harris & Boyd 1990; Harris, Wong & Shaw 1991; Harris & Boyd 1995; Lahti, Petersen & Boyd 2002; Lahti et al. 2002). However, the EP28-A3c guideline (CLSI 2008) recommends the Harris and Boyd method be used which is also the most common method used to partition a reference interval (Lahti et al. 2002; Ozarda 2016). Moreover, the Harris and Boyd method is preferred when there are two sub-groups, each with an equal number of reference individuals, within the reference sample group (Harris, Wong & Shaw 1991; Harris & Boyd 1995; Geffré et al. 2009; Ichihara & Boyd 2010).

According to the Harris and Boyd method (Harris & Boyd 1990; Harris, Wong & Shaw 1991; Harris & Boyd 1995), partitioning the reference interval into two sub-groups is recommended if the:

i. ratio between the sub-groups standard deviations (R) is greater than 1.5. The R is obtained by dividing the larger standard deviation by the smaller one. Harris, Wong and Shaw (1991) asserted that this criterion should apply regardless of the outcome of the other criterion (ii).

ii. normal deviate test score (z) exceeds the critical limit (z^*). The z value is determined by taking into account the means ($\bar{x}_1 \text{and } \bar{x}_2$), standard deviations ($s_1 \text{ and } s_2$) and sample sizes ($n_1 \text{ and } n_2$) of the two sub-groups using the formula $z = \frac{\bar{x}_1 - \bar{x}_2}{[(s_1^2/n_1)+(s_2^2/n_2)]^{1/2}}$. The z^* is dependent on the total sample size (N) and is determined using the formula $z^* = 3(\frac{N}{120})^{1/2}$.

Despite the field of reference intervals having being discussed for over 50 years, there is still considerable interest and expansion on the topic. Siest et al. (2013), in a recent review, aptly referred to the concept of reference values and intervals as ‘an unfinished symphony’. Possible reasons cited for continued interest in this field include:

i. The majority of reference intervals that exist were developed involving primarily Caucasian populations which limits their generalisability to other ethnic populations. Consequently, these reference intervals may be inappropriate for use in clinical settings that consist of diverse populations (Aytekin & Emerk 2008).

ii. Reference intervals that are currently being used are likely to have been established using clinical methods that have become obsolete. Consequently, use of these reference intervals may be inappropriate owing to significant technological advancements (Aytekin & Emerk 2008; Jung & Adeli 2009).

iii. Often the reference intervals that are currently being used have been established several years ago. Therefore, there is a need to validate the appropriateness of

these reference intervals for contemporary use (Aytekin & Emerk 2008; Jung & Adeli 2009).

The purpose of a reference interval is to provide guidance to clinicians for interpreting patients' clinical test results (Aytekin & Emerk 2008; CLSI 2008; Jung & Adeli 2009; Pavlov, Wilson & Delgado 2012). Moreover, once the normal reference intervals are determined in normal healthy individuals, future studies involving other individuals may be undertaken without the need for control groups (Hashemi et al. 2009). The reference intervals can be made accessible to clinicians in the form of tables, graphs and/or figures (Dybkær & Solberg 1987; CLSI 2008). They are most effective when the patient has similar demographic characteristics to the reference individuals selected for the development of the reference interval (Harris & Boyd 1990; Friedrichs et al. 2012). Moreover, the clinical test results obtained on patients should be measured using an instrument that is similar to the one used for the development of the reference interval (Harris & Boyd 1990).

8.2.2 Reference intervals for anterior segment variables measured using OCT

The application of anterior segment ocular biometry variable measurements obtained in studies involving non-African sub-populations as reference standards has remained a challenge for optometric personnel. Considering that there is limited knowledge on the description and characteristics of anterior segment variables within the South African context, a clinical biometric guideline may be beneficial in both clinical and research settings. The normal reference intervals for the different anterior segment variables, measured using OCT, can be used as a resource for the clinical interpretation of test results within the South African context. In this way, the clinical biometric guideline will provide optometric personnel with a reference tool that may be more appropriate in the South African context than relying on ocular biometry measurements obtained in studies involving non-African sub-populations. The baseline data within the clinical biometric guideline, obtained on a healthy South African young adult population, could be further compared to anterior segment data

obtained on other South African individuals including elderly populations and/or those with ocular diseases. In this way, the clinical biometric guideline may be able to enhance understanding of the changes and mechanisms that take place within the anterior segment due to ageing and/or ocular diseases. The clinical biometric guideline contributes to the growing body of literature focused on Africa that can be incorporated into the optometry curriculum as a locally relevant South African resource.

To develop the clinical biometric guideline with normal reference intervals, the anterior segment variables were measured using OCT in the right eyes of 700 healthy South African young adult individuals. The reference intervals were computed using the non-parametric method as endorsed by the CLSI (CLSI 2008). Table 8.1 presents the clinical biometric guideline with normal reference intervals for the anterior segment variables measured using OCT and represents the novel contribution of this study to the existing literature. For each anterior segment variable, the normal reference interval corresponds to the 2.5 percentile and 97.5 percentile of the reference distribution which represent the lower and upper reference limits respectively (Harris & Boyd 1995; Jung & Adeli 2009; Higgins 2012; Bland 2015b). This study therefore used a statistical based method to determine the normal reference intervals rather than simply presenting the range of measurements. The reference interval width (determined as the difference between the lower and upper reference limits) for all the corneal thickness measurements ranged from 132.48 µm (for the CCT zone) to 146.85 µm (for the peripheral inferior zone). The reference interval width for the AOD500 and TIA measurements ranged from 426.75 µm to 470.04 µm and 17.13º to 18.75º respectively. The 95% confidence intervals associated with both the lower and upper reference limits for each anterior segment variable are also presented within parenthesis (Table 8.1).

The clinical biometric guideline (Table 8.1) presents the normal reference intervals for anterior segment variables measured using OCT in a healthy South African young adult

population. Despite the study sample consisting of an equal number of South African Black and Indian young adults as well as males and females, the clinical biometric guideline presents the reference and confidence intervals for the total sample without partitioning. Using the Harris and Boyd method for partitioning the reference intervals (Harris & Boyd 1990; Harris, Wong & Shaw 1991; Harris & Boyd 1995), it was determined that the data did not meet the criterion to be partitioned on the basis of race and/or gender (all R values were less than 1.5). Thus, the normal reference intervals presented in this clinical biometric guideline pertain to the total sample of South African young adults included in this study.

Table 8.1: Clinical biometric guideline with normal reference intervals for anterior segment variables measured using OCT

CLINICAL BIOMETRIC GUIDELINE WITH NORMAL REFERENCE INTERVALS FOR ANTERIOR SEGMENT VARIABLES MEASURED USING OPTICAL COHERENCE TOMOGRAPHY		
ANTERIOR SEGMENT VARIABLE	**LOWER LIMIT (CI)**	**UPPER LIMIT (CI)**
Central corneal thickness (µm)	434.00 (431.50 to 436.50)	566.48 (563.98 to 568.98)
Minimum corneal thickness (µm)	428.00 (425.49 to 430.51)	561.48 (558.97 to 563.99)
Paracentral superior corneal thickness (µm)	465.00 (462.40 to 467.60)	600.00 (597.40 to 602.60)
Paracentral inferior corneal thickness (µm)	443.53 (440.93 to 446.13)	580.95 (578.35 to 583.55)
Paracentral nasal corneal thickness (µm)	455.00 (452.46 to 457.54)	590.48 (587.94 to 593.02)
Paracentral temporal corneal thickness (µm)	444.58 (441.99 to 447.17)	581.48 (578.89 to 584.07)
Peripheral superior corneal thickness (µm)	496.00 (493.24 to 498.76)	639.00 (636.24 to 641.76)
Peripheral inferior corneal thickness (µm)	463.05 (460.32 to 465.78)	609.90 (607.17 to 612.63)
Peripheral nasal corneal thickness (µm)	479.05 (476.40 to 481.70)	622.00 (619.35 to 624.65)
Peripheral temporal corneal thickness (µm)	463.53 (460.88 to 466.18)	603.48 (600.83 to 606.13)
Nasal AOD500 (µm)	359.80 (351.47 to 368.13)	786.55 (778.22 to 794.88)
Nasal TIA (º)	28.90 (28.56 to 29.24)	46.03 (45.69 to 46.37)
Temporal AOD500 (µm)	344.00 (335.26 to 352.74)	814.40 (805.66 to 823.14)
Temporal TIA (º)	28.24 (27.89 to 28.59)	46.99 (46.64 to 47.34)

CI = confidence interval

8.3 OBJECTIVE 8: COMPARE THE CLINICAL BIOMETRIC GUIDELINE TO ANTERIOR SEGMENT VARIABLES CURRENTLY AVAILABLE FOR OTHER AFRICAN SUB-POPULATIONS

A literature search revealed that few studies have reported on anterior segment variables in healthy African sub-populations living within the African continent. Table 8.2 summarises the findings of previous studies involving healthy African sub-populations that have reported on anterior segment variable measurements (Iyamu & Memeh 2007; Mercieca et al. 2007; Mohamed et al. 2009; Eballe et al. 2010; Gelaw et al. 2010; Iyamu et al. 2010; Iyamu & Eze 2011; Rampersad, Mashige & Jhetam 2011; Iyamu & Osuobeni 2012; Ntim-Amponsah et al. 2012; Sardiwalla et al. 2012; Iyamu, Iyamu & Amadasun 2013). The results of the present study particularly the means, ranges and normal reference intervals will be compared to the values reported in the other African sub-populations as shown in Table 8.2. This comparison was undertaken to assess the similarity and/or differences of the anterior segment variable measurements among the different African sub-populations.

The majority of studies involving African sub-populations were conducted in Nigeria and only two studies were conducted in South Africa (Table 8.2). With the exception of the study conducted in Cameroon (Eballe et al. 2010), all studies had samples consisting of 300 participants or less. The mean age of the samples suggests that the participants were primarily middle-aged adult individuals. Moreover, all of the studies have assessed and reported on only the CCT measurement with no attention given to corneal thickness measurements beyond the central cornea and/or ACA width variable measurements. Even though the studies were conducted within a relatively recent period (2007 to 2013), the majority of studies relied exclusively on ultrasound pachymetry to measure the CCT.

The mean CCT measurement found in the present study (501.91 ± 33.74 µm) is considerably lower than the values reported in all of the other studies involving African sub-populations living within the African continent (Table 8.2). In this study, the mean CCT

measurements ranged between 413 µm and 618 µm with the normal reference interval being from 434 µm to 566 µm. In general, most of the studies in Table 8.2 reported on the range of CCT measurements and the comparison revealed that even the minimum and maximum CCT measurements found is this study are much lower than that reported in other studies (Eballe et al. 2010; Iyamu et al. 2010; Iyamu & Eze 2011; Iyamu & Osuobeni 2012; Ntim- Amponsah et al. 2012). None of the previous studies reported on the normal reference interval for the CCT measurement. However, the lower limit of the reference interval noted in the present study (434 µm) is comparable to the minimum CCT measurement for most of the studies except those involving Nigerian samples. In contrast, the upper limit of the reference interval in the present study (566 µm) is considerably lower than the maximum CCT measurement reported in all studies.

No studies could be found that reported on peripheral corneal thickness (beyond the central cornea) and/or ACA width variable measurements for normal healthy African sub-populations living within the African continent. This lack of information limits the comparison of the mean, range and normal reference intervals (reported in the clinical biometric guideline) for peripheral corneal thickness and ACA width variable measurements observed in the present study to the findings of other studies.

Overall, this comparison revealed that the results concerning the CCT measurements in the present study were different compared with the values reported in other African sub-populations. This observation draws attention to the assumption that anterior segment variable measurements in one African sub-population cannot necessarily be extrapolated to other African sub-populations. Consequently, the varied mean CCT measurements imply that there is heterogeneity between and within the different African sub-populations (Detry-Morel et al. 2012). The comparison of the anterior segment variables, which in this case was only the CCT measurement owing to limited information, was useful as it suggests that there may be other factors that contribute to differences in ocular variable measurements within

the different African sub-populations. These results further suggest that there is a need for detailed studies involving the various African sub-populations aimed at developing clinical guidelines that can be applied by optometric personnel with the certainty that the information therein will aid in clinical eye examinations of the African individuals that present to clinical settings within the continent.

Table 8.2: Anterior segment variables in healthy African sub-populations

Country	Author (year)	Sample size	Mean age (years)	Technique/ Method	Variable	Results (μm)			
						Mean	Range Minimum	Range Maximum	Reference interval
Sudan	Mohamed et al. (2009)	94	NR*	Ultrasound pachymetry	CCT	530.15 ± 58.10	420	610	NR*
Ethiopia	Gelaw et al. (2010)	300	42.57 ± 16.71	Ultrasound pachymetry	CCT	518.68 ± 32.92	430	610	NR*
Ghana	Ntim-Amponsah et al. (2012)	253	58 ± 16.1	Ultrasound pachymetry	CCT	530.53 ± 35.64	423	650	NR*
Cameroon	Eballe et al. (2010)	485	31.4 ± 15.5	Ultrasound pachymetry	CCT	528.74 ± 35.89	440	670	NR*
Nigeria	Iyamu et al. (2010)	85	44.7 ± 15.1	Ultrasound pachymetry	CCT	550.0 ± 36.3	478	662	NR*
	Mercieca et al. (2007)	29	63.1 ± 11.2	Ultrasound pachymetry	CCT	535 ± 38	NR*	NR*	NR*
	Iyamu, Iyamu and Amadasun (2013)	95	44.9 ± 15.2	Ultrasound pachymetry	CCT	547 ± 29.5	487	618	NR*
	Iyamu and Memeh (2007)	39	45.2 ± 15.4	Ultrasound pachymetry	CCT	NR*	NR*	NR*	NR*
	Iyamu and Osuobeni (2012)	130	47.8 ± 16.8	Ultrasound pachymetry	CCT	548.97 ± 34.28	478	662	NR*
	Iyamu and Eze (2011)	95	47.1 ± 14.1	Ultrasound pachymetry	CCT	550.1± 33.1	478	662	NR*
South Africa	Sardiwalla et al. (2012)	200	20.1 ± 1.6	Scheimpflug photography	CCT	519.5 ± 38.6	442	642	NR*
	Rampersad, Mashige & Jhetam (2011)	105	29.27 ± 14.67	Scheimpflug photography	CCT	518.49 ± 33.01	440	606	NR*
	Current study	700	20.4 ± 1.8	Optical coherence tomography	CCT	501.91 ± 33.74	413	618	434.00 to 566.48

CCT = central corneal thickness, NR* = not reported

8.4 CONCLUSION TO THE CHAPTER

This chapter presented the results of phase two in this study. Phase two involved the development of a clinical biometric guideline with normal reference intervals for anterior segment variables measured using OCT. In addition, the clinical biometric guideline with normal reference intervals was compared to anterior segment variables currently available for other healthy African sub-populations living within the African continent.

CHAPTER 9: CONCLUSIONS AND RECOMMENDATIONS

9.1 INTRODUCTION TO THE CHAPTER

There is limited information on the anterior segment ocular biometry variables for African sub-populations living within the African continent. The few studies that have reported on corneal thickness measurements have either focused exclusively on CCT measurements (Mohamed et al. 2009; Ntim-Amponsah et al. 2012) or were part of general studies concerned with the relationship between CCT and IOP measurements (Iyamu et al. 2010; Sardiwalla et al. 2012). As a result only CCT measurements have been reported in the literature, focused on African sub-populations within the African continent, with limited attention to corneal pachymetry variables beyond the central cornea and/or ACA width variable measurements. Consequently, there is a gap in the literature as there are no normal reference intervals for anterior segment variable measurements in African sub-populations living within the African continent.

The absence of such information makes clinical examination of individuals within an African setting, such as South Africa, difficult because anterior segment biometry measurements obtained in studies involving non-African sub-populations have to be used as reference standards. Moreover, an understanding of the interocular differences and distribution of the anterior segment variables together with how these variables vary with demographic and ocular factors may aid in the screening, diagnosing and monitoring of certain ocular conditions. To this extent, accurate information on the anterior segment variables and normal reference intervals thereof would be useful in the clinical examination of South African individuals. Consequently, the aim of this study was to produce a clinical description of the anterior segment variables, measured using OCT, in a healthy South African young adult population. This clinical description facilitated the development of a clinical biometric guideline with normal reference intervals for the anterior segment variables measured using

OCT. This chapter provides the conclusion for this study and includes a summary of the study findings, conclusions and recommendations.

9.2 SUMMARY OF FINDINGS

The findings from this study indicate that the sample, drawn from a university population, consisted mainly of young adults aged between 17 years and 21 years. The mean age of the study sample was 20.4 ± 1.8 years which is consistent with the literature regarding the age of individuals who register and attend university. The sample consisted of an equal number of male (n = 350) and female (n = 350) participants with males being slightly older than females (p = 0.093). There was an equal distribution of 350 participants each in the Black and Indian race groups. The majority of participants were in their first year of study which was also noted when level of study was stratified for gender. Most participants were from urban (n = 416) areas compared with township (n = 150) and/or rural (n = 134) areas.

Approximately two-thirds of the sample (n = 437) reported having had a previous eye examination with the most recent eye examination conducted within the last two years prior to data collection in the study. Moreover, there was a significant association between gender and likelihood of a previous eye examination with females being more likely to have had a previous eye examination (p = 0.010). Less than one-third of the sample reported wearing spectacles (n = 200) which consisted of a greater number of female than male participants (p = 0.045). A few participants reported wearing contact lenses (n = 59) wherein none wore rigid gas permeable lenses and the last reported use of contact lenses was at least three weeks prior to data collection for the study.

The mean measurements for ocular variables including corneal diameter, average corneal curvature, corneal astigmatism, axial length, axial ACD and spherical equivalent were almost identical in the right and left eyes (p ≥ 0.071). Although the mean IOP measurement in the right eye was significantly higher than the mean IOP measurement in the left eye

($p < 0.001$), the mean interocular difference was only 0.20 mmHg which is unlikely to be clinically important. The majority of the sample (70.3%) showed spherical equivalent refractions that were classified as emmetropia. Almost all of the participants with spherical equivalent refractions that were classified as ametropia had myopia with less than 1% of the sample presenting with hyperopia. Approximately four out of every ten participants presented with refractive astigmatism of at least –0.25 D in either eye and with-the-rule astigmatism was more common than oblique as well as against-the-rule astigmatism.

Objective 1 sought to determine the interocular differences in anterior segment variables measured using OCT. The mean corneal thickness measurements in the different zones of the right and left eyes were similar with ICCs that were greater than 0.974 and mean interocular corneal thickness differences that were less than 6.5 µm. The ACA width variable measurements could not be determined in less than 1% of the sample because of poor quality ACA images that were found in three and two participants for the right and left eyes respectively. The mean ACA width variable measurements were almost identical in the right and left eyes with ICCs that were greater than 0.933. Moreover, the interocular differences for the mean nasal and temporal AOD500 and TIA measurements were less than 2.5 µm and 1° respectively. Data from only the right eyes of participants were analysed and presented for the remaining study objectives because of the high levels of interocular symmetry found in the present study.

Objective 2 focused on the distribution of anterior segment variables measured using OCT. For the corneal thickness measurements, the mean CCT measurement was 501.91 µm and ranged from 413 µm to 618 µm. Approximately five out of every ten participants presented with mean CCT measurements that were less than 500 µm whereas only two participants had mean CCT measurements that were greater than 600 µm. The mean CCT measurement was significantly thinner than the mean corneal thickness in each quadrant of the paracentral and peripheral cornea ($p < 0.001$). Moreover, the CCT measurement was

the least variable of all corneal thickness measurements in the different zones with the lowest standard deviation of 33.74 µm. For both the paracentral and peripheral cornea, the inferior and temporal quadrants were thinner than the superior and nasal quadrants respectively. The thinnest point on the cornea was most often located central (n = 659), followed by the inferotemporal (n = 29), inferior (n = 6) and temporal (n = 6) quadrants. The mean corneal thickness at the thinnest point (minimum corneal thickness) was 495.73 ± 33.89 µm and 1.23% thinner than the mean CCT measurement ($p < 0.001$). Moreover, the mean thickness difference between the minimum corneal thickness and CCT measurements was 6.18 µm (range from 2 µm to 31 µm) and was found to be 9 µm or lower in most of the participants (n = 668). The corneal thickness measurements in the different zones were normally distributed ($p \geq 0.095$) and resembled Gaussian curves with kurtosis and skewness ranges of –0.01 to –0.12 and 0.07 to 0.15 respectively.

For objective 2, regarding the distribution of ACA width variable measurements, the mean AOD500 measurement in the nasal and temporal ACAs were 551.93 µm and 553.09 µm respectively. Approximately two-thirds of the sample had mean AOD500 measurements that were 500 µm or greater for both the nasal and temporal ACAs. Only a few participants had mean AOD500 measurements that were less than 300 µm in either the nasal (n = 3) or temporal (n = 5) ACAs. The mean TIA measurement for the nasal and temporal ACAs were 36.58° and 36.77° respectively. In the present study, ~95% of the sample had mean TIA measurements that were 30° or more in the nasal and temporal ACAs. Moreover, none of the participants had mean TIA measurements of 20° or less for either the nasal or temporal ACAs. Overall, the ACA width variable (AOD500 and TIA) measurements were slightly higher in the temporal ACA than the nasal ACA. The nasal and temporal AOD500 and TIA measurements were not normally distributed ($p < 0.001$) and resembled non-Gaussian curves (kurtosis range of 0.03 to 2.51 and skewness range of 0.36 to 0.86).

Objective 3 investigated the racial variations in anterior segment variables measured using OCT. In the present study, Indian participants showed significantly higher corneal thickness measurements than Black participants for all zones ($p < 0.001$). Overall, the racial differences in corneal thickness measurements ranged from 29.10 µm to 36.38 µm. The mean CCT measurement was 487.21 µm and 516.60 µm in Black and Indian participants respectively and differed by ~29 µm between the two race groups. Just under two-thirds and one-third of the Black and Indian participants respectively had mean CCT measurements that were less than 500 µm. Moreover, the mean CCT measurement was significantly lower than the mean corneal thickness measurements in the four quadrants of both the paracentral and peripheral cornea for the Black and Indian participants ($p < 0.001$). For both the paracentral and peripheral cornea, the superior quadrant had the highest corneal thickness measurement in Black and Indian participants. The inferior and temporal quadrants showed the lowest corneal thickness measurements in the paracentral and peripheral cornea respectively in both the Black and Indian participants. For the majority of Black ($n = 326$) and Indian ($n = 333$) participants, the location of the thinnest point on the cornea was central.

For objective 3, regarding the racial variations in ACA width variable measurements, slightly higher median AOD500 measurements were found in Indian participants compared with Black participants for both the nasal (544 µm versus 534 µm with $p = 0.186$) and temporal (558 µm versus 536 µm with $p = 0.031$) ACAs. The majority of Black and Indian participants showed mean AOD500 measurements that were greater than 500 µm in the nasal (236 and 237 Black and Indian participants respectively) and temporal (225 and 243 Black and Indian participants respectively) ACAs. In general, only a few participants had mean AOD500 measurements of less than 300 µm in the nasal (one Black participant and two Indian participants) and temporal (one Black participant and four Indian participants) ACAs. The median TIA measurements were marginally higher in Black than Indian participants for both the nasal (36.07° versus 35.36° with $p = 0.068$) and temporal (36.01° versus 35.92° with

p = 0.437) ACAs. The majority of Black and Indian participants showed mean TIA measurements that were 30° or more in the nasal (341 and 325 Black and Indian participants respectively) and temporal (340 and 321 Black and Indian participants respectively) ACAs. None of the Black or Indian participants presented with mean TIA measurements that were 20° or less for either the nasal or temporal ACAs.

Objective 4 assessed the gender variations in anterior segment variables measured using OCT. Males had insignificantly higher corneal thickness measurements than females for all zones ($p \geq 0.137$). These gender differences for the corneal thickness measurements ranged between 0.35 µm and 3.93 µm. The mean CCT measurement in male participants was 503.67 µm compared with 500.14 µm in female participants ($p = 0.166$). In both males and females, the superior quadrant of the paracentral and peripheral cornea showed the highest corneal thickness measurement. The inferior and temporal quadrants of the paracentral and peripheral cornea respectively showed the lowest corneal thickness measurements in both gender groups. The thinnest corneal point was centrally located in more than 93% of both male (n = 332) and female (n = 327) participants.

With regard to objective 4, concerning the gender variations in ACA width variable measurements, females had higher median AOD500 measurements than males for both the nasal (543.00 µm versus 532.50 µm with $p = 0.959$) and temporal (546.00 µm versus 537.50 µm with $p = 0.600$) ACAs. The mean AOD500 measurements were 500 µm or greater for the majority of male and female participants in the nasal (239 and 234 males and females respectively) and temporal (233 and 235 males and females respectively) ACAs. Females had slightly higher median TIA measurements than males in the nasal (36.58° versus 35.27° with $p = 0.078$) and temporal (36.80° versus 35.46° with $p = 0.029$) ACAs. The majority of males and females showed mean TIA measurements that were 30° or more in the nasal (335 male and 331 female participants) and temporal (330 male and 331 female participants) ACAs.

Objective 5 focused on the effect of spherical equivalent refraction on the anterior segment variables measured using OCT. The corneal thickness measurements in all zones were significantly different among the three refractive error groups ($p \leq 0.001$) wherein hyperopes had on average 36 µm and 25 µm higher values than emmetropes and myopes respectively. A post-hoc analysis showed that emmetropes had significantly thinner corneas than myopes for all zones ($p \leq 0.002$). With the exception of the inferior quadrant of the paracentral and peripheral cornea ($p \geq 0.051$), emmetropes also had significantly thinner corneas than hyperopes ($p \leq 0.027$). Hyperopes showed thicker corneal thickness measurements for all zones compared with myopes though these thickness differences failed to reach statistical significance ($p \geq 0.115$). There were statistically significant differences for the ACA width variable measurements among the three refractive error groups ($p < 0.001$). A post-hoc analysis revealed that hyperopes had significantly lower nasal and temporal AOD500 and TIA measurements than emmetropes ($p \leq 0.047$) and myopes ($p \leq 0.013$). Moreover, emmetropes had significantly lower AOD500 and TIA measurements, in the nasal and temporal ACAs, than myopes ($p < 0.001$). It is important to note that as the sample consisted of few participants with hyperopia ($n = 4$), one should be cautious with interpretation of any comparisons related to the sample of hyperopes in this study.

In the other issues of objective 5, there were significant negative correlations between the anterior segment variable measurements and spherical equivalent refraction. The correlation coefficient for the corneal thickness variables ranged from –0.111 to –0.149 ($p \leq 0.003$) whereas for the ACA width variable measurements ranged from –0.125 to –0.222 ($p \leq 0.001$). The linear regression analysis showed that for every 1 D change in the spherical equivalent, the CCT, AveAOD500 and AveTIA measurements would change by 2.97 µm, 19.53 µm and 0.45° respectively.

In addressing objective 6, to develop a regression tree model to determine which anterior segment variables influence IOP measurements, the CART method was used to

automatically generate the regression tree models. Eleven independent variables, which consisted of eight anterior segment ocular variables and three demographic variables, were entered into the CART method. The unpruned regression tree model, which consisted of seven terminal branches, selected only four independent variables that were CCT, AvePeriCT, axial ACD and AveParaCT in order of decreasing importance. The pruned regression tree model, which consisted of five terminal branches, selected only three independent variables (CCT, AvePeriCT and axial ACD) omitting the AveParaCT from the unpruned regression tree model. In both the unpruned and pruned regression tree models, CCT was selected as the most important variable with a cut-off value of 527 µm. Overall, the IOP measurements in the terminal branches of the regression tree models ranged from 12.9 mmHg to 19.4 mmHg.

A clinical biometric guideline was developed for objective 7 and comprised of the normal reference intervals for anterior segment variable measurements, obtained using OCT, in a healthy South African young adult population. The normal reference intervals were computed using the non-parametric method as endorsed by the CLSI (CLSI 2008). The clinical biometric guideline also shows the 95% confidence intervals associated with the lower and upper reference limits for each anterior segment variable. The clinical biometric guideline with normal reference intervals therein for anterior segment variables, measured using OCT, was compared to the anterior segment variable measurements currently available for other healthy African sub-populations living within the African continent for objective 8. The mean CCT obtained in the present study differed when compared with the CCT measurements that are currently available for other healthy African sub-populations within Africa. The absence of information related to corneal thickness measurements beyond the central cornea and ACA width variable measurements in African sub-populations, from within Africa, limited the comparison of the other corneal thickness and ACA width variable measurements in the clinical biometric guideline.

9.3 CONCLUSIONS

The anterior segment variable measurements in the right and left eyes of healthy South African young adults are almost identical and show high levels of interocular symmetry. Moreover, the mean interocular differences for the corneal thickness and ACA width variable measurements, measured using OCT, are marginal and unlikely to be clinically significant. This implies that significant interocular differences in anterior segment variable measurements suggest the presence of ocular pathologies and/or erroneous measuring devices.

The corneal thickness measurements in healthy South African young adults differ from the results of other studies involving Caucasian, Asian and African sub-populations globally. The results of this study confirms the asymmetrical increase in corneal thickness measurements from the centre towards the periphery. The thinnest point on the cornea (minimum corneal thickness) is most often located within the central 2 mm corneal optical zone and is not coincident with the corneal apex where the CCT measurement is traditionally taken. Moreover, the relatively small thickness difference between the minimum corneal thickness and CCT measurements suggests that even though these two points are important for research, differentiation between them may not be relevant when planning refractive surgeries in healthy individuals. Corneal thickness measurements related to the central cornea (CCT and minimum corneal thickness) and beyond the central cornea (paracentral and peripheral cornea) are normally distributed in healthy South African young adults. The corneal thickness measurements obtained in this study provide baseline data from healthy South African young adult individuals.

The mean ACA width variable measurements in healthy South African young adults are comparable to some studies but differ from others that have reported on mean AOD500 and TIA measurements for various sub-populations globally. The majority of healthy South African young adult individuals have open non-occludable ACAs that show low risk for angle

closure. The ACA width variable measurements are slightly higher in the temporal than nasal ACA. The AOD500 and TIA measurements for the nasal and temporal ACAs in healthy South African young adults are asymmetrically distributed and resemble non-Gaussian curves. The ACA width variable measurements obtained in this study provide baseline data from healthy South African young adult individuals.

Indian participants have higher corneal thickness measurements than Black participants. The magnitude of the racial variations in corneal thickness measurements suggest that they may have important clinical implications and need to be considered in the diagnosis and management of corneal anomalies and/or pathologies. Despite the racial differences in corneal thickness measurements between healthy South African Black and Indian young adults, these two samples have similar corneal architectural structure and pachymetry profiles. The ACA width variable measurements in healthy South African Black and Indian young adults are comparable. Based on the nasal and temporal ACA width variable measurements, the ACA configuration in these two South African young adult samples are similar and show low risk for angle closure.

The anterior segment variable measurements in healthy South African young adult males and females are comparable. To this extent, no clinically significant gender related differences in corneal thickness and ACA width variable measurements were observed in healthy South African young male and female individuals. The same pattern of gender related differences was observed when the anterior segment variables were compared between males and females in the Black and Indian race groups. This implies that healthy South African young adult males and females have similar corneal pachymetry profiles and architectural structures as well as ACA configurations. Moreover, the nasal and temporal ACA configurations show low risk for angle closure in both genders on the basis of the AOD500 and TIA measurements.

The anterior segment variable measurements vary depending on refractive error. Corneal thickness measurements are lowest in emmetropes, followed by myopes and hyperopes. The ACA width variable measurements are lowest in hyperopes, followed by emmetropes and myopes. Even though the anterior segment variables were significantly correlated with spherical equivalent refraction, the low magnitude of the correlation coefficients suggest that they may be clinically insignificant. Nevertheless, the influence of refractive error should be considered when evaluating anterior segment variable measurements obtained using OCT.

In the present study, an alternative way of evaluating the influence of anterior segment variables on IOP is presented. The regression tree models not only validate the influence of CCT on the IOP but also draw attention to the importance of corneal thickness measurements beyond the corneal optical zone. The regression tree models, with the terminal branches therein, provide a realistic approximation of the IOP based on the measurements of other anterior segment variables. Such information may be useful to determine which patients require monitoring of the IOP based on other routinely measured anterior segment variables.

The comparison of the clinical biometric guideline with normal reference intervals for the anterior segment variables measured using OCT, developed in objective 7 of this study, to the anterior segment variables currently available for other healthy African sub-populations living within the African continent gives credibility to the amalgamated theoretical construct that was used to inform this study. The evolution and human variation amalgamated theoretical construct posits that the variation in human physical characteristics is owing to natural selection and biological adaptation due to environmental conditions. Even though only the CCT measurement from this study was compared with the CCT measurements in other studies involving healthy African sub-populations from within Africa, because of limited information, the discrepancies suggest that anterior segment variable measurements in a

particular African sub-population should not be extrapolated to other African sub-populations.

9.4 RECOMMENDATIONS

Phase one of this study provided a clinical description of anterior segment variables, measured using OCT, in a healthy South African young adult population. Phase two of this study involved the development of a clinical biometric guideline with normal reference intervals based on the clinical description of the anterior segment variables in phase one of the study. This section outlines the recommendations that are made as a result of the study findings.

9.4.1 Clinical practice

The clinical biometric guideline can be used as a reference guide to assist eye care personnel when examining South African individuals in clinical settings. In this way, it can aid in the clinical decision-making process whereby the clinical biometric guideline can provide guidance to the clinician about the normal reference interval for a particular variable (Arseneau & Balion 2016). Thus the clinical biometric guideline, which contains anterior segment variable measurements and normal reference intervals thereof, can serve as a locally relevant alternative instead of solely relying on values from non-African sub-populations when interpreting anterior segment ocular biometry test results within a South African clinical context. It is recommended that the clinical biometric guideline be used together with consideration of other symptoms and/or signs in the examination and management of corneal and/or ACA anomalies in South African individuals. Moreover, the findings of this study suggest that optometrists and ophthalmologists consider the effect of demographic and/or ocular factors on anterior segment variable measurements when examining South African individuals specifically Black and Indian individuals .

9.4.2 Optometry education

The findings of this study serve as an impetus for consultation between the optometry academic and professional stakeholders (optometry higher education institutions in South Africa such as UKZN, South African Optometric Association, Health Professions Council of South Africa, etc.) to collaborate towards the review and update of the optometry curriculum in South Africa. The aim and findings of this study align strongly with the call for the Africanisation of higher education and contribute to providing an African perspective of anterior segment variable measurements. Consequently, it is recommended that the findings of this study be integrated with the existing knowledge concerning anterior segment ocular biometry measurements, from non-African sub-populations, within the South African optometry curriculum. In this way, the optometry curriculum in South Africa will also contain information and resources that are contextually relevant (Pascoe & Norman 2011).

9.4.3 Research applications

This study provides baseline data, from a healthy South African young adult population, which can be used as a foundation for future research that is focused on characterising anterior segment ocular biometry changes in other individuals such as the elderly and those with ocular diseases particularly glaucoma. In this regard future studies may be conducted, on elderly individuals and those with ocular diseases, without the need for a control group (Doughty & Zaman 2000; Hashemi et al. 2009). Therefore, it is recommended that the results of this study serve as a foundation for future research focused on understanding the age related changes that occur in the anterior segment as well as the risk factors and/or mechanisms associated with ocular diseases in South African individuals.

9.5 STRENGTHS AND LIMITATIONS

One of the strengths of this study relate to the characteristics of the study sample which included a relatively large number of young South African adults with an equal gender and race distribution. According to Gräsbeck (2004), individuals in an optimum state of health

are aged between 20 years and 30 years. Consequently, the inclusion of essentially healthy participants with normal IOPs allowed for computation of the normal reference intervals from the data collected on this sample. The study used standardised data collection examination protocols which included a comprehensive analysis of the corneal thickness and ACA width variables. A high-resolution Fourier-domain OCT device was used in conjunction with inbuilt fixation targets to minimise measurement errors associated with off-centre and off-axis fixation. Moreover, several measurements were taken for the anterior segment variables using the OCT device and the average thereof was used for data analysis.

Possible limitations of this study include participants' self-reporting of race as has been done in other studies to classify race (Sample et al. 2009; Qin et al. 2012) and the inclusion of only two South African race groups. Even though the study age range facilitated the inclusion of healthy participants without ocular and/or systemic diseases in the sample, the limited age range implies that the results of this study must be interpreted with caution when applied to older and younger South African individuals as well as those with IOP anomalies. For example, particularly the findings related to the ACA width variables may not be generalised to middle-aged and elderly South African individuals. Moreover, limiting the age range of participants implies that the effect of age on the anterior segment variable measurements could not be assessed and this may have been more important for particularly the ACA width variable measurements. Only a few participants presented with hyperopia which limited the ability of the study to properly confirm the influence of hyperopia on the anterior segment variables. Nevertheless, the study results showed that the effect of hyperopia on the anterior segment variables is consistent with the findings of other studies that included a greater proportion of participants with hyperopia (Dacosta et al. 2008; Uçakhan et al. 2008; Mohamed et al. 2009; Mostafa 2014; Kadhim & Farhood 2016).

Although it is acknowledged that gonioscopy may have allowed for better qualitative assessment of the ACA rather than van Herick's technique, the limitations associated with

gonioscopy particularly its contact nature countered against including this technique in the screening procedures to evaluate participants' eligibility. The non-random order of the data gathering procedures, specifically the applanation tonometry and axial biometry procedures, could have induced systematic errors. As the applanation tonometry and axial biometry measurements required corneal contact and anaesthetic, it was difficult to control for systematic errors (if any). Of the two techniques that required corneal contact, the applanation tonometry measurement was performed first as the IOP measurement was considered more important than the axial biometry measurements in the context of the present study.

There are some limitations associated with the use of the OCT device for data collection that have to be acknowledged. The corneal pachymetry map extends over a central 6 mm area and excludes corneal thickness measurements beyond this region. This implies that anomalies that affected the cornea beyond the central 6 mm area may have been undetected in the corneal pachymetry map. However, based on the other ocular characteristics it is unlikely that any of the participants had anomalies such as pellucid and Terrien's marginal degenerations. Moreover, the vertical ACAs were not imaged due to the effects of the eyelashes and/or eyelids as well as the need to manipulate the latter. Consequently, the ACA width variable measurements obtained in this study are not applicable to the ACAs in the vertical meridian. In addition, the ACA was imaged under standardised lighting conditions with the room lights switched off. This implies that ACA width variable measurement changes induced by changes in lighting are unknown.

The ACA landmarks in this study, particularly the scleral spur, were manually identified as has been done in several other studies (Müller et al. 2006; Leung et al. 2010; Wang et al. 2011; Cumba et al. 2012; Lozano et al. 2018). Even though repeated measurements of manual ACA width variable measurements have shown good repeatability in previous studies (Li et al. 2007; Radhakrishnan et al. 2007; Kim et al. 2011; Tan et al. 2011; Cumba

et al. 2012), this may have introduced some subjective error. To assess the extent of the subjective error because of manual measurement of the ACA width variables, the researcher re-measured a proportion of the ACA images after the period of data collection and the ACA width variable measurement. The re-measured ACA width variable measurements showed good agreement with the original measurements with ICCs that were greater than 0.964. Even though some studies have used customised programmes to semi-automatically measure the ACA width variables, manual identification of the scleral spur was still needed as the first step in the measurement process (Li et al. 2007; Leung et al. 2010). Moreover a recent study, which used an integrated analysis software program, reported that manual correction of the location of the scleral spur was needed as this reference point was incorrectly identified (Shimizu et al. 2017). To date, there is no software available to automatically identify the ACA structures and measure the ACA width variable measurements with the iVue-100 OCT device.

9.6 SUGGESTIONS FOR FUTURE RESEARCH

This study was limited to anterior segment variables measured in young South African adult individuals from two race groups. Therefore, future studies should include measurements of posterior segment variables and be extended to individuals from other South African race groups. Moreover, participants in this study did not have any ocular and/or systemic diseases because conditions such as glaucoma, diabetes mellitus and hypertension can influence anterior segment variable measurements (Doughty & Zaman 2000; Mohan et al. 2007). Future studies should therefore include participants with ocular and/or systemic diseases to investigate the effect of the latter on the anterior segment variable measurements.

Future studies should include individuals with a wider age range and IOP anomalies to confirm if the same anterior segment variables influence IOP in the regression tree models because the sample in the present study included healthy individuals with a limited age

range. It is also possible that other ocular variables associated with the posterior segment such as posterior scleral rigidity and retinal nerve fibre layer thickness might also influence IOP. Consequently, future studies should investigate the influence of posterior segment variables on IOP using the CART method as this may lead to an enhanced understanding of which ocular variables and their respective cut-off values influence IOP.

Some studies have suggested that Schwalbe's line may be a more reliable ACA landmark when measuring ACA width variables with OCT (Wong et al. 2009; Cheung et al. 2011; Qin et al. 2013). Consequently, future research studies should evaluate the ACA width variable measurements when measured in relation to Schwalbe's line instead of the scleral spur. Moreover, future studies should also consider the use of customised software analysis programmes that allow for semi-quantitative measurement of the ACA width variables after manual identification of the ACA reference point.

9.7 CONCLUSION TO THE CHAPTER

This study has provided a clinical description of anterior segment variables, measured using OCT, in a healthy South African young adult population. Moreover, a clinical biometric guideline was developed that contained anterior segment variable measurements and normal reference intervals thereof. As such, the findings of this study help to fill the current gaps in the literature concerning anterior segment variable measurements particularly in a South African context. The results of this study can therefore assist eye care personnel to enhance the quality of service when examining South African individuals. In this way, the findings of this study have the potential to influence the interpretation and decision-making process in a clinical eye examination and subsequently have an effect on the quality of visual health and care for South African individuals.

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LIST OF APPENDICES

APPENDIX I – SCREENING QUESTIONNAIRE AND DATA COLLECTION SHEET

Participant number: _____

Section 1: Demographic data and history

Age: _____

Age 17 to 23 years		Age 24 to 30 years	

Gender:

Male		Female	

Race:

Indian		Black	

Year of study: _____

Degree registered for: _____

Registered campus:

Edgewood		Howard college		Medical school		Westville	

Where is your homeland? _____

Would you classify this place as urban or rural?

Urban		Township		Rural	

When was your last eye test? _____

Do you wear glasses/spectacles?

No for glasses/ spectacles		Yes for glasses/ spectacles	

Do you wear contact lenses?

No for contact lenses		Yes for contact lenses	
Soft contact lenses		Rigid contact lenses	

If yes for contact lenses, when last did you wear your lenses? _____

Are you taking any medication?

No for medication		Yes for medication	

If yes please specify: _____

Do you have any medical conditions?

No for medical conditions		Yes for medical conditions	

If yes please specify: _____

Do you have any ocular conditions?

No for ocular conditions		Yes for ocular conditions	

If yes please specify: _____

Have you had any injuries to your eyes?

No for injuries to eyes		Yes for injuries to eyes	

If yes please specify: _____

Have you had any surgeries to your eyes?

No for surgeries for eyes		Yes for surgeries to eyes	

If yes please specify: _____

Section 2: Screening results

Distance visual acuity (LogMAR):

Unaided	OD:	OS:	OU:
Aided	OD:	OS:	OU:

Current spectacle prescription:

OD:		**OS:**	

Auto refraction and visual acuity:

OD:		**OS:**	

Subjective refraction and visual acuity:

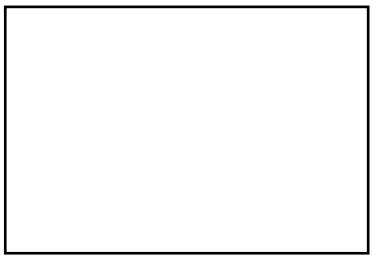
OD:		**OS:**	

Ophthalmoscopy:

OD		**OS**
	____ media ____ **____ cup-disc ratio ____** **____ fovea ____** **____ periphery ____** **____ other ____**	

Slit lamp examination:

OD		OS
_____	**Eyelids and lashes**	_____
_____	**Bulbar conjunctiva**	_____
_____	**Palpebral conjunctiva**	_____
_____	**Cornea**	_____
_____/ _____	**van Herick (Nasal/ temporal)**	_____/ _____
_____	**Lens**	_____



Intraocular pressure:

OD: ___/ ___/ ___ = ___ mmHg	**OS:** ___/ ___/ ___ = ___ mmHg
Time: _____	**Method: Nidek non-contact**

APPENDIX II – DATA GATHERING DATA COLLECTION SHEET

OD:

External corneal diameter (HVID): _____/_____/_____ = _____ mm

Corneal curvature

K 1: _____/_____/_____ = _____ D	**K 2:** _____/_____/_____ = _____ D

Corneal astigmatism: _____/_____/_____ = _____ D

Axis : _____/_____/_____ = _____

Axial length: _____/_____/_____ = _____ mm

Anterior chamber depth: _____/_____/_____ = _____ mm

OS:

External corneal diameter (HVID): _____/_____/_____ = _____ mm

Corneal curvature

K 1: _____/_____/_____ = _____ D	**K 2:** _____/_____/_____ = _____ D

Corneal astigmatism: _____/_____/_____ = _____ D

Axis : _____/_____/_____ = _____

Axial length: _____/_____/_____ = _____ mm

Anterior chamber depth: _____/_____/_____ = _____ mm

Intraocular pressure:

OD: ___/ ___/ ___ = ___ mmHg	**OS:** ___/ ___/ ___ = ___ mmHg
Time: _____	**Method: Goldmann Applanation**

Optical coherence tomography

Cornea

OD:

	CCT	MinCT	ParaSup	ParaInf	ParaNas	ParaTemp	PeriSup	PeriInf	PeriNas	PeriTemp
1										
2										
3										
AVE										

OS:

	CCT	MinCT	ParaSup	ParaInf	ParaNas	ParaTemp	PeriSup	PeriInf	PeriNas	PeriTemp
1										
2										
3										
AVE										

Anterior chamber angle

OD:

	TEMPORAL		NASAL	
	TIA	AOD500	TIA	AOD500
1				
2				
3				
AVE				

OS:

	TEMPORAL		NASAL	
	TIA	AOD500	TIA	AOD500
1				
2				
3				
AVE				

APPENDIX III – ETHICAL CLEARANCE CERTIFICATES

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

08 April 2013

Ms. N Rampersad
Department of Optometry
Faculty of Health Sciences
University of KwaZulu-Natal

PROTOCOL: A comparison of corneal and anterior chamber biometry and their associations to ocular parameters among Indian and Black University of KwaZulu-Natal students aged 17-30 years. REF: BE289/12.

EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 20 November 2012.

The study was provisionally approved pending appropriate responses to queries raised. Your responses dated 20 March 2013 to queries raised on 13 February 2013 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given full ethics approval and may begin as from 08 April 2013.

This approval is valid for one year from **08 April 2013.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2004), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/ResearchEthics11415.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its next meeting taking place on **14 May 2013.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

[redacted]

Professor D.R Wassenaar
Chair: Biomedical Research Ethics Committee

Professor D Wassenaar (Chair)
Biomedical Research Ethics Committee
Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001, Durban, 4000, South Africa
Telephone: +27 (0)31 260 2384 **Facsimile:** +27 (0)31 260 4609 **Email:** brec@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx
Founding Campuses: Edgewood Howard College Medical School Pietermaritzburg Westville

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Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

24 April 2018

Ms. N Rampersad
Department of Optometry
Faculty of Health Sciences
University of KwaZulu-Natal

PROTOCOL: A comparison of corneal and anterior chamber biometry and their associations to ocular parameters among Indian and Black University of KwaZulu-Natal students aged 17-30 years. REF: BE289/12.

***New Title:* A clinical description of anterior segment variables measured using optical coherence tomography in a healthy South African young adult population: the development of normal reference intervals.**

We wish to inform you that your Application for Amendments to change the title to the above received on 18 April 2018 for the above study has been **noted and approved** by a sub-committee of the Biomedical Research Ethics Committee.

This approval will be ratified at the next BREC meeting to be held on 12 June 2018.

Yours sincerely

[redacted]

Ms A Marimuthu
Senior Administrator: Biomedical Research Ethics

APPENDIX IV – APPROVAL LETTER FROM REGISTRAR

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

28 February 2013

Ms Nishanee Rampersad
School of Health Sciences
Westville Campus
UKZN
Email: rampersadn@ukzn.ac.za

Dear Ms Rampersad

RE: PERMISSION TO CONDUCT RESEARCH

Gatekeeper's permission is hereby granted for you to conduct research at the University of KwaZulu-Natal towards your postgraduate studies, provided Ethical clearance has been obtained. We note the title of your research project is:

"A comparison of corneal and anterior chamber biometry and their associations to ocular parameters among Indian and Black University of KwaZulu-Natal students aged 17-30 years"

It is noted that you will be constituting your sample by randomly approaching students on all campuses to conduct a clinical study.

Data collected must be treated with due confidentiality and anonymity.

Yours sincerely

[redacted]

Professor J J Meyerowitz
REGISTRAR

APPENDIX V – APPROVAL LETTER FROM DEAN AND ACADEMIC LEADER

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

21 February 2013

Ms A Marimuthu

BREC Administration

Westville Campus

UKZN

Dear Ms Marimuthu

Applicant Ms N Rampersad: REF: BE289/12.

Comparison of corneal and anterior chamber biometry and their associations to ocular parameters among .... UKZN students .."

This letter serves to confirm that Ms Rampersad as applicant, has the permission of the Dean and Head of School and the Academic Leader of Research in the School of Health Science to utilize the equipment in the Optometry Clinic on Westville Campus at UKZN to collect data pertaining to the above project.

Yours sincerely

[redacted]

Prof HJ van Heerden

Academic Leader for Research

School of Health Sciences

School of Health Sciences
Postal Address: University of KwaZulu-Natal, School of Health Sciences, Westville Campus, Private Bag X 54001, Durban, 4000
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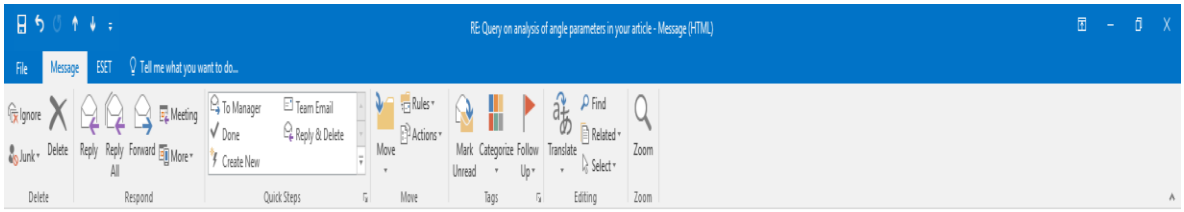
APPENDIX VI – EMAIL CORRESPONDENCE (DR LEUNG)



Fri 2014/11/28 08:43

Nishanee Rampersad

RE: Query on analysis of angle parameters in your article

To Christopher Leung

Cc Rekha Hansraj

Dear Professor Leung

Thank you for the response. I am aware that the oct software has calipers (for angle degrees and linear units) which can be used to do the manual measurements. I was hoping to make the analysis semi-automated by just identifying the scleral spur and obtaining the other measurements (AOD and TIA) automatically. I do understand regarding the Matlab program.

Kind regards
nishanee

From: Christopher Leung [mailto:tlims00@hotmail.com]
Sent: 27 November 2014 07:52 PM
To: Nishanee Rampersad
Subject: RE: Query on analysis of angle parameters in your article

Dear Nishanee,

You need to learn the basic language of Matlab to write the program. You may need to check with Optovue if the anterior segment images captured by iVue are dewarped and whether iVue has the software for angle measurement. With apologies, our in-house software may only be shared with research collaborators.

Best wishes,

Chris Leung

From: Rampersadn@ukzn.ac.za
To: tlims00@hotmail.com
CC: HANSRAJR@ukzn.ac.za
Subject: Query on analysis of angle parameters in your article
Date: Wed, 26 Nov 2014 10:02:11 +0000

Dear Professor Leung

My name is Nishanee and I am a postgraduate student at the University of KwaZulu-Natal in South Africa. I am currently investigating the parameters of the anterior ocular segment. Please can you advise regarding the analysis of angle parameters in the article titled 'Anterior chamber angle measurement with anterior segment optical coherence tomography' published In 2008 in the 'Investigative ophthalmology and visual science' journal.

In your study a program written using Matlab was used to analyse the angle parameters. Please can you advise on how such a program can be written. Also by any chance would you and your colleagues be willing to share your program with me to analyse the images (in jpeg format) I have captured using the iVue OCT device.

Thank you in advance and looking forward to hearing from you, kind regards

APPENDIX VII – CONSENT FORM (ENGLISH)

Study title: A comparison of corneal and anterior chamber biometry and their associations to ocular parameters among Indian and Black University of KwaZulu-Natal students aged 17-30 years

I _____ confirm that I have been informed about this research study focused on corneal and anterior segment parameters in healthy Indian and Black UKZN students aged 17 to 30 years and requested to participate. I confirm that my participation is voluntary and understand that all information will be kept confidential throughout the study. Furthermore I understand that I have the right not to answer any of the questions asked and withdraw from the study at any point without any consequences.

I hereby give consent for the following parts of this study

Part of study	**Yes**	**No**
Ability to see (visual acuity)		
Ocular health examination		
Pressure in the eye (intraocular pressure)		
Measurement of the parameters in the eye (ocular biometry)		

I am aware that if I have any queries about the study and my rights as a participant, I may contact the research student, Nishanee Rampersad, on the number 031 260 7562.

_____ _____

Participant signature Date

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Email: BREC@ukzn.ac.za

APPENDIX VIII – INFORMATION DOCUMENT (ENGLISH)

Study title: A comparison of corneal and anterior chamber biometry and their associations to ocular parameters among Indian and Black University of KwaZulu-Natal students aged 17-30 years

Dear Participant

You will agree that each of us is different in terms of height, weight and shoe size. But what about our eyes ... are there differences in the size and shape (parameters) of our eyes? Previous studies have reported differences in the prevalence rates of eye diseases and refractive errors (vision problems that require glasses or contact lenses to see clearly) among Indian and Black people. A new instrument has become available to measure the parameters of the eye by taking images of the internal structures without even touching the eye. Therefore this study is attempting to determine if there are differences in the eye parameters in healthy Indian and Black individuals.

Invitation to participate:
You are thus invited to participate in this study by allowing measurements of your eyes to be taken and analysed.

What is involved in the study?
There will be a screening procedure in which a questionnaire and tests to determine how well you can see, the health and pressure of your eyes will be determined. All tests performed are within the scope of optometry. Thereafter images of your eyes will be taken without making any contact with your eyes. As part of taking measurements of your eyes, two tests will require minimal contact with your eyes. Rest assured that an anaesthetic will be instilled into your eyes so that you do not feel anything. All tests will be performed by a trained optometrist and are routinely used when performing eye examinations. There are no risks associated with this study as it is an evaluation of the parameters of your eyes.

Your participation in this study does not directly benefit you, however it is hoped that your participation will aid in understanding the eye measurements in Indian and Black people. This will help greatly in the assessment, diagnosis and management of eye related diseases among Indian and Black people. Furthermore you will be informed of your visual and ocular health status.

Your participation in this study is voluntary and you have the right to withdraw at any time without any consequences. In addition if you do not wish to answer any question that is asked of you, you do not have to. All test results and images captured will be securely kept in a locked cupboard for a minimum of 5 years and thereafter incinerated.

Confidentiality:
Information gathered will be collated and reported such that it does not lead to the identification of specific persons. Your personal details and identity will remain confidential throughout the study procedure.

Contact details of researcher:
Ms Nishanee Rampersad tel: 031 260 7562 email: rampersadn@ukzn.ac.za

Contact details of research supervisor:
Dr R Hansraj tel: 031 260 7089 email: hansrajr@ukzn.ac.za

APPENDIX IX – ISIVUMELWANO SOBULUNGA (ISIZULU)

Isihloko sesifundo: Ukuqhathanisa umehleko wobungako boketshezi kanye nobugqinsi bontwentwesi olungabonakaliyo kubafundi abampisholo kanye namandiya, abaneminyaka esukela ku 17-30 ubudala,nyuvesi Yakwazulu-Natal

Mina _____ ngiyavuma ukuthi ngiceliwe ukuba ingxenye kuloluwaningo, olucwaninga ubugako boketshezi kanye nobugqinsi bontwetwesi olungabonakaliyo emehlweni ami kanye nezempilo kuwona, ngokuqhathanisa umphumela oyotholakala emehlweni amandiya kanye nabantu abampisholo. Ngiyavuma ukuba ingxenye kuholucwaningo, futhi kusothandweni lami konke engikwenzayo kanti ngiyayiqonda nemiyalelo yokuthi umphumela wocwaningo ngami uyogcinwa uyimfihlo, kuze kube sekupheleni kocwaningo ngaphezu kwalokho nginelungelo lokungaphenduli uma ngingathamdi futhi nginelungelo lokuhoxa nomanini uma ngingasathandi ukuqhubeka neqhaza lami kulesifundo.

Isivumelwano sokuba ingxenye kublucwaningo

Ingxenye yesitunlo	**Yebo**	**Qtta**
Indlelala yesimo sokubpna (indlela yokubonisisa)		
Ukuhlolelwa isimo sempilo ezigabonakeliyo		
Isimo esingabonakaliyo (inkinge enyabonakeliyo		
Ukuqhathaniswa kobunga bezinkinga		

Ngiyazi ukuthi uma nginemibuzo mayelana nesifundo kanye namalungelo ami, njengegxenye yclwaningo, ngingaxhumana nomfundi owenza lesisifundo ngalolucwaningo, u-Nishanee Rampersad ku-031 260 7562

_____ _____

Kusayina oyingxenye Usuku

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APPENDIX X – IDOKODO LOKWAZISA (ISIZULU)

Isihloko sesifundo: Ukuqhathanisa umehleko wobungako boketshezi kanye nobugqinsi bontwentwesi olungabonakaliyo kubafundi abampisholo kanye namandiya, abaneminyaka esukela ku 17-30 ubudala, Inyuvesi Yakwazulu-Natal

Ngiyakubingelela

Uzongivumela ngokuthi sisonke-nje asilingani ngobude, isisindo kanye nosayizi bezicathulo esibagqokayo. Izifundo ezedlule zisibikele kakhulu ngezifo eziningi ezahlukahlukene ezitholakala emehlweni, kanye nezinkinga ezithile ezigcina zinomthelela wesidingo sezibuko okungaba ezigqokwayo noma ezinanyathiselwayongqo emehlweni kumandiya nabantu besizwe esiminyama ukuze babone kahle. Kunensiza kusebenza esikhona kusimanje ekuyiyo esilawulayo ukuthola ukuthi ihlo lakho limi kanjani kanye nokubukeka kwalo ngaphandle kokulithinta. Ngaleyo ndlela lesisifundo sidinga ukuthola umehleko uma ukhona wezifo ezitholakala ngokuqhathanisa abantu abampisholo namandiya.

Isicelo sokuba ingxenye kulolucwaningo
Ngaleyondlela uyacelwa ukwba ube ingxenye kulolucwaningo, usivumele ukuba sithole ububanzi bamehlo kanye nogqinsi olungabonakaliyo emehlweni akho futhi sihlaziye ngakho.

Okudidiyelwe edidiyelwe kulesisifundo?
Kuzoba nokuhlolwa kwamehlo akho okuyobe kuhamba nemibuzo mbendulwano eyobe iphuma kungoti wezamehlo ukuqinisekisa nkuthi amehlo akho abona kangakanani kuphinde kubhekelelwe isimo sokuphila kwawo kanye nengcindezi anayo engaba wumthelela ezifweni ezicashileyo. Ukuqinisekisa lesosimo nendlela yokuphepha kuzofakwa iconsi lomuthi ozokwenza ihlo lako libendikindiki futhi ungezwa lutho uma linokuthinteka. Konke ukuhlolwa kwamehlo kuzokwenziwa odokotela bamehlo futhi ukuhlola amehlo okungumsebenzi wabo wemihla ngemihla. Abukho ubungozi obungaba ngumthelela wocwaningo emehlweni akho.

Akukho nzuzo noma inkokhelo oyoyithola ngokuba ingxenye yaloluawaningo nakuba kunethemba lokuthi ukuba ingxenye kwakho kuzosiza ekuqondisiseni kabanzi ukuthola umehluko walesisimo emehlweni amandiya kanye nabantu abampisholo. Lokhu kuzosiza kakhulu ekutholeni ikhambi lokwelapha kanye nendlela yokumelana nezifo eziphathelene namehlo kubantu bendlu emnyama kanye namandiya. Ngaphezu kwalokho uyobe sewaziswa ngesimo sezempilo nendlela yesimo sokubona kwamehlo akho kanye nesimo sokuba bukhali kwawo uma ebuka.

Ukuba imgxenye kulolucwaningo kusothandwewi lakho, kanti unelungelo lokuhoxa noma nini, ngaphandle kokuphazamiseka. Uma kunemibuzo ongathandi ukuyiphendula unelungelo lokungaphenduli. Yonke imiphumela eyotholakala ngocwaningo iyokhiyelwa emakhabetheni thizeni isikhathi okungaba iminyaka emihlanu, emva kwalokho iyobe seyishiswa.

Imfihlo
Ulwazi oluhlaganisiwe laba umphumelo ngocwaningo, luyonganyelwa ngendlela yokuthi ngeke kusetshenziswe igama lomuntu, kuzoqinisekiswa imfihlakalo engaba umthelela wencanzelo ngawe. Kanye nomphumela wakho ocwaningweni. Lokho kuyogcinwa kuyimfihlo kuzona zonke izingxenye zocwaningo.

Indlela yokuxhumana nomcwaningi
Nishanee Rampersad ucingo: 031 260 7562 incwadi kagesi:rampersadn@ukzn.ac.za
Indlela yokuxhumana nongamele ukwenziwa kocwaningo
Dr R Hansraj ucingo: 031 260 7089 incwadi kagesi: hansrajr@ukzn.ac.za

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APPENDIX XI – PUBLICATION 1

A REVIEW OF AFRICAN STUDIES ON CENTRAL CORNEAL THICKNESS

African Vision and Eye Health
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A review of African studies on central corneal thickness

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Recently, there has been increasing interest in understanding central corneal thickness (CCT) measurements in various populations. This may be related to the influence of CCT in the diagnosis, classification and management of glaucoma. In addition, CCT measurements are also important for monitoring corneal diseases and contact lens wear, indicating the overall health of the cornea and assessing eligibility for refractive surgery. This article reviews studies that have reported CCT measurements in non-glaucomatous African sub-populations. The CCT measurements, gender associations and limitations of these studies are highlighted. The findings of these studies and their implications are discussed in relation to global studies reporting on CCT measurements.

Introduction

Central corneal thickness

Central corneal thickness (CCT) measurements have been widely researched with studies appearing in the literature for over a century. Assessing CCT has diagnostic and therapeutic applications such as monitoring corneal diseases and contact lens wear, indicating the health of the cornea and endothelial pump, assessing eligibility for refractive surgery and interpreting intraocular pressure (IOP) measurements.[1] The first documented report on CCT measurements in the human eye, obtained using an optical device, appeared in 1880.[2] Since then, there have been several advancements in measurement techniques, and currently, a wide range of contact and non-contact devices are available for measuring CCT.[1] Although ultrasound devices are regarded as the gold standard,[3] devices based on the principles of Scheimpflug photography,[4,5,6] specular microscopy,[7,8,9] ultrasound biomicroscopy,[10,11] slit-scanning topography[12,13,14] and optical coherence tomography[15,16,17] are increasingly being used for clinical CCT measurements. Furthermore, studies conducted in countries such as China, India, Japan, United States of America and Australia suggest that CCT measurements vary widely between ethnic groups and geographical areas.[6,9,18,19,20]

Central corneal thickness measurements are known to influence IOP measurements recorded with applanation tonometers.[21,22] Several studies[16,18,19,23,24,25] have reported that IOP is overestimated in thicker corneas and underestimated in thinner corneas. Goldmann applanation tonometry, the clinical gold standard for IOP,[26] is calibrated on a theoretical assumption of a 520 µm CCT measurement.[21,27,28] Thus, any variation in CCT will alter the balance between the corneal resistance to indentation and the surface tension of the tear film.[29] In an early study, Ehlers[28] concluded that any deviation of 70 µm on either side of 520 µm would alter the IOP by 5 mmHg. It was further noted that IOP may be incorrectly interpreted by as much as 7 mmHg for every 100 µm deviation in CCT.[30] More recently, Eballe et al.[31] suggested that IOP would change by 2.8 mmHg per 100 µm change in mean CCT. Despite several researchers acknowledging the influence of CCT on IOP measurements, there is little agreement as to how the measured IOP should be adjusted to account for the CCT measurement.[32] This has resulted in several correction algorithms being posited[21,33,34] but none have been widely used or accepted.[35,36]

Glaucoma and central corneal thickness

Glaucoma is the second leading cause of global blindness and results in irreversible visual impairment.[37] Primary open angle glaucoma is the most common type of glaucoma.[37] There is a higher prevalence of primary open angle glaucoma among African populations[35,38] with 19.4% of the total global population affected living in sub-Saharan Africa.[39] Several studies[40,41,42,43] have identified primary open angle glaucoma as an important cause of irreversible blindness in African countries including Ghana, Nigeria, Gambia and Ethiopia. Moreover, primary open angle glaucoma presents at an earlier age and progresses more rapidly among African populations than non-African populations.[35,44,45,46]

Accurate measurements of IOP are essential in the screening, diagnosis and management of glaucoma.[33,47] Previous studies have highlighted the role of CCT as an independent risk factor for glaucoma.[48,49] Moreover, Kaushik et al.[50] suggested that thinner CCT measurements are related to greater susceptibility for glaucomatous changes. As a result, assessment of CCT has become an important part of an ocular examination since it provides information about the risk and clinical characterisation of the various glaucoma disorders.[48,51,52] Since IOP is the only known risk factor that can be pharmacologically manipulated in the treatment of glaucoma,[53,54] accurate IOP measurements are essential to assess the response and effectiveness of glaucoma management strategies.[55]

The literature shows that considerable CCT data have been collected in several American, Asian and European populations.[4,6,7,8,9,12,17,18,19,23,53] In contrast, only a few studies have investigated CCT in African populations living within the African continent. Considering the consequences of glaucoma and its prevalence in the African continent, it is important to understand the distribution of CCT measurements in African sub-populations. The purpose of this article is to review CCT measurements reported in normal (non-glaucomatous) populations from African countries including Nigeria, Cameroon, South Africa, Ghana, Ethiopia and Sudan.

African studies on central corneal thickness

Table 1 shows the various studies that have investigated and reported on CCT measurements in normal African sub-populations.[31,32,35,54,55,56,57,58,59,60,61,62] Half of the studies (n = 6) have been undertaken in West-Africa (Nigeria). The instrument used to measure CCT is an important consideration when mean CCT measurements are compared across different studies. All studies, with the exception of the two involving South African samples,[61,62] used ultrasound devices to measure CCT. As seen in Table 1, differences in mean CCT measurements are apparent even when ultrasound devices are used since values of ~550 µm were found in some studies[56,57,58,60] while values closer to ~530 µm were reported in other studies.[31,32,55]

Overall, there is a broad distribution (range: 519 µm – 550 µm) of CCT measurements in the various African sub-populations. The highest and lowest CCT measurements were reported in a Nigerian sample[60] (550 µm) and the Ethiopian and South African samples[54,62] (519 µm), respectively. This is interesting considering that the mean age of two of these samples[54,60] differed by only four years yet the difference in mean CCT is 31 µm. Overall, higher mean CCT measurements have been reported in Nigerian populations compared with other African sub-populations (Table 1). Even the minimum CCT measurements (from the ranges reported) are considerably higher in studies involving Nigerian samples[56,57,58,60] compared with the other African samples.[31,54,55,62] One study from Nigeria[35] reported a mean CCT of 535 µm which is slightly different from that reported in other Nigerian studies.[56,57,58,60] The sample used by Mercieca et al.[35] was considerably smaller (n = 29) and older (63.1 ± 11.2 years) than the other Nigerian samples[56,57,58,60] which may explain this discrepancy (Table 1).

Mean CCT measurements (~530 µm) were comparable for the studies conducted in Cameroon, Sudan and Ghana.[31,32,55] In contrast, the studies conducted in South Africa reported lower mean CCT values (~520 µm) despite including relatively young samples.[61,62] This difference may be explained by the use of devices based on Scheimpflug photography to measure CCT in the South African studies.[61,62]

TABLE 1: Summary of studies of central corneal thickness in African populations.

Authors	Country	Sample size (gender allocation)			Mean age in years		CCT technique	Mean CCT (µm)		Mean CCT (µm)	
		n	Male	Female	Mean	Range		Mean	Range	Males	Females
Iyamu et al.[58]	Nigeria	85	49	36	44.65 ± 15.11	20–69	Ultrasound pachymetry	550 ± 36.3	478–662	552.8 ± 38.5	546.3 ± 33.3
Iyamu and Osuobeni[57]	Nigeria	130	77	53	47.8 ± 16.8	20–79	Ultrasound pachymetry	548.97 ± 34.28	478–662	551.00 ± 37.20	546.06 ± 29.62
Iyamu et al.[58]	Nigeria	95	56	39	44.9 ± 15.2	20–69	Ultrasound pachymetry	547.0 ± 29.5	487–618	553.2 ± 33.5	542.6 ± 27.8
Iyamu and Memeh[59]	Nigeria	39	21	18	45.2 ± 15.4	20–75	Ultrasound pachymetry	NR*	NR*	561.8 ± 44.9	541.5 ± 31.1
Iyamu and Eze[60]	Nigeria	95	56	39	47.1 ± 14.1	20–69	Ultrasound pachymetry	550.1 ± 33.1	478–662	552.0 ± 36.4	544.5 ± 28.8
Mercieca et al.[35]	Nigeria	29	17	12	63.1 ± 11.2	17–68	Ultrasound pachymetry	535 ± 38	NR*	541 ± 47	522 ± 22
Eballe et al.[31]	Cameroon	485	163	322	31.4 ± 15.5	5–75	Ultrasound pachymetry	528.74 ± 35.89	440–670	530.27 ± 34.83	527.97 ± 36.41
Gelaw et al.[54]	Ethiopia	300	184	116	42.57 ± 16.71	18–87	Ultrasound pachymetry	518.68 ± 32.92	430–610	517.96 ± 32.74	519.83 ± 33.31
Mohamed et al.[55]	Sudan	94	60	34	NR*	NR*	Ultrasound pachymetry	530.15 ± 58.10	420–610	NR*	NR*
Sardiwalla et al.[61]	South Africa	200	100	100	20.1 ± 1.6	18–25	Scheimpflug photography	519.5 ± 38.6	442–642	516.7 ± 40.1	522.3 ± 37.1
Rampersad et al. (2011)[62]	South Africa	105	29	76	29.27 ± 14.67	18–82	Scheimpflug photography	518.49 ± 33.01	440–606	NR*	NR*
Ntim-Amponsah et al.[32]	Ghana	253	112	141	58 ± 16.1	21–90	Ultrasound pachymetry	530.53 ± 35.64	423–650	NR*	NR*

*NR, not reported; CCT, central corneal thickness.

With the exception of two studies,[54,61] all studies involving African sub-populations reported higher CCT measurements in males (Table 1). However, only Mercieca et al.[35] reported a statistically significant gender difference of 19 µm (541 µm vs. 522 µm, $p = 0.0035$), while the majority of studies reported gender differences which failed to reach statistical significance.[31,54,56,57,59]

Although these studies have provided useful information on CCT measurements in African sub-populations, there are some limitations associated with them which influence the interpretation of their findings and conclusions. Some of these limitations include small sample sizes,[35,59] a wide age range of participants,[31,32,54] use of contact CCT measurement techniques[32,54,59] and unequal distribution of male and female participants.[31,55,60] Moreover, all studies with the exception of Gelaw et al.[54] used convenience sampling to recruit study participants. In the study by Gelaw et al.[54] a power calculation was performed to determine the sample size needed, while none of the other studies included information regarding the sample size estimation. Lastly, some of the studies[35,56,57] reported on clinic-based samples which may not be representative of the general population due to the inherent selection bias associated with such samples.

Discussion

The interest in this review lies in better understanding the reported CCT measurements in normal African sub-populations. Due to the potential of CCT measurements in influencing IOP and subsequently glaucoma diagnosis and management,[33,47,48] this corneal parameter has received much attention in recent literature. Particularly in Africa, interest in understanding CCT measurements may also be related to the call for Africanisation of knowledge. As a process, Africanisation involves placing renewed emphasis on problems experienced in Africa by generating knowledge about these problems and striving to create African solutions for them.[63] It can then be proposed that by researching CCT in African populations, one may be able to better understand the role of CCT measurements in non-glaucomatous and glaucomatous individuals within an African context.

According to a meta-analysis which included 300 studies conducted over a period of 31 years, Doughty and Zaman[64] reported an expected CCT measurement of 535 µm. Moreover, when an ultrasound device is used, the expected mean CCT is higher averaging 544 µm.[64] When compared to the mean CCT measurements reported in African studies included in this review, only studies involving the Nigerian samples[56,57,58,60] are comparable to the suggested normal value (544 µm). All studies involving the other African sub-populations reported considerably lower mean CCT measurements.[31,32,54,55,61,62] This implies that there are variations in mean CCT measurements in the different normal African sub-populations. This trend has also been observed in different Asian sub-populations (Chinese, Japanese, Filipino and Malay) where a wide range of CCT measurements have been reported by researchers.[65,66,67,68] It is possible that environmental and climatic factors are responsible for these African and Asian sub-population CCT differences.[69]

Studies that have compared CCT measurements among Caucasians, Hispanics, Asians and African-Americans have reported significantly thinner measurements in the latter group.[65,66,70,71] Two other studies[69,72] compared CCT measurements between North African individuals and those from Europe including France and Russia. Both studies[69,72] concluded that the North African participants had significantly thinner mean CCT measurements when compared to their European counterparts. Dimasi et al.[53] suggested that differences in the thickness and composition of the stromal layer may account for the varied CCT measurements obtained in the different race groups.

The mean CCT measurement in African-Americans, when using ultrasound pachymetry, ranges between 525 µm and 535 µm.[65,66,70] This implies that the mean CCT measurements in African sub-populations (Table 1) may not necessarily be similar to those values reported for African-Americans. The precise reason for this difference is not known. The mean CCT in Caucasians[65,66,70] and Asians (predominantly Chinese),[65,67] when using ultrasound pachymetry, ranges between 553 µm and 563 µm, and 566 µm and 570 µm, respectively. This suggests that, on average, normal African sub-populations have thinner mean CCT measurements than Caucasians and Asians but thicker than the average CCT reported in African-Americans. However, this comparison should be interpreted with caution since other factors such as age, anthropometric measurements, gender distributions and refractive error influence CCT measurements.[23,57,64,73]

The distribution of CCT measurements follows a Gaussian curve in the general population.[53] Studies involving non-African populations have reported that CCT measurements are normally distributed.[4,6,68] However, only one African study,[61] from those included in this review, described the distribution of CCT measurements which was shown to be normally distributed. In addition, previous studies have suggested that CCT and gender are related with thicker mean CCT measurements in males than females.[9,19,35,66] This trend was also observed in majority of the African studies[56,57,58,59,60] included in the review. Furthermore in most of the African studies, the gender difference in CCT measurements was not statistically significant as has been reported in other studies.[8,23,65,74]

Conclusion

The broad distribution of mean CCT measurements reported in the studies reviewed suggests that variations exist among the different African sub-populations. These results have important implications for the assessment and interpretation of CCT and IOP measurements in African sub-populations. This review is limited to studies conducted on normal healthy African samples and excludes those that have included individuals with systemic conditions[75] (diabetes mellitus and

hypertension) and glaucoma disorders[76,77], as these factors can influence CCT measurements.[1,48,64,78] In conclusion, this review draws attention to the assumption that CCT measurements in one African population cannot necessarily be extrapolated to other African populations. This implies that there may be other factors, even within the same race group, that contribute to differences in CCT measurements.

Acknowledgements

Competing interests

The authors declare that they have no financial or personal relationships which may have inappropriately influenced them in writing this article.

Authors' contributions

N.R. wrote the manuscript and R.H. provided feedback on the structure and content of the manuscript.

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APPENDIX XII – PUBLICATION 2

IDENTIFYING THE CRITICAL FACTORS THAT INFLUENCE INTRAOCULAR PRESSURE USING AN AUTOMATED REGRESSION TREE

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Identifying the critical factors that influence intraocular pressure using an automated regression tree

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Background: Assessment of intraocular pressure (IOP) is an important test in glaucoma. In addition, anterior segment variables may be useful in screening for glaucoma risk. Studies have investigated the associations between IOP and anterior segment variables using traditional statistical methods. The classification and regression tree (CART) method provides another dimension to detect important variables in a relationship automatically.

Aim: To identify the critical factors that influence IOP using a regression tree.

Methods: A quantitative cross-sectional research design was used. Anterior segment variables were measured in 700 participants using the iVue100 optical coherence tomographer, Oculus Keratograph and Nidek US-500 ultrasonographer. A Goldmann applanation tonometer was used to measure IOP. Data from only the right eyes were analysed because of high levels of interocular symmetry. A regression tree model was generated with the CART method and Pearson's correlation coefficients were used to assess the relationships between the ocular variables.

Results: The mean IOP for the entire sample was 14.63 mmHg ± 2.40 mmHg. The CART method selected three anterior segment variables in the regression tree model. Central corneal thickness was the most important variable with a cut-off value of 527 µm. The other important variables included average paracentral corneal thickness and axial anterior chamber depth. Corneal thickness measurements increased towards the periphery and were significantly correlated with IOP ($r \geq 0.50$, $p \leq 0.001$).

Conclusion: The CART method identified the anterior segment variables that influenced IOP. Understanding the relationship between IOP and anterior segment variables may help to clinically identify patients with ocular risk factors associated with elevated IOPs.

Introduction

Glaucoma is an optic neuropathy that sometimes results in irreversible blindness.[1] After cataracts, glaucoma is the second most prevalent cause of global blindness,[2] and it is estimated that almost 80 million people worldwide will be affected by this optic neuropathy by the year 2020.[3] Because of the high prevalence of this ocular disease, the economic and social implications of glaucoma have been outlined in recent studies.[4,5] In Africa, primary open-angle glaucoma (POAG) is more prevalent than primary-angle closure glaucoma, and over the next 4 years, the prevalence of POAG in Africa is projected to increase by 23% corresponding to an increase from 6.2 million to 8.0 million affected individuals.[3] Consequently, in Africa, there have been recommendations to incorporate glaucoma screening procedures into routine eye examinations as well as implement glaucoma blindness control programs.[6,7]

The assessment of intraocular pressure (IOP) is a fundamental clinical test used for the screening, diagnosis and management of glaucoma.[1,8] IOP is still considered as an important risk factor for glaucoma,[1,9] but previous studies have reported that other ocular anterior segment variables are also useful in screening for individuals at risk for glaucoma.[10,11,12,13] For example, the Ocular Hypertension Treatment Study highlighted the importance of central corneal thickness (CCT) in evaluating risk for POAG.[10] Some studies have indicated that other anterior chamber variables (such as depth and angle width) may be useful for evaluating risk for developing angle closure glaucoma.[12,13,14] As a result, the relationship between IOP and anterior segment ocular variables has been investigated in both population-based[15,16,17] and clinic-based[18,19,20] studies.

Investigating the relationship between IOP and anterior segment ocular variables may be useful for better understanding the association between these ocular variables and IOP.[8] This knowledge may help to clinically identify patients with ocular risk factors associated with elevated IOPs.[21] The association between IOP and CCT is well known with several studies[22,23,24] noting higher IOP measurements in eyes with thicker CCT measurements. In contrast, the literature related to IOP and corneal curvature is inconsistent, with some studies[20,25] reporting no association while other studies[15,16,19,21,26] reported significantly higher IOPs in eyes with steeper corneal curvatures. No associations have been found between IOP and corneal diameter[27] or anterior chamber angle (ACA) variables.[15,28,29]

The majority of the studies have used traditional statistical methods, such as correlation and regression analyses, to assess the relationship between IOP and anterior segment ocular variables.[15,16,17,19] However, these statistical methods may result in erroneous conclusions especially when their inherent assumptions are misunderstood and/or results are inaccurately interpreted.[30,31] In addition, both correlation and linear regression analyses only show linear relationships and may omit the more complex relationships that exist when you have more than two variables.[32,33] Not surprisingly therefore, several researchers have cautioned against misinterpreting a large significant correlation between two variables as a causal relationship between the two variables of interest.[30,32,33]

In the absence of any ocular abnormalities, ocular variables for the right and left eye of the same individual are related.[34,35] Furthermore, the different ocular variables, within the same eye, may be inherently related and correlated. The related nature of clinical variables, from a particular biological system, is not exclusive to optometry and has also been shown in dental and medical research.[31,36] Multiple regression analysis is often used to make predictions and suggest explanations for a dependent variable when there are more than two independent variables.[36] When clinical variables, which are used in multiple regression analysis, are highly correlated, it results in mathematical coupling and collinearity.[36,37] Collinearity can distort the relationship between two ocular variables especially when both variables of interest are highly correlated with another ocular variable.[30] Therefore, a statistical method that overcomes some of these challenges is preferred for assessing the relationship between IOP and multiple anterior segment ocular variables.

Classification and regression tree (CART) is an analysis method that is able to detect which variables are important in a relationship or model.[38,39] This method is useful for large data sets that contain multiple variables that may have non-linear relationships.[40,41] The CART method has several advantages including that it can be used with skewed data, requires minimal input from the researcher because of an automatic independent variable selection process, is able to handle collinearity together with missing variables and displays information in a way that is simple to interpret even for individuals with limited statistical backgrounds.[41,42,43]

The CART method generates a regression tree model when a dependent variable is predicted based on multiple independent variables.[44] In a regression tree model, the dependent variable is continuous while the independent variables may be either continuous or categorical.[41,43] Furthermore, regression tree models are simple to present and resemble the process used in clinical reasoning as they are generated based on a logical sequence of 'if-then' statements or decision rules.[44] For this reason, the CART method is said to have greater practical relevance in clinical situations.[42] To this end, several studies have produced regression trees, using the CART method, for clinical conditions including myocardial infarction,[45] dental caries,[46] asthma,[47] dry eye,[48] keratoconus[49] and low vision rehabilitation.[50]

Graphically, regression tree models consist of a single node (call the root) and consecutive internal nodes that are defined by a characteristic-independent variable and its respective cut-off value that splits the data into two sub-groups.[40,41,42] At each internal node, the CART method iteratively evaluates all the independent variables and automatically selects the variable and its cut-off value that is most efficient in splitting the data into two sub-groups containing similar values for the dependent variable.[41,43,51] Consequently, regression tree models are generated using binary recursive partitioning because of the two-way split at each internal node.[42,44] The process of splitting the sub-groups is continued until the data cannot be split any further resulting in terminal nodes.[40] The root node contains all cases in the data while each terminal node depicts the number of cases (from the data) and the mean value of the dependent variable located within that branch.[40]

Regression tree models that consist of too many branches are unnecessarily large and complex.[40] Such a model is likely to 'overfit' the data resulting in poor generalisability to new data.[40,42,49] Thus, a pruning process is applied to the initial large regression tree model, which removes internal nodes that are considered 'noise' and contribute no predictive power to the regression tree model.[51] Consequently, pruning often results in a smaller regression tree model.[40] Furthermore, pruned regression trees have better predictive accuracy because they go through a cross-validation procedure to select the optimal-sized tree.[43]

The aim of this study was to identify the critical anterior segment ocular variables that influence IOP using an automated regression tree. By using the CART method, it is hoped that the statistical analysis would validate which anterior segment variables have the most influence on IOP. In this way, the CART method may also suggest mechanisms of anterior segment variables affecting IOP that may not have been investigated previously.

Methodology

The study employed a quantitative cross-sectional research design and was conducted at the University of KwaZulu-Natal eye clinic. The study population consisted of black

and Indian students from the University of KwaZulu-Natal. Two-stage random sampling was used to recruit 700 (350 black and 350 Indian) participants aged between 17 and 30 years. Participants were tested using screening procedures to determine their eligibility in accordance with the study inclusion criteria. The screening procedures included case history (ocular and medical), logarithm of the minimum angle of resolution (LogMAR) distance visual acuity, autorefraction (using the Nidek AR-1) and subjective refraction, slit-lamp biomicroscopy, ophthalmoscopy and non-contact tonometry (via the Nidek NT530P). Participants were excluded with visual acuity (unaided or best corrected) worse than 0 LogMAR, IOP greater than 21 mmHg, contact lens wear in the past 3 weeks or previous history of ocular trauma and/or surgery, systemic and/or ocular diseases and currently on medication. Thereafter, data collection procedures were performed on eligible participants.

Corneal thickness and ACA variables such as the angle-opening distance taken at 500 µm (AOD500) and trabecular-iris angle (TIA) were scanned and measured using the Optovue iVue100 optical coherence tomographer (OCT). This Fourier-domain OCT is capable of generating 25 000 A-scans per second with an axial and transverse resolution of 5 µm and 15 µm, respectively.[52] A pre-programmed algorithm in the iVue100 OCT defines the corneal epithelium and endothelium as the anterior and posterior boundaries, respectively.[52] The corneal thickness is automatically determined as the distance between these two boundaries. The AOD500 and TIA were measured using the inbuilt angle tools in the iVue100 OCT. As per the manufacturer's recommendations,[52] repeat scans were taken when the scan was labelled as poor on the laptop screen or had a scan quality index of < 27. During scanning, the real-time images of the participant's eye with either the cornea or ACA were monitored on the laptop screen.

The corneal pachymetry scan protocol which consists of eight radial (6 mm) line scans of 1024 A-scans each was used to measure corneal thickness.[52] During corneal scanning, participants were instructed to look at the internal fixation target. The corneal pachymetry scan protocol displays the average corneal thickness in a 6 mm × 6 mm pachymetry map (Figure 1). This pachymetry map (Figure 1) is divided by rings into three corneal sections (central, paracentral and peripheral). CCT is defined as the average thickness in the central 2-mm ring. The middle and outermost rings, of 5-mm and 6-mm diameter, denote the paracentral and peripheral corneal sections, respectively. The paracentral and peripheral cornea are further divided into eight zones (superior, superior-temporal, temporal, inferior-temporal, inferior, inferior-nasal, nasal and superior-nasal). The average thickness in the central, paracentral and peripheral corneal sections (17 zones) are displayed in the corneal pachymetry map using a false-colour display (Figure 1). In this study, the average paracentral corneal thickness (ParaCT) and average

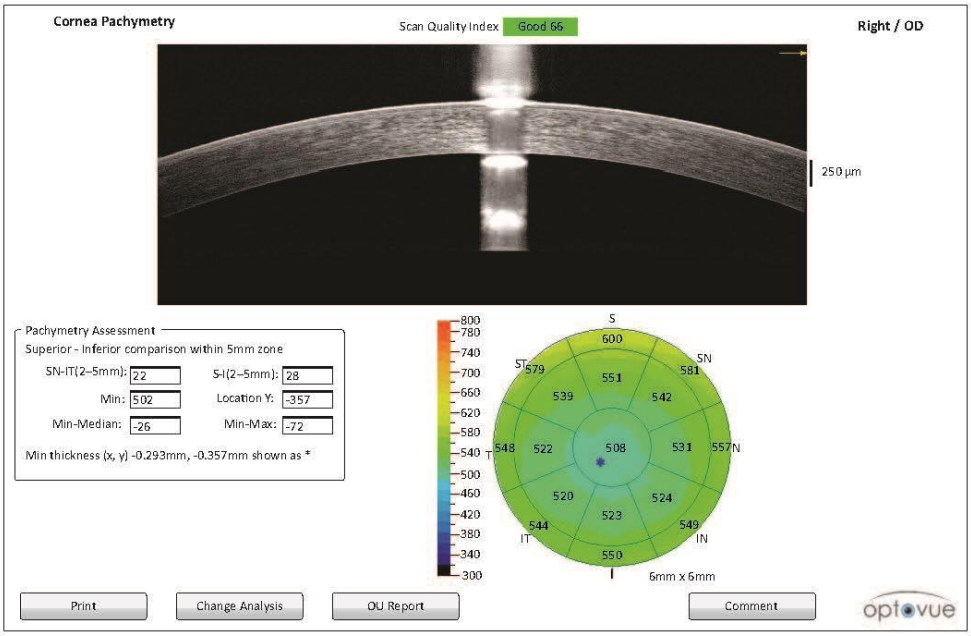


FIGURE 1: Corneal pachymetry map showing the mean corneal thickness in the centre and each zone in the paracentral and peripheral cornea.

peripheral corneal thickness (PeriCT) were computed as the average of the eight zones therein.

The cornea angle scan protocol was used to image and measure the ACA variables (AOD500 and TIA). The cornea angle scan consists of a single (5 mm) line scan of 1024 A-scans.[52] The ACAs in the horizontal meridian (nasal and temporal) were measured as they are unlikely to be distorted by the eyelids[53] and have better repeatability than ACAs in the vertical meridian.[54] During cornea angle scanning, participants were instructed to look at the inbuilt external fixation target mounted on the side of the iVue100 OCT while the line scan was centred on the limbus (nasal or temporal). This ensured that the limbal surface was aligned to the OCT light beam and that the cornea appeared flattened to minimise diffraction and distortion.[53,55] The cornea angle scan protocol displays the ACA analysis using a gray-scale display (Figure 2).

The ACA variables (AOD500 and TIA) were determined using the method described by Pavlin et al.[56] and subsequently used in several other studies.[26,57,58] This method involved identifying ACA landmarks including the angle recess, scleral spur, point on the trabecular meshwork 500 µm anterior to the scleral spur and the corresponding perpendicular point on the iris surface.[56,59] The AOD500 represents the linear distance (in µm) from the point on the trabecular meshwork to the perpendicular point on the iris surface[56] (Figure 2). In this study, the average AOD500 was computed as the average of the nasal and temporal AOD500 measurements. The TIA represents the angular measurement (in degrees) of the triangle formed by the angle recess, point on the trabecular meshwork and the perpendicular point on the iris surface[56] (Figure 2). In this study, the average TIA was computed as the average of the nasal and temporal TIA measurements.

Previous studies have reported that OCT devices have good repeatability and reproducibility for measuring corneal thickness[60,61] and ACA variables.[59,62] Because the ACA variables (AOD500 and TIA) were measured manually, the researcher re-measured the ACA variables on 10 randomly selected participants after data collection. The re-measured ACA measurements showed good agreement with the original measurements (intraclass correlation coefficients ≥ 0.965). Corneal curvature and diameter were measured using the Oculus Keratograph, which is considered reliable and has been used in previous studies.[63,64] Anterior chamber depth (ACD) was assessed using the Nidek US-500 A-scan ultrasound device, which has been used in previous studies to measure axial biometry.[65] The IOP was measured with a Goldmann applanation tonometer, which is regarded as the gold standard for measuring IOP.[66] To promote standardisation, all measurements were performed by one researcher and three measurements per variable were recorded and averages computed.

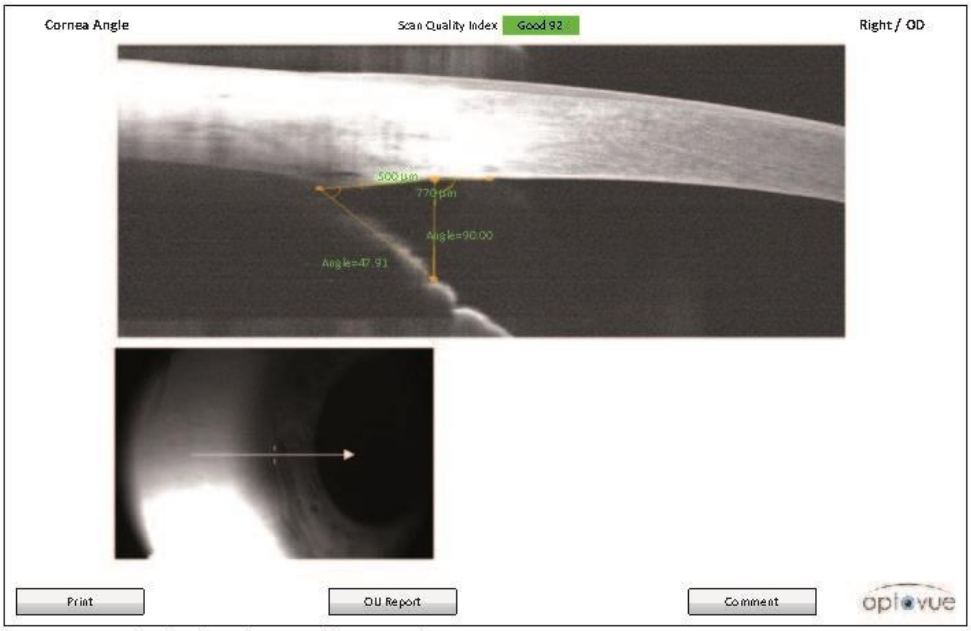


FIGURE 2: Cornea angle analysis showing the ACA variables (AOD500 and TIA).

Data were captured and analysed with two software packages namely the Statistical Package for Social Sciences and the R Package. The Shapiro–Wilk's test and graphical inspection of histograms were used to assess the distributions of the data concerned. Descriptive statistics included means and standard deviations. Interocular symmetry and the reproducibility of ACA measurements were assessed using intraclass correlation coefficients.[35] Dependent-sample *t*-tests were used to assess differences in corneal thickness measurements in the different corneal sections. Pearson's correlation coefficient was used to assess the relationship between study variables. The RPART function in the R Package was used to generate the regression tree models. Eleven independent variables were entered into the CART method including three demographic covariates (gender, age and race) and eight anterior segment ocular variables (CCT, average ParaCT, average PeriCT, corneal diameter, average corneal curvature, axial ACD, average AOD500 and average TIA). The study adopted a 95% significance level where $p \leq 0.05$ were considered statistically significant.

Ethical considerations

Ethical approval for the study (reference number BE 189/12) was obtained from the Biomedical Research and Ethics Committee of the University of KwaZulu-Natal. All participants provided written informed consent after a discussion of the nature of the study procedures involved. All ethical guidelines, in accordance with the Declaration of Helsinki, were adhered to during the study.

Results

The study sample included 700 participants with an equal distribution of male ($n = 350$) and female ($n = 350$) participants. Furthermore, 50% of the sample consisted of South African blacks and the other 50% were South African Indians. The participants' ages ranged between 17 and 29 years, with a mean of 20.42 ± 1.80 years. The preliminary analysis showed that anterior segment ocular variables of the right and left eyes were similar (intraclass correlation coefficients ≥ 0.880). The IOP measurements of the right and left eye were also similar with a mean difference of only 0.27 mmHg and intraclass correlation coefficient of 0.884. Therefore, data from only the right eyes of the 700 participants were analysed because of the high levels of interocular symmetry.

Table 1 shows the ocular characteristics of the study participants. The mean IOP for the entire sample was 14.63 mmHg ± 2.40 mmHg (range, 10 mmHg – 21 mmHg). The CCT was significantly thinner than both the average ParaCT (mean difference of 19.15 µm, $p \leq 0.001$) and average PeriCT (mean difference of 44.91 µm, $p \leq 0.001$). The IOP was significantly correlated ($r \geq 0.50$, $p \leq 0.001$) with corneal thickness measurements in all three sections (central, paracentral and peripheral). Even though IOP was significantly correlated with corneal diameter, axial ACD and average AOD500, the correlation coefficients noted were weak ($r \leq 0.15$, $p \leq 0.016$). There was no association between IOP and average corneal curvature ($p = 0.689$) or TIA ($p = 0.858$).

TABLE 1: Means and standard deviations for ocular characteristics.

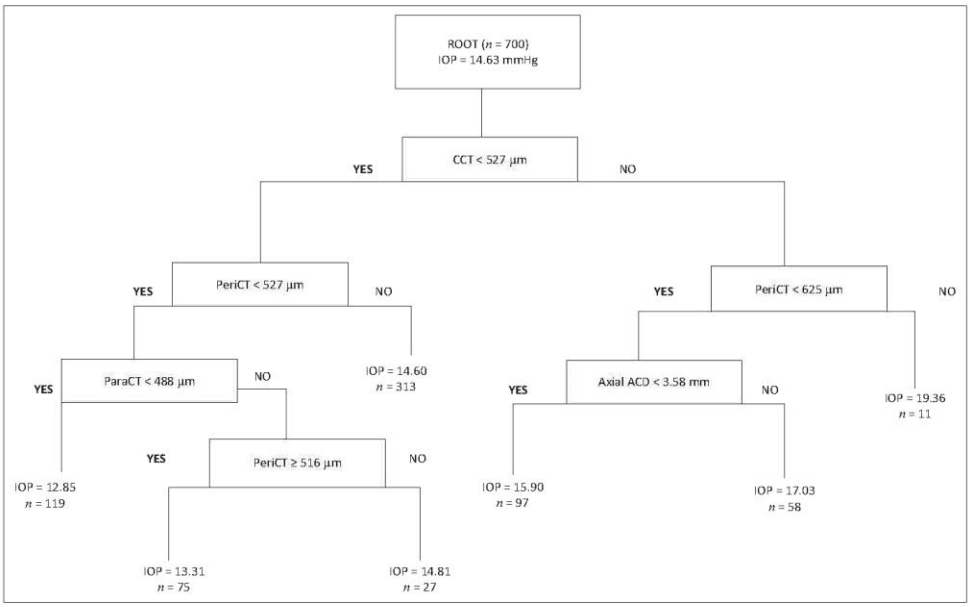
Characteristic	Mean ± s.d.
IOP (mmHg)	14.63 ± 2.40
CCT (µm)	501.91 ± 33.74
Average ParaCT (µm)	521.06 ± 34.56
Average PeriCT (µm)	546.82 ± 35.71
Corneal diameter (mm)	11.95 ± 0.42
Average corneal curvature (D)	43.19 ± 1.54
Axial ACD (mm)	3.43 ± 0.24
Average AOD500 (µm)	552.51 ± 110.68
Average TIA (°)	36.68 ± 4.65

IOP, intraocular pressure; CCT, central corneal thickness; ACD, Anterior chamber depth; AOD500, Angle-opening distance taken at 500 µm; TIA, trabecular-iris angle; s.d., standard deviation.
$n = 700$.

The unpruned and pruned regression tree models, with the decision rules, generated automatically by the CART method are shown in Figures 3 and 4, respectively. The first box in both regression tree models (Figures 3 and 4) is the root node which contains all cases ($n = 700$) and displays the mean dependent variable (IOP = 14.63 mmHg). The successive boxes in grey show the internal nodes which contain the different independent variables and their respective cut-off values. Each independent variable occupies a level with level one being more important than level two and so on. If the condition (independent variable and its respective cut-off value) is satisfied, the tree is followed along the left branch (shown as YES in the regression tree models). However, if the condition is not satisfied, the tree is followed along the right branch (shown as NO in the regression tree models).

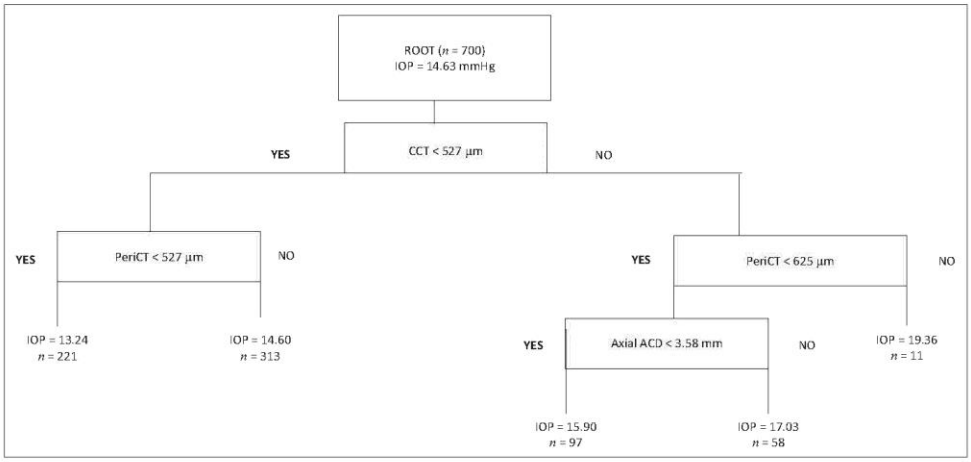
Only 4 of the 11 independent variables were selected for inclusion in the unpruned regression tree model. The selected variables were, in order of decreasing importance, CCT, PeriCT, axial ACD and ParaCT (Figure 3). Cross-validation was then used to prune this regression tree model to automatically generate an optimal-sized regression tree. The pruned regression tree model consisted of only three independent variables (CCT, PeriCT and axial ACD) omitting the ParaCT from the unpruned tree (Figure 3). There were 7 and 5 terminal branches in the unpruned and pruned regression tree models, respectively (Figures 3 and 4). In addition, any further splitting of the data set did not show any significant improvement in the regression tree model.

In both regression tree models (Figures 3 and 4), CCT was the most important independent variable with a cut-off value of 527 µm as identified at level one. At level two, the PeriCT was identified as the next most important variable with cut-off values of 527 µm and 625 µm for CCT values that were < 527 µm and ≥ 527 µm, respectively. In participants with CCT ≥ 527 µm and PeriCT < 625 µm, the predicted IOP differed by ~1.25 mmHg depending on whether the axial ACD (level three) was < 3.58 mm or ≥ 3.58 mm. The highest IOP (19.36 mmHg) was found in 11 participants who had CCT ≥ 527 µm and PeriCT ≥ 625 µm. In the unpruned regression tree model (Figure 3), the lowest predicted IOP of 12.85 mmHg was noted in participants ($n = 119$) with CCT and PeriCT < 527 µm together with ParaCT < 488 µm. In the



IOP, intraocular pressure; CCT, central corneal thickness; ACD, Anterior chamber depth.

FIGURE 3: Unpruned regression tree model, automatically generated by the classification and regression tree method, for prediction of intraocular pressure.



IOP, intraocular pressure; CCT, central corneal thickness; ACD, Anterior chamber depth.

FIGURE 4: Pruned regression tree model, automatically generated by the classification and regression tree method, for prediction of intraocular pressure.

pruned regression tree model (Figure 4), the majority of participants (n = 534) had CCT < 527 µm and IOP measurements < 15 mmHg. The IOP was 13.24 mmHg in 221 participants with both CCT and PeriCT < 527 µm. The IOP was 14.60 mmHg in 313 participants who had CCT < 527 µm but PeriCT ≥ 527 µm.

Discussion

The aim of this study was to identify which anterior segment ocular variables significantly influence IOP. Instead of solely using traditional statistical methods that require an a priori deliberate selection of which variables to analyse, from the

researcher and/or statistician, the CART method was also used. This method is often used in data mining, makes no assumptions about the data and automatically selects the most important variables in a relationship or model.[38,39] The results showed that four anterior segment variables influenced IOP. Three of these variables were measures of corneal thickness (CCT, PeriCT and ParaCT) while the other was the axial ACD.

Both regression tree models showed that CCT (at level one) was the most important anterior segment ocular variable that influenced IOP. This is not surprising as several studies have reported strong associations between IOP and CCT in normal individuals[22,23,24] and individuals with glaucoma.[67] Even though such associations have been reported consistently in the literature, the exact reason for this association is unclear. However, it could be a consequence of both IOP and CCT being measured at the corneal optical zone and the characteristics therein. For example, the corneal optical zone, which has a diameter of 4 mm, is thought to have a uniform spherical curvature.[68] A regular corneal surface is important because applanation tonometry measurements are estimated based on the force needed to applanate a certain area.[69]

A fixed area of flattening is especially important for Goldmann applanation tonometry because, at an applanation diameter of 3.06 mm, the opposing effects of corneal rigidity and the surface tension of the tear film are cancelled out.[69] Furthermore, the corneal optical zone has reduced thickness,[70,71] is more compact and has lower mean collagen inter-fibrillar separations[72] compared to the corneal periphery. These differences between the corneal optical zone and periphery could account for differences in resistance to applanation tonometry.[73] It is speculated that these anatomical, physiological and topographical differences may also account for the association between IOP and CCT at the corneal optical zone. This explanation is reasonable because it has been shown that corneal biomechanical properties influence IOP.[19,74] Furthermore, in this study the IOP measurements in the root node were split based on cut-off CCT value of 527 µm, which is similar to the theoretical calibrated CCT measurement (520 µm) for Goldmann applanation tonometry.[75]

After CCT, the next important anterior segment variables were PeriCT, ParaCT and axial ACD. Corneal thickness beyond the central optical zone is not routinely measured in clinical practice. However, the results suggest that these corneal thicknesses may be important determinants of IOP. No studies could be found that investigated the relationship of IOP and corneal thickness measurements beyond the central optical zone (peripheral corneal thickness). The paucity of literature regarding IOP together with peripheral corneal thicknesses may relate to the fact that IOP is also not usually measured beyond the corneal optical zone. However, such measurements may be useful estimates of IOP, especially in instances of refractive surgeries, central corneal ulcers, epithelial oedema and high irregular astigmatism.[73,76] Moreover, studies conducted on IOP measured at points beyond the corneal optical zone have reported reliable IOPs that are in agreement with IOPs measured at the central optical zone.[73,76] The exact reason for the influence of peripheral corneal thicknesses on IOP is not readily explained. However, it may not be related to the thinnest corneal point being located at the corneal apex, as previously thought, but rather in the infero-temporal cornea.[70,77] It is also likely that corneal rigidity will vary in relation to the different corneal thickness profiles and may also influence IOP.[19,74]

In this study, the mean CCT recorded with the iVue100 OCT was ~502 µm. Previous studies[78,79] involving young South African adult samples, with similar demographic characteristics, have reported mean CCT measurements of ~519 µm. Thus, mean CCT in this study was thinner when compared with other studies involving similar South African samples. This finding may be accounted for by using different instruments to measure CCT because this study used a device based on optical coherence tomography while previous studies[78,79] used devices based on Scheimpflug photography. The overestimation of CCT measurements by Scheimpflug photography devices compared with optical coherence tomography devices have also been reported when CCT measurements were compared on the same study sample.[71] The mean CCT in this study is also lower than the normal expected CCT measurement of 535 µm reported by Doughty and Zaman[80] in their meta-analysis. Thus, possible factors that may explain this discrepancy include differences in study design, instrumentation, sample size and ethnicity.[80,81]

The normal axial ACD is about 3 mm with a wide range of 2.6 mm – 4.6 mm.[82] In this study, the mean axial ACD (3.43 mm) and axial ACD cut-off value (3.58 mm) in the regression tree models were within this expected range. Surprisingly, participants with axial ACDs deeper than the cut-off value had slightly higher IOPs (~1.25 mmHg). Tomoyose et al.[15] theorised that higher IOPs may not necessarily be associated with narrow anterior chambers when the ACA is open in normal individuals. In this study, axial ACD was selected as one of the important anterior segment ocular variables that influenced IOP. This finding is in contrast to previous studies,[15,26] which report no association between IOP and ACD. This difference may be due to a cohort effect because studies that noted no association between IOP and ACD consisted of primarily older Japanese participants.[15,26] It should be noted that Tomoyose et al.[15] reported on axial ACD, while Kawase et al.[26] reported on limbal ACD measurements.

In this study, the average AOD500 was 552.51 µm, which is similar to the calculated average AOD500 measurements by Cheon et al.[83] (555.50 µm) and Leung et al.[84] (549.50 µm). The average TIA was 36.68°, which is comparable with the mean TIA of 35.90° reported in a sample of young German adults (mean age of 32.1 years) by Müller et al.[55] when evaluated with another spectral-domain OCT. Despite also using a young adult sample (mean age of 25.93 years), Hosseini et al.[85] reported slightly higher mean TIA measurements (39.36°) when assessed with a Scheimpflug photography device.

In this study, no ACA variables were selected by the CART model to influence IOP. Furthermore, IOP was not associated with average TIA, whereas there was only a weak association with average AOD500 ($r = 0.09$; $p = 0.016$). These results are in agreement with previous studies that also reported no meaningful association in normal non-glaucomatous eyes between IOP and ACA variables.[28,29] However, other studies[17,21] that used gonioscopy to evaluate ACA width have reported that IOP and ACA width are related. Although both these studies further commented that the associations found were marginal[21] and would only result in small changes in IOP (0.2 mmHg for every 10° change in ACA width).[17]

In this study, other corneal variables (excluding CCT which has been discussed above) have revealed interesting results regarding their relations with CCT, roles in the CART analysis and associations with IOP. Consistent with previous studies,[7,0,71,77] corneal thickness increased significantly from the corneal centre towards the periphery. It is speculated that the normal thickening of the cornea towards the periphery is because of the increase in stromal collagen fibrils in the corneal periphery compared with the centre.[86] Both corneal curvature and diameter were not selected by the CART method for inclusion in the regression tree models. This finding is consistent with the lack of strong associations seen between IOP and corneal curvature or diameter as has been reported in other studies.[20,25,27]

Despite an equal distribution of male and female participants in the study sample, gender was not detected as an important factor in the regression tree models. This finding is consistent with some studies that also reported that IOP is not affected by gender.[8,18] Contradictory findings have been reported regarding IOP and age. Studies involving Asian individuals reported that IOP decreases with increasing age,[15,16,26] whereas other studies reported that IOP increases with increasing age.[8,87] In this study, IOP was not affected by age, which may be attributed to the small range of participants' ages in this study in contrast to other studies that reported associations between IOP and age.[8,26,87]

The mean IOP in the general population ranges between 11 mmHg and 21 mmHg.[1] The mean IOP of 14.63 mmHg in this study is almost identical to that reported by Sardiwalla et al.[78] Despite using a non-contact tonometer, Sardiwalla et al.[78] also measured IOP in a young South African adult sample and reported a mean IOP of 14.6 mmHg ± 2.80 mmHg. In contrast, the mean IOPs reported in several older South African samples[88,89] were smaller (13.7 mmHg – 13.9 mmHg) than those found in this study, which may be attributed to the influence of age on IOP.[15] This difference may also be related to differences in sample sizes wherein the studies with lower mean IOP measurements[88,89] consisted of larger study samples. Because this study only included participants with IOPs ≤ 21 mmHg, all sub-groups of participants shown in the terminal nodes of the regression tree models (Figures 3 and 4) can be considered as variations of an essentially normal young South African adult population, although some eyes with IOP ≤ 21 mmHg could have normal-tension or low-tension glaucoma. However, the age range in this study (17–30 years) probably excluded such instances. From the regression tree models, it can be seen that based on some anterior segment ocular variables, there is a wide range of normal IOP (12.85 mmHg – 19.36 mmHg) in this young South African adult population.

Strengths of this study include the use of young South African adults consisting of an equal gender distribution with normal IOPs (≤ 21 mmHg) and standardised data collection examination protocols. A Fourier-domain OCT was used in conjunction with inbuilt fixation targets to minimise measurement errors associated with off-centre fixation. In addition, this study used an interesting multivariate statistical method to determine which anterior segment variables significantly influenced IOP. Even though the CART method is able to split the data by only one independent variable at a time,[41,42] this method still allowed the regression tree models to grow to 4 and 3 levels in the unpruned and pruned regression trees, respectively.

Possible limitations of this study include the narrow age range of participants and inclusion of participants with apparently normal IOP. This implies that the results of this study may not be generalised to older or younger South African individuals and those with IOP anomalies. Therefore, it is recommended that future studies include individuals with a wider age range and individuals with IOP anomalies to confirm if the same anterior segment variables influence IOP in such cases. Lastly, it is possible that other ocular variables and perhaps those of the posterior ocular segment such as posterior scleral rigidity and retinal nerve fibre layer thickness as well as axial length and refractive error might also influence IOP. Thus, it is recommended that future studies investigate the influence of posterior segment variables on IOP using the CART method as this may lead to an enhanced understanding of which ocular variables and their respective cut-off values influence IOP.

Conclusion

In this study an alternate way of evaluating the influence of anterior segment ocular variables on IOP is presented. Because IOP is an important consideration for glaucoma, understanding the relationship between anterior segment variables and IOP is important in screening for elevated IOP. Furthermore, there is a need to comprehend the critical factors that influence IOP in a simple to understand way in the context of clinical values instead of solely relying on correlation coefficients and p-values of significance. There are some important clinical implications that may be drawn from this study. Firstly, the regression tree models not only validate the profound influence CCT has on the IOP but also draw attention to the importance of corneal thickness measurements outside the corneal optical zone. The regression tree models further provide eye care clinicians with a realistic approximation of IOP based on the measurements of other anterior segment ocular variables. This information may help practitioners in

detecting which patients require monitoring of IOP on the basis of other routinely measured anterior segment ocular variables.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

N.R. wrote the manuscript and R.H. provided feedback on the structure and content of the manuscript.

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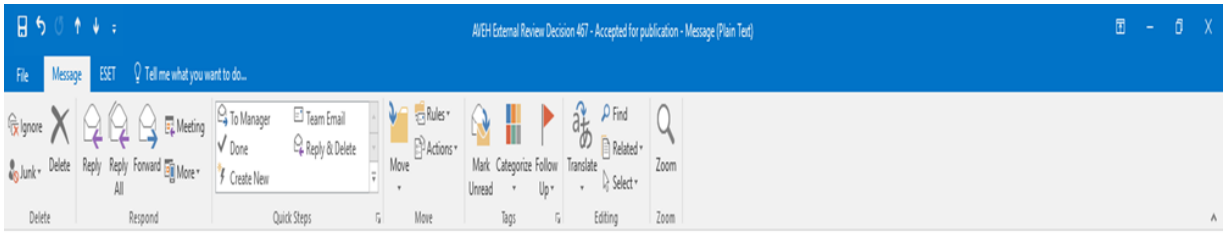
APPENDIX XIII – EMAIL FROM EDITOR FOR PUBLICATION 3



Thu 2018/11/01 14:51

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AVEH External Review Decision 467 - Accepted for publication

To Nishanee Rampersad

Cc Rekha Hansraj

We removed extra line breaks from this message.

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Ref. No.: 467
Manuscript title: Distribution of corneal thickness measured using optical coherence tomography in South African young adults
Journal: African Vision and Eye Health
ISSN: 2413-3183, E-ISSN: 2410-1516

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Dear Ms Nishanee Rampersad

The journal has a double-blinded peer review process and your manuscript was assessed by two expert independent reviewers. Read our peer review process https://aosis.co.za/policies#peer_review.

Thank you for your revised manuscript. We have reached a decision regarding your submission. I am pleased to inform you that your manuscript has now been accepted for publication.

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Kind regards,
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Frequently Asked Question
What can I expect from the publication procedure?

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On the acceptance of a manuscript for publication by the Editor-in-Chief, the editorial staff will work towards preparing the manuscript for online publication by performing a technical review of the publication process. The accepted manuscript will be prepared and handed over from the review office to the Finalisation and Publication Office.