DEVELOPMENT OF AN ALGORITHMIC APPROACH FOR THE EARLY DETECTION AND MANAGEMENT OF KERATOCONUS

by

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Ethical clearance: BREC/ BE385/19

SUPERVISOR: Prof VR Moodley

STUDENT'S DECLARATION

I, Ms Lynett Masiwa, hereby declare that:

i. The thesis submitted for the Degree Doctor of Philosophy (PHD) Health Sciences, in the School of Health Science at the University of KwaZulu Natal is my original work.

ii. This thesis has not been previously submitted to University of KwaZulu Natal or any other institution of higher learning for fulfilment of requirements of academic qualification by me or any other person.

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SUPERVISOR'S DECLARATION

We hereby declare that the preparation of this project was supervised in accordance with guidelines of research supervision laid down by the University of KwaZulu Natal.

As the candidate's supervisor, I agree to the submission of this thesis.

Supervisor: Prof Vanessa Raquel Moodley

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I, Lynett Erita Masiwa declare that this thesis titled “DEVELOPMENT OF AN ALGORITHMIC APPROACH FOR THE EARLY DETECTION AND MANAGEMENT OF KERATOCONUS” submitted for the Doctor of Philosophy (Health Sciences) degree to the University of KwaZulu-Natal, is my own work generated from my own investigations. I have stated all sources to the best of my knowledge. This work has not been submitted for any other degree elsewhere.

Should this thesis be accepted, I consent that it may be made available for copying, inter-library loan, and that the title and summary may be available to other persons outside the University.

The structure of the thesis is presented in the form of chapters including the introduction of the study, reviewed literature, research methodology, results obtained, discussion of results, model development and conclusions.

Lynett Erita Masiwa

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Preface

I have always been interested in the sciences. I pursued a first degree in biomedical science, as a pre-med program as a way of informing the decision on which sector of the health field I wanted to focus on; with paediatric medicine being the strongest contender at that point. At the end of these insightful three years at Griffith University, I settled on eye care and fortunately got accepted into the Dublin Institute of Technology where I successfully completed the honours program in Optometry. I then proceeded straight into private clinical practice in Dublin and quickly confirmed I had made the right decision; serving people was my purpose and vision care was going to allow me to do that.

Before much time had passed, as a keen learner; I found myself pursuing additional practical training so I could be the most informed clinician I could possibly be. I enrolled in the MSc of Clinical Optometry with Cardiff University and this marked my initial interest in research. I took a strong liking to the cornea scientifically and focused on this structure for my final project titled "*A study of collagen and keratocytes in the Avian stroma"*. This study gave me a new appreciation of the corneal ecosystem; the importance of its ability to maintain its integrity for continued functionality was not lost on me.

As I continued my professional career as an Optometrist, working between the University of Zimbabwe and private practice in Harare, I found that I was seeing more corneal abnormalities than I had previously encountered in clinical practice in Dublin. I saw pre-pubescent children that would present for their first ever clinical examinations with advanced signs of keratoconus and visual impairment that could no-longer be corrected with spectacles. This hindered my capacity to successfully help these patients and provide good functional vision as many would need to go straight into the surgical options.

Surgical options, for the most part, were inaccessible to the public sector patients. Harare had, and still has, very few ophthalmology surgeons doing corneal procedures and, as a result, some repair options are not readily available. In addition, these specialised procedures always come at a very high cost which makes them inaccessible to many. It is for this reason I decided to look into ways of diagnosing Keratoconus earlier so that those affected could be successfully managed with preventative procedures and relatively affordable curative options before becoming visually impaired.

Dedication

I would like to dedicate this labour of love to my father, the late Rtd. Col O.C. Masiwa and my mother Maria Masiwa for being my number one cheerleaders in all of my life. I would have not known I could dream big had you not showed me the way, even when I doubted myself you consistently reminded me that Masiwas are made of sterner stuff!

I would also like to dedicate it to my husband, Evans and my two children Noa and Nile who often had to go without me or share my attention with this project, I greatly appreciate their patience and support on this journey.

Last but not least, I would like to dedicate it to my siblings for always supporting and believing in me; Masiwa is indeed a brand name.

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I would like to thank the University of Kwa-Zulu Natal for the scholarship which enabled me to pursue this qualification at a time when it would have otherwise been impossible. I acknowledge the University of Zimbabwe for being my local home during these studies. I would like to acknowledge my supervisor Professor Vanessa Moodley without whom this seed would not have been planted nor seen fruition.

I would like to acknowledge the Zimbabwe Ministry of Primary and Secondary Education and the provincial education director of the Harare Metropolitan province for allowing me to visit the selected primary schools. The school headmasters of North Park primary school, David Livingstone Primary School, Blakiston Primary School and Warren Park 2 Primary School deserve a special mention for collaborating with us and helping us coordinate site visits, ensuring the study was a success.

I also acknowledge the participation of The University of Zimbabwe third and fourth-year optometry students of 2021/22 and Ms. Definite Nyarirangwe that helped me during my data collection activities, you certainly lightened the load.

I would also like to thank Dr Ron Mhizha of The Eye Institute for allowing me access to his advanced clinical instruments, without which some of my data collection would have not been done.

Lastly the statisticians I worked with, for helping me navigate Red Cap and STATA and bring meaning to the figures, thank you.

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Abbreviations

KC	Keratoconus
KSS	Keratoconus Severity Score
UV	Ultra violet
CXL	Collagen crosslinking
CLEK	Collaborative longitudinal evaluation of keratoconus
ASOCT	Anterior surface optical coherence tomography
CS	Contrast sensitivity
BAD	Belin/Ambrosio enhanced ectasia display
FFKC	Form Fruste Keratoconus
VKC	Vernal Keratoconjunctivitis
IL	Interleukins
TNF	Tumour necrosis factor
MMP	Matrix metalloproteinase
ALDH	Aldehyde dehydrogenase catalase
LCA	Leber congenital amaurosis
DUSKS	Dundee University Scottish Keratoconus study
UVR	Ultraviolet radiation
ADH	Alcohol dehydrogenase
I-S	Inferior-superior dioptric asymmetry
KISA	Keratometry, I-S value, Skew radial axis and Astigmatism as a percentage
KRIS	Keratoconus risk investigative survey
KCR	Keratoconus Risk

VDU	Visual display unity
UZO	University of Zimbabwe Optometry clinic
BCVA	Best corrected visual acuity
MRCZ	Medicines research council of Zimbabwe
JREC	Joint research ethics committee
UKZN	University of Kwa Zulu Natal
UVA	Unaided visual acuity
ROC	Receiver operating curve
SDG	Sustainable Development Goal
FHX	Family history
CCT	Central corneal thickness
CT	Corneal Thickness
AS	Anterior surface
ATR	African traditional religion

ABSTRACT

Empirical evidence, supported by anecdotal evidence suggests that some Keratoconic pre-pubescent children present for their first clinical examinations with advanced signs of KC and visual impairment that cannotr be corrected with readily accessible optical aids. This is evidenced by higher prevalences of KC reported in some African communities. This negatively impacts on the lives of these children and hinders the practitioner's capacity to successfully manage the patient and provide good functional vision, often resulting in visual impairment. The study set out to verify this observation and to offer a potential solution to the problem that is the late presentation of young subjects with KC residing in Harare.

Method: A questionnaire, Visual acuity check, retinoscopy and anterior segment assessment were used to award subjects attending primary school in urban Harare aged 6-12years a keratoconus risk score as per scoring sheet developed. A comprehensive exam including refraction, slit lamp exam and keratometry were then performed on the high-risk subjects for the diagnosis of clinical KC. Topography, contrast sensitivity measurement and pachymetry map analysis were then performed for the diagnosis of pre-clinical KC.

Results: 1159 subjects were recruited, 57% were female, 99% of African ethnicity and Christian background. Prevalence of clinical KC was found to be 630: 100 000 and pre-clinical KC was found to be 1360:100 000. Anterior surface abnormalities were present in 30% of the subjects considered to be high risk for the development of KC. The age range of the subjects diagnosed with clinical KC was 8-12years. VKC, reduced VA, itchy eyes and eye rubbing were the most frequently encountered symptoms.

Conclusion: The odds of having KC are increased if the child is aged between 8 and 12 years and of African ethnicity, regardless of gender. Increased probability of developing KC was found in the presence of VKC, reduced VA, itchy eyes and frequent eye rubbing.. The early detection and management algorithm developed will allow for the timely diagnosis of KC and in turn offer improved prognosis as the earlier management of the condition will be possible with all treatment options still viable.

CHAPTER 1

1.1 Introduction

Keratoconus (KC) is a well-documented, but insufficiently understood, corneal ectasia typified by changes in refractive error, corneal curvature steepening and corneal thickness variations that are associated with visual impairment[1–3]. Its first appearance in literature dates back to the 18th century; the first elaborative explanation offered by Nottingham in 1854[4]. Symptoms of KC include blurred vision, photophobia, problems with glare and frequent refractive error changes[5–9]. Present day clinical practice for the diagnosis of KC involves identification of the following signs; reduced central corneal thickness and pachymetry map discrepancies and corneal assessment signs such as Vogt's striae, Fleischer's ring, Rizutti's sign, Munson sign and corneal scarring secondary to steepening[1,2,4,10–12].

1.2 Background

Diagnosis of KC does not require all the aforementioned signs to be present; the practitioners subjective clinical judgement is the deciding factor. Varying definitions and terms associated with a clinical examination such as a scissors reflex on retinoscopy, irregular astigmatism, steep keratometry readings, distorted mires and thickness and topographical variations on a topography map with additional subclinical signs makes for inconsistent diagnosis[13]. This may lead to different practitioners employing different management plans, some of which may be unfavourable for certain patients.

KC can be classified descriptively by morphology and disease progression or quantitatively by diagnostic indices[14]. Morphology classification, based on corneal shape, distinguishes KC into either round (nipple) shape, characterised by a small cone diameter with the cone frequently located in the lower nasal quadrant or oval (sagging) shape; characterised by a larger cone diameter that extends to the corneal periphery with the cone frequently located on the lower temporal quadrant[3]. Diagnostic indices classify KC severity as

measured on a quantitative scale, determined by analysing different corneal parameters, such as corneal elevation[15], central corneal thickness[16,17] or a combination of different indices[18,19]. Classification may also be determined by documenting the clinical signs evident on a slit lamp examination, topography and the best corrected visual acuity achieved, as seen with the Amsler-Krumeich scale[20] and the Keratoconus Severity Score(KSS) [21]. As corneal assessment techniques continued to evolve courtesy of technological advances; more scales have been proposed; such as the ABCD scale which takes tomography findings into consideration when grading KC[22].

Current literature has the age of onset of KC broadly pegged as some point in prepubescent years, in the second decade of life or early adulthood and then stabilising in the 3rd or 4th decade [23–25]. Factors that have been noted to increase the risk of developing KC include positive family history for the condition, atopic conditions, vernal keratoconjunctivitis and connective tissue disorders such as osteogenesis imperfecta and Down's syndrome[26–31]. It is also thought to have a genetic component to it which is significantly relevant in communities that practice endogamy and consanguineous marriages[32–35].

KC affects both men and women but is thought to develop earlier and progress more rapidly in men[7]. A study of an adolescent population found KC to be more prevalent amongst the females compared to males[36]. Another school of thought suggests that KC is equally prevalent amongst males as it is females [35,37,38]. Debatably, some studies report a higher prevalence amongst males compared to females by varying degrees with 5 times as high being the highest relative risk factor reported [5,24,34,39–41].

Incidence of KC ranges between 1.3 and 25 per 100 000 each year and prevalence ranges between 8.8 and 4 290 per 100 000 (Table 1)[4,42]. The studies presented on Africa to date give overestimated values due to the high-risk populations analysed. A higher prevalence has been reported in Arabic nations which are typically characterised by Muslim religion group and high UV exposure compared to the cooler climates in

the northern hemisphere leading researchers to believe the higher prevalence may be associated with increased sun exposure[42] and consanguinity[34,39,43].

Table 1: KC prevalence by continent

MIDDLE EAST		EUROPE		NORTH and SOUTH AMERICA		ASIA PACIFIC		AFRICA	
Country	Prevalence / 100 000	Country	Prevalence / 100 000	Country	Prevalence / 100 000	Country	Prevalence / 100 000	Country	Prevalence /100 000
Saudi Arabia[43]	4790	Finland[6]	28.8	USA[44]	600	India[45]	2300	Egypt[46–50]	1700-34000
Israel[34]	2340	France[51]	750	USA[25]	54.5	Japan[52,53]	17.3	Kenya[54]	30 890
Iran[37] Iran [55]	830 1400	Russia[56]	0.2-0.4	USA[57]	17.5	South Korea[58]	37.36	Nigeria[59]	440
Egypt[46]	1120	UK[60]	57	Mexico[36]	1800	China[61]	960	South Africa[62]	24 210
Lebanon[63]	3300	Denmark[64]	86			New Zealand[65]	520	Gambia[66]	900
Palestine[67]	1500	Macedonia[68]	6.8						
		Netherlands[69]	265						
		Denmark[70]	44						
		Holland[71]	2.5						

The progressive condition has no cure but the visual impairment it induces can be conservatively managed through the use of spectacles and/or contact lenses. Optical devices are employed to aid vision but not treat the disease. KC can be managed surgically with procedures such as collagen crosslinking, the use of intacs and penetrating keratoplasty[72,73]. Collagen crosslinking (CXL) is a relatively new procedure with the longest follow up recorded to date being thirteen years post intervention[72,74]. It has been shown to stop the advancement of KC, in some cases regress KC as shown by a decrease in corneal steepness by up to 2D

and even improve both uncorrected and best corrected visual acuity post treatment [75]. Due to the success of the procedure, variations of the original procedure; such as accelerated cross linking, continue to be developed for the management of corneal ectasia[76]. Penetrating keratoplasty is often the last resort to restore vision in advanced KC, particularly in the presence of significant visual impairment due to corneal scarring[77].

In addition to the actual prevalence of KC in Zimbabwe being unknown; risk factors for the development of KC and the age of onset have not been investigated. Paediatric KC has been reported to be more aggressive as it is typically characterised by high rates of progression[78]. Anecdotal evidence suggests a high occurrence of KC in Harare, with pre-pubescent children presenting for their first ever clinical examinations with advanced signs of keratoconus and visual impairment that can no-longer be corrected with spectacles. These late signs, consistent with advanced KC, include corneal hydrops and significantly distorted mires on keratometry and their presence suggests that the condition predates their presentation for the eye exam. This often hinders an eye care practitioners' capacity to successfully help the patient and provide good functional vision as many would need to go straight into the surgical options.

KC progression remains the main area of concern once diagnosed as it has a huge impact on prognosis. There is need to detect, document and manage progression of KC for the best evidence-based clinical practice to be applied. Previous research showed an increase in corneal steepening of between 0.70D and 1.23D in one year[79]. Middle Eastern populations and younger populations demonstrated the fastest rate of change[79]. A study by Tuft et al., (1994) investigated consequential factors that influence progression and found that keratometry findings, presenting visual acuity, ethnicity and age all significantly affected the time to corneal graft[80]. Younger patients and those with steep keratometry readings required an earlier graft[80], highlighting the importance of early diagnosis and interventions for best visual outcome. Ferdi et

al., (2019) also recommend that thought be given to the method used for monitoring progression as a variation of 0.50D was noted between Pentacam assessments compared to Orbscan assessments[79].

The landmark collaborative longitudinal evaluation of KC (CLEK) study followed 1200 subjects and reported that visual acuity weaker than 20/40 and keratometry readings greater than 52D were associated with reduced quality of life comparable to that experienced with advanced macular degeneration[81]. The presence of corneal scarring results in a reduction in contrast sensitivity, which also impacts on quality of life. High contrast visual acuity charts therefore underestimate the loss of function associated with KC[81]. These findings all speak to the importance of early diagnosis for best visual function and good quality of life to be maintained.

Late diagnosis of KC renders management options such as CXL and spectacle use non-viable. This leaves patients with limited ways of alleviating the associated visual impairment. Donor corneas for penetrating keratoplasty have to be imported as there is no cornea donor bank in Zimbabwe. As a result, penetrating keratoplasty remains one of the most expensive ocular procedures, making it inaccessible to the average Zimbabwean family. In the post-COVID-19 era, donor corneas have become even more scarce and unavailable as donor banks noted a decrease in supply and a reduction in the occurrence of the procedure[82,83]. More stringent screening regiments of donor tissues as recommended by the Eye Bank Association of America and other similar regulatory bodies will also have an impact on the cost of acquiring donor corneas[84]. . Inability to access this level of treatment then leaves the affected children with moderate to severe visual impairment, with very little hope for improved vision.

It is therefore imperative that the diagnosis of KC occurs early enough so that those affected can be successfully managed with relatively affordable, accessible options before becoming visually impaired. In managing KC, the local hospitals do not have anterior segment tomographers and hence the need to be proactive in the investigation of KC, so as to effectively reduce the prevalence of preventable blindness in

Zimbabwe and other similar low resource settings. Developing an algorithm for the early diagnosis of KC will both contribute to literature and management of KC patients in Zimbabwe.

Bourne et al., (2021) estimate that 90% of visual impaired people live in low-middle income countries[85]; which includes Zimbabwe, the Southern African country within which this study was based. Zimbabwe has a high rate of unemployment with 40% of the population living off $2/day[86]. According to the International Agency for the Prevention of Blindness (IAPB), the Southern African region is well below the recommended number of eye care professionals required to service the population[87,88]. Zimbabwe has a population of 17 million people who are serviced by approximately 40 ophthalmologists and 60 optometrists. The WHO recommends 4 surgeons per million in population and 20 optometrist per million in population[87].

Various corneal changes measurable on topography, tomography and aberrometry have been noted as early signs of KC[89–92]. The displacement of the thinnest part of the cornea from the central position to infero-nasal or infero-temporal positions is a common finding in ectatic disease [8,92,93]. High resolution ultrasound has proven that changes in the corneal epithelial layer cell distribution from evenly distributed to a donut shape predate stromal layer changes [90,94–97]. Another early sign of KC is a variation in the anterior/posterior corneal astigmatism relationship with the posterior cornea showing signs of steepening earlier than the anterior cornea [17,98–100].

A measure of corneal biomechanics has also shown that keratoconic eyes display a higher deformation amplitude compared to normal corneas[101–103]. Pachymetry variations in corneal thickness from the central cornea to the periphery with a difference greater than 100µm need further investigation as this may be an early sign of KC[92,104,105]. Higher order aberrations; particularly spherical aberrations and coma were shown to be more significant in ectatic eyes[106,107]. These changes have been shown to predate the clinical signs evident on slit lamp that are synonymous with reduced visual performance. Changes in corneal protein

concentration and structural modifications in the corneal epithelium and stroma have been noted as part of the reasons the cornea is more susceptible to structural modifications in KC[108,109]. Hormonal changes associated with puberty; characterised by changes in oestrogen and androgen hormone levels, have been shown to have a strong influence on these proteomic changes and changes in corneal thickness[110]. Clinical signs have to date been used to diagnose KC with the age of onset being marked as 12years old[31,78,79]. It is therefore plausible to expect pre-clinical signs of KC in a younger population under the age of 12. In addition, adults would be expected to have established disease and not early pre-clinical disease. Identifying and documenting the changes that are consistently present can therefore be employed in the early detection of KC.

1.3 Problem statement

Pre-pubescent children currently present for their first clinical examinations with advanced signs of KC and visual impairment that can no-longer be corrected with spectacles. Inability to correct with spectacles is a sign of KC progression. This hinders the practitioners' capacity to successfully manage the patient and provide good functional vision.

1.4 Research Questions

- What is the prevalence of keratoconus amongst children between the ages of 6 and 12 years in urban Harare?
- Is KC prevalence a function of age in the 6-12 year category?
- Does corneal tomography detect keratoconus earlier than keratometry in the urban population of Harare between the ages of 6 and 12 years?
- What is the relationship between age and clinical signs of keratoconus in children under the age of twelve years resident in urban Harare?
- What is the pre-clinical profile of early keratoconic patients?

1.5 Aims and Objectives

Aim

To develop an algorithm for the identification of pre-clinical and early clinical KC in children in urban Harare.

Objectives

- Determine the risk profile of children with keratoconus in urban Harare
- Determine the prevalence of keratoconus in children in urban Harare, Zimbabwe
- Document the pre-clinical signs of keratoconus in children identified as high risk for keratoconus
- Determine the age most associated with early signs of keratoconus in children living in urban Harare
- Develop an algorithmic approach for the early detection and management of keratoconus

1.6 Type of Study and Method

Study Design

A cross-sectional analytical study of school students aged between 6 and 12 years resident in suburban Harare.

Method

Four primary schools in urban Harare were pre-selected prior to the data collection process. A modified Keratoconus Risk Investigator Score (KRIS) questionnaire (Appendix 1a) was used to manually collect and record information on demographics, ocular history; family history and general health history. The questionnaire was dropped off at the chosen schools along with the written consent forms for the parents/guardians to complete and return to the schools prior to the data collection visits. Preceding the main data collection, a pilot study was carried out. The pilot group constituted forty 11-12 year students at

a primary school in Harare. This data was included in the main research. The pilot included an assessment of the procedures to be followed and a trial of the Red-Cap data capture tools.

The data collection process was separated into two phases;

- Phase 1

Phase 1 comprised the school screening activities. Students with signed consent forms and completed questionnaires were included in this study. In addition to the pre-completed questionnaires, visual acuity recordings were performed by third- and fourth-year Optometry students using a Snellen visual acuity chart. A pen torch with a +10.00DS lens or hand-held ophthalmoscope were used to assess the anterior ocular segment for general signs of vernal conjunctivitis.

The information gathered was then recorded on a scoring sheet provided and each subject awarded a total score for the risk of developing of KC. Each subject was provided with a result slip to take home stating whether no further action was required or they needed to be seen for the full comprehensive eye exam.

A point system was developed and used to identify the children considered to be at a higher risk for developing KC. The point system is detailed in Table 2 below.

Table 2KC risk factor scoring system

Parameter	Score
Positive family history of KC	3
VA of 6/9 or worse in at-least one eye	2
Positive for vernal conjunctivitis	2
Positive for Down Syndrome	3
Positive family history of spectacle use	1
Positive for atopy	2
Positive for itchy eyes	1
Positive for eye rubbing	3
Positive for asthma/hay fever	1

Any subject scoring a total of 5 or more points were considered to be at risk for developing KC and referred to the University of Zimbabwe Optometry clinic for a comprehensive eye exam. A diagnosis of Clinical KC was denoted in the presence of positive slit lamp findings for any signs of KC and keratometry readings greater than or equal to 45 Dioptres in either meridian. Those diagnosed with clinical KC were then managed accordingly and discharged from the study. The other subjects without clinical KC at the end of the comprehensive eye exam were recalled for additional corneal imaging on a separate day. This marked the end of phase 1.

- Phase 2

All the subjects that had been recorded as not having KC following the clinical exam in phase 1 were then required to undergo corneal topography and anterior segment optical coherence tomography (ASOCT) scan using the Optovue iVue OCT, topography scan using the Topcon Ref-Topographer RT-7000 and contrast sensitivity (CS) measurement using the Pelli-Robson CS chart. A positive diagnosis of preclinical KC was awarded in the presence of corneal steepening characteristic of KC on topography, and/or two other signs associated with the development of KC including but not limited to variations in corneal thickness, reduced CS, displacement of corneal centre and a corneal thickness less than 480µm[111].

All data was captured electronically using Red Cap database and processed using STATA.

1.7 Definition of terms

Keratoconus: a corneal ectasia characterised by corneal steepening, stromal thinning and changes in the corneal shape.

Pre-clinical KC: also termed subclinical KC or KC suspect is used to describe a cornea with documentable signs associated with KC in the presence of a normal VA, normal keratometry and normal slit lamp exam.

1.9 Outline of study as presented in this Thesis

This write up is segmented into six chapters detailing the background, literature review, method, results, discussion and conclusion. The conclusion chapter includes a summary of the findings of this study, future research and recommendations. A detailed breakdown of the chapters is detailed below;

Chapter 2: Literature review

- 2.1 Prevalence of KC by Geographical location
- 2.2. KC Risk factors

Chapter 3: Method

- 1.1 Introduction
- 1.2 Study Design
- 1.3 Study area and population
- 1.4 Study population
- 1.5 Study sample and size
- 1.6 Data Collection tools by Objective
- 1.7 Pilot study
- 1.8 Data collection process
- 1.9 Data Analysis
- 1.10 Data management
- 1.11 Ethical consideration

Chapter 4: Results

- 1.1 Introduction
- 1.2 Demographic details

6.4 Recommendations

6.5 Conclusion

1.10 Conclusion

Early detection of KC will ensure that all probable KC management avenues are still viable options at the time of diagnosis. This will in-turn offer better eye care services to the paediatric Zimbabwean population and minimise the degree of visual impairment experienced by the patients. It will also improve access to care as optical devices to improve vision in early to mild Keratoconus are relatively more affordable. The development of a sensitive and specific screening routine for KC will be beneficial to many low resource settings. Documenting the prevalence and age of onset for this condition in the study population will contribute to literature and inform the public health sector of the appropriate interventions required and the age to introduce ocular health screening programs.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

Keratoconus is the most researched corneal ectasia[112] such that the term corneal ectasia is often used interchangeably with the name keratoconus although other types such as keratoglobus and pellucid marginal degeneration exist. Publications on KC have seen an increase in recent times with the increasing popularity of refractive surgery[112]. Corneal surgery is the most prevalent method for refractive surgery[113,114]. Research has shown that keratoconus along with flap abnormalities, can be considered an avoidable post- operative surgical complication of refractive surgery leading to the increase in success rates of the procedure[115,116]. It is for this reason much interest and investment has gone into this topic. That said for the sake of this literature review I shall focus on KC as a non-iatrogenic phenomenon.

In this chapter I shall focus on the prevalence of KC and the risk factors associated with the development of KC. Prevalence is the proportion of people in a population with a particular disease or attribute at a specified point in time or over a specified period of time [117]. Risk factors refer to identifiable characteristics that precede an outcome[118]. I shall discuss the prevalence of KC by continent as the entity has been shown to be influenced by geographical location. Risk factors can be used to classify a population as either high risk or low risk such that the high risk subgroup demonstrates a higher probability of a positive outcome for the condition under consideration. There are various facets one could approach KC with but prevalence and risk factors have been chosen for this review as I feel they offer the most holistic appreciation of the condition

2.2 Prevalence of KC

2.2.1 Africa

Population based KC prevalence studies have not been done on the African continent as yet. Existing African studies have focused on the prevalence of KC in high risk groups such as patients suffering from vernal keratoconjunctivitis (VKC) or patients already seeking care for allied reasons in a medical setting[28,66]. Although the findings are not transferable to the general population, they do give an idea of the significance of KC as an eye health care concern in Africa.

A 2011 retrospective study in Gambia by Wade et al looked at the epidemiological features of allergic conjunctivitis and associated ocular and systematic conditions[66]. 7912 patient records were reviewed and of these 624 patients were positive for allergic conjunctivitis and were equally distributed between males and females. 54.5% of these patients that were diagnosed with allergic conjunctivitis were under the age of 15 years and 0.9% of eyes evaluated were found to have KC. This converts to a prevalence of 900: 100 000 in this high risk population. This is a relatively low percentage compared to findings in another similar more recent study by Caputo et al., (2016) which found a KC prevalence eight times higher. This may be due to the fact that in this study, diagnosis of KC was based on clinical findings only which may have missed subclinical cases and mild KC resulting in under diagnosis and under estimation of the condition. This demonstrates the importance of the investigation techniques and assessments employed for diagnosis. Superior investigative techniques have been shown to improve sensitivity in the diagnosis of KC[89,90] and hence an increase in number of positive findings as shown in a similar study by Totan et al., (2011). Totan et al (2011) found that in the same study group 26.8% were positive for KC when quantitatively diagnosed using video keratography maps, whereas only 8.5% were correctly identified on slit lamp examination and 18.3% by keratometry[119]. The SLE alone was the least sensitive method for the diagnosis of KC which ties in with the study by Wade et al in Gambia under estimating the prevalence of KC in their study group. In addition, environmental considerations would have expected a study in Gambia to yield a higher percentage of KC prevalence than a European based study further suggesting under estimation in the Gambia.

A cross-sectional study of 3049 school aged children (7-14 years) in Rwanda also sought to detail the epidemiological signs and other systematic ailments in children diagnosed with VKC. 4% of the study group was diagnosed with VKC[28]. Of this 4%; 1.7% had KC or high astigmatism. This converts to a prevalence of 68: 100 000. Auto keratometry and clinical signs were used in the diagnosis of KC in this study which may explain the relatively low prevalence in this high risk group. The nature of the assessment of the cornea employed; auto keratometry, only evaluates the central anterior corneal radius of

curvature[89,120,121] and can easily overlook some key traits associated with the presence of KC resulting in the under estimation of the prevalence.

A Kenyan study of 123 patients under the age of 30 years but above 8, at Kenyatta National Hospital eye clinic also focused on the prevalence of KC in people with allergic conjunctivitis and reported the highest prevalence on the continent to date[54]. The subjects underwent a comprehensive eye examination which included refraction by retinoscopy, keratometry, slit lamp exam, placido disc assessments and pentacam scan. The corneal assessment methods employed may explain the high prevalence rate reported due to the increased sensitivity of the comprehensive assessment. This well documented study found that KC was consistently a cause for significantly reduced visual acuity where present[54]. The prevalence of KC was found to be 10 600:100 000 by clinical diagnosis, 14 400:100 000 by keratometry and 30 900:100 000 by topographical diagnosis [54]. Although the small sample size of a high risk group under consideration may also explain the astronomical values reported, it is still noteworthy to appreciate the value of a comprehensive exam with advanced corneal imaging for the diagnosis of KC. The subjects were primarily affected by allergic conjunctivitis which is considered a predisposing factor for the development of KC[29,122,123]. This also explains the relatively high prevalence rate reported in this study. Interestingly, the highest prevalence of 42 100: 100 000 was reported in the 10-14 years age group. One would expect the prevalence to increase with age but this was not the case. A prevalence of 23 700: 100 000 was reported in the 15-19 years age-group, 13 300: 100 000 in the 20-24 years age-group and 7 800: 100 000 in the 24-30years age group. This may be due to the fact that allergies are more problematic in the 10-14yr age group and tend to resolve as the person gets older[124] so the older age groups would not be seeking treatment at the same rate as the younger age brackets. A prevalence of 13 100:100 00 was reported for the 8-9 year age group. This is a note-worthy finding as literature suggests that the age of onset of KC is the second decade of life[23,42,52,125]. Having such a high prevalence in this age group suggests that the age of onset as earlier than reported in literature.

A prevalence range of 1 120-34 000: 100 000 is reported from various studies in Egypt[46–50]. The varied wide range of figures can be attributed to different locations and different populations evaluated. The different researchers employ similar advanced corneal assessment methods and similar diagnostic definitions of KC which displays a commendable level of clinical practice in Egypt. Elbedewy et al., (2019) carried out a retrospective study on 8 124 patients presenting for refractive surgery. This is the largest sample group encountered and they used Pentacam tomography to establish a prevalence of 1 120: 100 000 with no gender preferences established. This is a plausible finding as the corneal assessment method employed is very sensitive to the presence of KC. The large sample size evaluated also gives credibility to these findings. The Holladay criteria was used for the diagnosis of KC[126]. This a good criteria to apply as it is sensitive for the early detection of KC[120,126]. Interestingly, another hospital based study of 1202 refractive surgery patience found a prevalence of 17 500: 100 000[48]. Saro et al., (2017) report a prevalence that is more than fifteen times greater than Elbedewy et al. This is a significant difference and may be attributed to the difference in study method. The higher prevalence was reported in a cross-sectional observational study which would have the researchers in better control of the output whereas Elbedewy et al., (2019) would have depended on previously gathered data in a retrospective study. This large discrepancy highlights the importance of the research method selected as similar detailed corneal assessments that include posterior corneal analysis were employed in both studies.

Saro et al., (2017) also report a gender discrepancy with males being more affected than females in contrast to Elbedewy et al., (2019) who reported no gender influence. Saro et al (2017) findings are consistent with previous publications that also report a higher prevalence amongst males[5,24,34,39–41]. KC was evident in the 11-15yrs age group with 6.2% of them reported to have KC, this is consistent with the pre-pubescent age of onset suggested elsewhere[23,52,71]. The highest prevalence of KC by age group in this study was 22 900: 100

000 which is significantly lower than the 42 100: 100 000 reported by Sn et al. (2018) in Kenya. This was found in the 31-35yrs age group in this study in contrast to the younger 10-14yr age group in Kenya. This can be attributed to the difference in study population investigated which differ both in age and risk factor profile. The Kenyan study population is a younger population being treated for allergic conjunctivitis which may explain the higher prevalence in a younger population. By nature of the condition, it would be expected to find a higher prevalence of KC in the older age group as more people get diagnosed later in life as the condition progresses.

A relatively smaller study by Ahmed et al., (2021) of 100 paediatric patients being treated for allergic conjunctivitis at Cairo hospital yielded a higher prevalence of 34 000:100 000[47]. Advanced corneal assessment methods were employed in the diagnosis of these patients; CSO topographer and the Wave-Light Oculyzer, enabled the researchers to diagnose pre-clinical KC as well. This may explain the relatively higher prevalence along with the fact that the population sample is a high risk sample group of children with ocular allergies so the higher prevalence could be misleading. Although it is valuable in highlighting the presence of KC in this paediatric population, the findings would be more valuable with a larger sample group. The high prevalence is comparable to the findings reported in a similar high risk group by Sn et al (2018) who also found a high prevalence of 30 900: 100 000 as described earlier in this chapter.

A separate study in Egypt by Sidkey et al.[49] reported a prevalence of 4 800:100 000. This is relatively low compared to other studies in Egypt described above. This can be attributed to differences in sample group; this study evaluated children aged 6-18yrs that had astigmatism greater than or equal to 2Dioptres. High astigmatism is prevalent among KC patients[4,127]so the high occurrence of KC in this population is expected but the smaller sample group of 547 may explain the relatively lower prevalence when compared to other studies in Egypt. The second lowest prevalence of KC described in an Egyptian population is 1 700:100 000[50]. This was found in patients presenting for LASIK and is significantly lower compared to findings

from similar study populations as reported by Saro et al[48] but is comparable to the 1 120: 100 000 reported by Elbedewy et al.,[46]. One thing all the studies do highlight is the importance of a comprehensive corneal assessment in the diagnosis of KC and that KC is a condition of concern in Egypt.

A retrospective study of 1210 subjects presenting for contact lens fittings in South-Africa reported a prevalence of 24 210: 100 000 in this high risk subgroup[62].The convenient sample group had subjects aged between 10yrs and 64yrs of age. A clear disadvantage of the retrospective nature of this study is the fact that the researchers do not explicitly know the actual corneal assessment method used for the corneal power measurement as they detail two options; oculus keratograph and the one position keratometer. The capabilities of these two instruments are vastly different; knowing the method of assessment would go towards better appreciating the prevalence of KC reported. Clinical signs found on slit lamp exam (SLE); corneal thinning, Munson's sign, Fleischer's ring, Vogt's striae, Rizzuti's sign and/or corneal scarring, were used to diagnose KC. Diagnosis of KC by SLE alone has been shown to underestimate the prevalence of KC[54,89]. This further brings into question the prevalence reported. It is for these reasons we can only glean the occurrence of KC in South Africa and not know its actual prevalence from this study. Similarly, another medium sized study in Nigeria of 1 144 students aged between 4yrs of age and 24 years of age reports a prevalence of 440: 100 000 which can be taken as a guiding figure for the suggested prevalence of KC in Nigeria although it is not the true prevalence of the condition.

2.2.2 Middle East

A cross-sectional multi-centre study of paediatric patients aged 6-21 years in Saudi Arabia has recorded a high prevalence of KC at 4 790: 100 000[43]. Paediatric patients presenting to emergency centres without a history of eye complaints were recruited into this study. The 6-11year age sub-group was found to have a KC prevalence of 1 150:100 000. This age bracket had an equal representation of girls and boys which eliminates any gender bias. The commendable use of two experienced ophthalmologists for the subjective

diagnosis of KC and the inbuilt Pentacam indices such as the Belin/Ambrosia enhanced ectasia display (BAD) scores for the objective diagnosis of KC minimised the number of false positives recorded. There was a time saving benefit in the sole use of the pentacam analysis for the diagnosis of KC; however, had they included refraction and slit lamp exam of the patients in addition to corneal tomography it would have assisted in the diagnosis of the nine cases that the assessors initially failed to get a consensus on. The prevalence reported may be on the high side for KC because the positive findings did not exclude other corneal ectasias that may have similar signs on corneal tomography. The medium sized sample size of 522 makes these findings statistically significant.

Although a higher prevalence of KC has been suggested for Arabic and Middle Eastern populations [14], a relatively lower KC prevalence of 2 500: 100 000 was reported in a population based study in Mashhad [35]. This finding was consistent with the findings in a separate cross sectional study of 982 subjects in Jerusalem which reported a KC prevalence of 2 340: 100 000 [34]. This value may be lower than that reported in Saudi due to the use of a higher cut off for the central corneal steepening (≥ 50D) as the diagnostic finding for KC although both studies based diagnosis of KC on topography. The findings of this study are also comparable to a prevalence of 3 300: 100 000 found in a study of 92 randomly selected Lebanese students at a public hospital that also used topography findings for KC diagnosis[63]. The subjective definition of KC may have resulted in the slightly higher prevalence in Lebanon as it depended on the ophthalmologists evaluation of the topography print outs. Also worth noting from this study is that consanguinity was recorded in 9.7% of the study sample which may also explain the higher prevalence reported. In addition, the study in Mashhad[35] excluded contact lens users from their sample which would possibly exclude people with KC resulting in an underestimation of the prevalence of KC. However, the use of stratified cluster sampling of the university population minimised the impact of these exclusions. The study in Jerusalem by Millodot et al., (2011) did not exclude contact lens wearers and yielded a similar prevalence value therefore showing that excluding contact lens wearers did not have a significant impact on

the findings of the study in Mashhad. Millodot et al., (2011) reported the KC prevalence to be 1.07% in females and 4.91% in males which supports the aetiology argument that KC is more widespread in men than women. The researchers took into consideration the demographic data and other risk factors that would have rendered some participants high risk for developing KC in both Mashhad and Jerusalem. This went towards identifying and including the individuals susceptible to KC development in the study which may have contributed to the high prevalence values reported. It is important to note that these studies may have reported relatively higher prevalence figures compared to the European and American studies due to the use of advanced corneal assessments such as corneal tomography which have been shown to be more sensitive in the diagnosis of KC[89,128]. This also highlights the contribution of ethnicity to the prevalence rates.

The Shahroud Eye Cohort Study of 2009 was a population-based study in Iran [37]. Random cluster sampling of people aged 40 to 64 years was done and the included informed consenting volunteers. The Holladay criteria was utilised for the diagnosis of KC. The sizeable sample group of 4589 participants considered for this study had more females (57.7%) than men (42.3%). This thought-provoking study is one of the few studies found that looks at an older age group. As KC is expected to have developed by this stage, the findings of this study can be considered a true representation of the prevalence of KC in the Iranian population as selecting an older age group ensures the value found does not under estimate the prevalence due to late diagnosis of the condition. The prevalence of KC in this study was found to be 730: 100 000 with 45% of these having bilateral KC. This is relatively low compared to other studies in the region. In this study 36% of the patients with KC had monocular KC, this can be explained by the notion that KC is an asymmetric condition[4,24,129]. That said, with this finding it is also plausible to suggest that KC can be a monocular condition considering the fact that in this age group, we would expect the progression of KC to have stopped[80,129] and so do not expect the fellow non-keratoconic eye to develop KC at this stage. The

large sample group is a strong quality of this study and the use of a thorough eye exam and Pentacam scans shows that the diagnosis of KC was well considered.

Although more females were recruited for this study, the difference between the male prevalence of 0.72% and the female prevalence of 0.79% is not statistically significant therefore challenges the gender specific aetiology argument for KC. 1.02% of the study group were diagnosed with form fruste keratoconus (FFKC). Combining FFKC and KC gives us a total prevalence of 1.75 % (830:100 000) which confirms the relatively higher prevalence of KC in the Middle East compared to the rest of the world. This is closer to 1.4% prevalence reported in a separate study in Iran of a younger population[55]. This finding contradicts reports that the prevalence of KC decreases with age[24] and rather suggests KC prevalence is consistent. The 1.75% is also comparable to the findings of a similar study in Egypt which reported a KC prevalence of 1.12% with an equal distribution between males and females[46].

2.2.3 Europe

KC prevalence studies in predominantly European communities report lower prevalence figures than those reported in Asian and Middle Eastern populations. A prevalence of 0.3% was reported in a retrospective study of the Netherlands medical records by Godefrooij et al. [69]. A large sample group of the general population aged between 10-40 years was considered making the findings plausible considering this is the age group in which KC diagnosis mostly occurs. However, a prevalence of 265:100 000 is relatively high for a predominantly Caucasian population when compared to studies in the USA. This may be due to the availability and accessibility of advanced diagnostic technology throughout the Netherlands which would make KC diagnosis easier and more accurate.

A separate retrospective study of the National Danish Patient Register reports a prevalence of 40:100 000 when considering people of Danish heritage and a slightly higher value of 44:100 000 when considering the general Danish population [70]. This was considered an increase in prevalence compared to previous records

which was explained by improved investigative techniques following the introduction of CXL. The Asian/Middle Eastern sub group of the Danish immigrants was found to have the highest prevalence of KC which is consistent with numerous reports of the highest prevalence of KC being in the Asian/Middle Easter populations[41,52,60,61]. Another retrospective study of 2254 subjects in Macedonia reported a KC prevalence of 6.8:100 000[68]. This remarkably low value may be due to a number of reasons; it is not clear from the write up the ocular assessments carried out and the guidelines applied for KC diagnosis. This value may be true as it is but also plausible to consider the condition as being underdiagnosed in Macedonia.

A UK based retrospective study of 382 medical records detailing KC patient information between 1989 and 1998 concluded that the prevalence of KC amongst Caucasians is 0.1% and that of Asians is 0.2% [60]. Although some of the records considered included volunteer's no-longer resident in the study setting at the time of the analysis, the information borne from the analysis pertaining to prevalence and the possibility of ethnic influence on the prevalence of KC is still valuable. A prevalence of 57:100 000 in the Caucasian community is more in line with expected findings such as those previously published prevalence of 0.05% reported following a 48 year-long study in Minnesota [25].

The study by Caputo et al. (2016) in Italy that focused on prevalence of KC in a high risk group of patients presenting at a hospital for vernal keratoconjunctivitis treatment reported a KC prevalence of 770: 100 000[130]. This is relatively low for such a high risk population compared to findings reported from similar populations in Africa[28,47,54,131] but high for a predominantly Caucasian population. The sample group of 651 considered in this study is expected to yield a higher value as these subjects are deemed to be susceptible to the development of KC. The age range of 7-23 years may result in a lower percentage than the true value as some may have not yet developed KC clinical signs for a positive diagnosis. 75.73% of the study group was males which is another weakness in the sample selection as it brings in a gender bias. Considering the

increased probability of finding KC patients in the high risk sample group under consideration, the reported prevalence value of 770:100 000; which is relatively high for a European country is still noteworthy and should be considered in its context.

Coincidentally, the KC prevalence in Italy is comparable to a prevalence of 750: 100 000 reported for the French population following a study of 670 males between the ages of 18 and 25 enlisted into the French army[51]. This study also utilised topography for the corneal assessment which may explain the increased findings of KC as it is more sensitive to the presence of KC than a SLE alone. However, this finding from the study of males only; that are known to have an increased risk of developing KC cannot be taken as the prevalence of KC in France due to flawed sample selection. It is also known that the French army includes a lot of African recruits from previous French colonies which may explain the relatively high prevalence of KC for a European population. Although suspiciously high, the findings were still lower than the 26 800: 100 000 prevalence reported in Turkey [119]. The study group in Turkey was much smaller with 82 subjects predominantly male that also utilised topography and the modified Rabinowitz-McDonnel for the diagnosis of KC. The method of analysis may explain the increased occurrence of KC but even with that, the variation is quite significant. This weakness can be attributed to the small sample size and skewed gender balance of the study population. The use of a high risk population; subjects with VKC, as the study sample means this value is not transferrable to the general populous. Generally speaking, the prevalence of KC in Europe can be considered to be lower than other locations such as Africa and the Middle East.

2.2.4 North and South America

One of the earliest reports on prevalence of KC was by Kennedy et al., (1986) following a retrospective study of patients in Minnesota. A prevalence of 54.5:100 000 was reported following a non-standardised subjective clinical diagnosis by ophthalmologist in the years between 1935 and 1982[25]. Although an insight into KC prevalence is delivered by this study the non-standardised approach in diagnosis and retrospective nature of the study may have resulted in the under-estimation of the prevalence of KC. Hofsetter et al.,

(1959) reported a higher prevalence of 600: 100 000 with no change in prevalence noted after the age of 40 years[44]. The higher prevalence may be due to the use of a keratoscope by Hofsetter et al. (1959) in the diagnosis of KC. The fact that the age group prevalence does not change after the age of forty ties in with the recommendation that KC tends to stabilise in the 3rd decade of life and no new cases are expected then[129,132]. A separate study of medical records in Minnesota by Reeves et al., (2009) reported a KC prevalence of 17.5: 100000. Although it has been proposed that KC prevalence does not vary with age; the senior age group (over 65 years) of the subjects may explain this relatively low figure as the condition is not acutely active at this stage and patients with the condition may not actively seek treatment for it.

A retrospective study in Mexico of 500 patients between 10 and 20 years old found a KC prevalence of 1.8% which converts to 1 800: 100 000[36]. In this study population, KC was more prevalent in females than males as was also seen by Hofsetter et al., (1959). This is the highest prevalence value reported in the region to date. However, the retrospective nature of the study does not include details on the criteria used for diagnosis and tests done to ascertain the reliability of this figure. As evidenced by the weaknesses of these studies detailed above, epidemiological studies on KC in the Western countries would offer some light on this unknown.

2.2.5 Asia Pacific

The Asia Pacific region has been highlighted along with the Middle Eastern territory as having a high prevalence for KC. One of the studies with findings that support this view point is the Central India eye and medical study by Jonas et al (2009). A large study of 4711 rural residents of Central Maharashtra aged 30 years and above was the first of its kind in the country. All the subjects underwent a detailed eye exam which included refraction, keratometry, tonometry, slit lamp exam, pachymetry and ultrasonography biometry. KC diagnosis was made if corneal power ≥48D. A prevalence of 2 300: 100 000 was reported[45]. This value is identical to the findings elsewhere reported by Millodot et al (2010) where they also found a

high prevalence of KC in Jerusalem. More advanced assessments such as topography and tomography may have resulted in a higher prevalence in this study as keratometry alone has been shown to under-diagnose KC. 2300:100 000 is significantly higher than the 229:100 000 prevalence reported amongst the Asian community resident in the United Kingdom by Pearson et al (2000). This variation brings into light the influence of the prevailing environment on KC prevalence.

KC incidence among Asian and Māori ethnic groups has been reported to be significantly higher than that seen in Caucasian populations[32,133,134]. A study of 1 916 students in New Zealand reported a KC prevalence of 520: 100 000[65]. The well thought out ocular exam in this study included refraction and pentacam scans with the BAD-D pentacam index used as the deciding factor in the diagnosis of KC[89]. This finding is comparable to the findings reported by Kennedy et al (1986) in Minnesota but is lower than what would have been expected given the ethnicity of the population under consideration and the use of more advanced examination tools such as the pentacam but can be a guiding figure as it is higher than what is proposed in old literature; 50: 100 000[23,25].

A large population based study of the South Korean population reported a KC prevalence of 0.04% which converts to 40: 100 000[58]. This finding strongly disputes the generalisation of high KC prevalence in the Asian population and highlights the importance of localised studies and the impact of geographical location. A separate population based study in Beijing of 3 468 patients that completed a comprehensive eye exam including an anterior segment OCT scan reported a KC prevalence of 0.96%; 960: 100 000[61]. In this study KC was diagnosed as corneal power ≥48D. The prevalence of KC in China is over twenty times that of South Korea despite their geographical proximity. The use of anterior surface optical coherence tomography (ASOCT) as part of the ocular assessment may have contributed to this difference as ASOCT is significantly more sensitive in the diagnosis of KC compared to topography[89].

2.3 Risk factors

The aetiology of KC is still an inconclusive topic but many factors have been identified as contributing factors that increase the risk of developing KC. Some literature suggests that an environmental factor is essential to act as a trigger in a genetically inclined individual [42] for KC to develop. However, this does not explain the individuals that develop KC despite the absence of the commonly associated symptoms such as eye rubbing and hence the need for continued research around this topic. Increased asymmetry between an individuals' pair of normal eyes may be the first sign noted in a KC suspect[135]. In this section, I will discuss several environmental factors that have been associated with an increased risk of KC development.

2.3.1 Eye rubbing and other mechanical abrasion

Eye rubbing has been implicated repeatedly as a causative factor for KC in various literature dating back to 1961[25,135–140]. Eye rubbing is said to occur in 84% of KC patients[141]. Bawazeer et al., (2000) assessed characteristics in 49 KC patients comparing them against 71 control patients and concluded that eye rubbing made a person 5.38 times more likely to develop KC than a non-rubber. Severe eye rubbing was documented in 70% of patients with KC by Ridley F (1961). This ideology is further supported by the findings of Karseras et al., (1976) that reported eye rubbing as the dominant aetiological factor of KC progression in 66% of KC patients [139]. A separate study by Korb et al., (2003) reported an even higher finding; 93.3% of KC patients rubbed their eyes extensively[138]. This is comparable to the findings reported by the Dundee University Scottish Keratoconus study (DUSKS) which found extensive eye rubbing in 89% of the 200 KC patients they assessed[5].

A case study of unilateral KC which developed in a patient that habitually rubbed that one eye because the other hand was occupied by work also supports the influence of eye rubbing on the development of KC [137]. The eye that was rubbed developed KC showing that the non-rubbed eye acted as a control. The healthy

eye with the same genetics was in the same environment, experienced that same diet and gets the same level of sun-protection and so the fact that it stayed healthy is a finding of this study that cannot be ignored. This notion has also been supported by a more recent analysis that analysed age and sex matched subjects with unilateral KC or asymmetric KC[142]. This questionnaire-based study convincingly found that eye rubbing and the subjects habitual sleep position contributed to the asymmetric nature of the condition. A review by Rabinowitz et al., (2021) also suggests that eye rubbing and eye compression act as a trigger for patients with a KC predisposition given the multifactorial nature of the condition which may have the same clinical signs but differing pathophysiology[143]. The CLEK study of 2007 which followed 1 209 patients across the USA found 50% of the KC patients they studied rubbed their eyes[81]. KC patients with VKC are known to rub their eyes a lot and were shown to have significantly thinner and steeper corneas in a study by Naderan et al., (2017)[122].

Corneal mechanical trauma secondary to hard contact lenses wear has also been highlighted as another causative factor for the development and progression of KC[140]. It has been noted to result in the apoptosis of keratocytes [144] and also increase protease inflammatory mediators such levels of Interleukins (IL6), Tumour necrosis factor (TNF α) and matrix metalloproteinase (MMP-13) that were measured in tear concentration before and after a controlled rubbing period [136,145–147]. An excess of activities that cause oxidative damage such as UV exposure, stimulate the degradation processes in the cornea as the cornea is unable to process reactive oxygen species due to a lack of enzymes such as aldehyde dehydrogenase catalase (ALDH 3) [148,149].This chain of events is also thought to be how eye rubbing contributes to the development and progression of KC.

A recent study of 166 subjects that evaluated risk factors for the development of KC concluded that CL use was insignificant in developing KC[38]. This is however a minority view as a review by Crawford et al., (2020) also linked CL use to ocular surface inflammation as the lens causes micro-trauma on contact with

the cornea. This is then intermediated by IL1 and other apoptotic mediators which result in the death of corneal keratocytes leading to reduced anterior and posterior keratocyte density[150]. An increase in inflammatory molecules and MMPs in the tear film due to CL use has also been documented along with reduced corneal nerve density[150]. These events along with CL induced dry eyes lead to an inevitable marked increase of inflammatory markers; a constant state of stress, in keratoconic CL users which can therefore not be excluded as a contributory factor to the severity of disease. It is plausible that loss of keratocytes also contributes to the collagen matrix remodelling that is characteristic of KC. The fact that KC progressions occurs regardless of CL use suggests that it is indeed a contributory factor to the presence of disease but not a causative factor.

A separate retrospective study of 199 patients connected CL wear to the use of CLs in 53 patients[151]. Prior to CL use, absence of KC had been established post a slit lamp exam, refraction, keratometry using a Bausch and Lomb keratometer and pachymetry. KC was defined as the presence of paracentral corneal steepening and thinning in this study. The ocular exam and corneal assessment performed prior to CL fitting in this study was too weak to conclusively exclude the presence of KC prior to the CL fitting. The subjects may have already had sub-clinical KC present but would not have been diagnosed through keratometry and a slit lamp exam giving a false negative. The study also suggested that it took an average of 12.2 years post CL fitting for KC to develop but without comparing this group to a control group, it is not reliable to say this would not have happened despite the use of contact lenses. The retrospective nature of the study also limited reliability of these findings as some key variables such as corneal thickness were only recorded in some of the patients and not all. It is therefore an inaccurate conclusion to blame KC development exclusively on the use of CLs. McMonies et al., (2016) suggest that trauma caused by eye rubbing prior to CL wear predisposes the affected cornea to an even more significant inflammatory reaction post CL use. The eye rubbing would have triggered wound healing activities that are then exaggerated in

response to CL use[152]. This line of thought is more consistent with other earlier publications; CLs may be a contributory factor but not a causative factor.

2.3.2 Atopy

Atopy (asthma, eczema, psoriasis, hay fever etc.) has been linked to the development of KC as numerous studies have found a higher incidence of these conditions in persons diagnosed with KC compared to the general population[5,153,154]. Atopy was reported to increase the chance of KC development by 3.67 times[29]. Karseras et al (1976) reported 32.6% patients of the 75 KC patients they assessed suffered from hay fever and 33.3% had asthma compared to 0.59% in the general population[139]. This finding is comparable to the report of 30% of KC patients having hay fever in the DUSKS [5]and is also supported by findings in recent studies which report atopic conditions in 44.1% of KC patients[65]. Atopy is reported to be more of a risk factor in the Caucasian race compared to Asians as it was documented in 38% of Caucasian KC patients in comparison to just 18% of Asian KC patients with asthma being highlighted as the most common form of atopy followed by eczema[32].

It is still unclear whether the atopic conditions have a separate effect on the cornea which compromises its integrity making it more susceptible to deformation or it's the eye rubbing linked to the presence of atopy which serves as the trigger for KC. Despite the lack of clear pathogenesis; Thyssen et al., (2017) concluded that adults with atopic dermatitis had a significantly increased risk of developing conjunctivitis, keratitis and KC compared with the general population. Their assessment of 10 038 cases of patients with mild to severe dermatitis showed that these subjects had a 10fold higher risk of developing KC compared to the general population[123]. The CLEK reported 53% of the KC patients had some type of atopic condition. The influence of eye rubbing was also confirmed following a literature review which awarded eye rubbing an odds ratio of 3.09 (95% CI: 2.17-4.00). This shows the strength of association between eye rubbing and

KC. These repeated links of atopic conditions to KC can therefore not be mere coincidence but a relevant consideration when assessing an individual for the risk of developing KC.

2.3.3 Ethnicity

Asian ethnicity has been associated with increased incidence of KC particularly those with deeper pigmentation e.g. Indians, Pakistan etc. compared to Caucasians resident in northern Europe and fair skinned Asians[32,60,155] . An analysis of 338 subjects, predominantly Asian or Caucasian in the Leicester area by Pearson et al (2000) offered some interesting findings. The well curated retrospective study over a ten year period evaluated patient records of those referred for a contact lens assessment or corneal graft. These groups are known to have a high incidence of KC and so was a good sample to characterise KC patients. They reported a KC prevalence of 29:100 000 for Caucasians compared to 138:100 000 for Asians residing in the UK[60]. In the 10-44 years age bracket, in which the condition is most active the prevalence was 229 per 100 000 for Asians and 57 per 100 000 for whites, a relative prevalence of 4 is to 1 in favour of the Asians. They reported a higher prevalence in males compared to females in both studies which is consistent with findings reported elsewhere[5,34,39–42]. The Asian patients were also younger at diagnosis compared to the Caucasian sub-group suggesting a more aggressive condition in the Asian community. This was also further supported by the fact that the Asians and black subjects were found to progress to corneal graft stage compared to the Caucasian subjects. Similar findings were reported in New Zealand where despite the fact that Caucasians constituted 60% of the study subjects; it was found that the Māori participants were more likely to have KC[65]. Given similarities in age, environments and lifestyles of the subjects recruited in the study, the differences in prevalence can only be attributed to the difference in ethnicity.

A 1994 study by Tuft et al., investigated factors that affect KC progression and found that ethnicity significantly shortened the time between diagnosis and need of a corneal graft[80]. Although Pearson et al.,

(2000) suggested that this was due to the black subjects presenting with more advanced disease at first presentation[60], this study of 2 723 patients over seven years showed that changes in keratometry, cylindrical refraction, visual acuity, ethnicity and age significantly contributed to the rate of progression of KC [80].Various researchers have looked into the prevalence of KC among subjects with VKC and have consistently found KC to be one of the debilitating conditions in the group[27,28,131]. Hashemi et al., (2020) in a systematic review of 29 articles concluded that atopy significantly increased the risk of developing KC[156]. Atopic conditions have been shown to be more prevalent in the black race and non-Caucasian communities[157–160] which then follows that KC will be more problematic in the black and non-Caucasian races. Not only does the severity of disease vary on racial lines; the overall genetic background and the genes responsible for atopic disease are different in each population although all heterogeneous disorders[160].

2.3.4 Genetics

A positive family history increases the risk of developing KC by 15-67 times [30,42]. Positive family history has been echoed as a significant risk factor by numerous studies including a study of 18 pairs of twins[37,135,161,162]. Although not all KC subjects have relatives with the condition; the incidence of KC has been shown to significantly increase in communities that practice consanguinity; children of consanguineous parents have a fourfold increased risk of developing KC compared with children of unrelated parents [33,162] further supporting a genetic link. When the parents are less closely related, the risk is reduced. Previous studies have inconsistently proposed modes of inheritance as autosomal dominant, autosomal recessive, sex linked and sporadic[6,163]. It has been proposed that various KC linked symptoms are actually varied phenotypic expressions of these genes hence the asymmetric nature of the condition[6,163]. A research team in China narrowed the gene pool to EPCAM, SHROOM3, SYNE1, TEK, and TTN as the

prospective pathogenic genes of familial KC after evaluating ten patients from five families suffering from KC[162]. Although not conclusive, the insights provided further support the influence of genetics in the development of KC.

Twin studies have generally supported a genetic link of the condition with reports of concordant monozygotic twins[161,164]. A study of 18pairs of twins; 13 monozygotic and five dizygotic, found that only one dizygotic twin pair was discordant for KC once again supporting the genetic link theorem. The more prevalent idiopathic KC events are reported to be heterogeneous in nature[141]. Collagen genes, interleukin-1 system genes and proteases system genes have been considered and excluded as causative by various research groups[163]. These exclusions are significant leaps towards establishing the associated genes.

A small section of the chromosome 21 gene between markers D21S1905 and D21S1409 has been positively implicated in the development of KC in patients with Down syndrome[163]. Significantly, 36 genomic loci (see Figure1 below) have been implicated in the development of KC as they result in the degeneration of the collagen matrix and affect the cell differentiation pathway thus causing disease[165]. The chromosomal regions 5q32-q33, 5q21.2, 14q11.2, 15q2.32 previously localised by Bisclegia et al. [166] were confirmed by Hardcastle et al. These leaps in genome sequencing don't only confirm genetic involvement but also offer valuable information on the pathogenesis of KC.

Region	Cytoband	Chr.	Coordinates	SNP	A1	A2	log(OR)	log(OR) SE	P-value	Genes within the region
1*	1q24.2	1	169018902..169073504	rs1200108	A	G	−0.163	0.026	4.52E−10	***ATP1B1***
2*	1q25.1	1	174990905..175010262	rs6669560	T	C	0.156	0.026	2.92E−09	***MRPS14***
3*	1p22.2	1	207981419..208022291	rs761276	A	G	−0.137	0.024	8.02E−09	*CD34*,***CD46***
4*	2q22.1	2	141867420..141878395	rs116792882	T	C	−0.686	0.110	4.82E−10	***LRP1B***
5	3q26.31	3	171565463..172000456	rs4894414	T	C	0.304	0.029	1.21E−26	***FNDC3B***,*TMEM212*
6	5q11.2	5	52424518..52631507	rs12515400	T	C	0.217	0.025	3.16E−18	*FST*,***ITGA2***,*MOCS2*
7	5q23.2	5	121269498..121426675	rs840464	T	G	0.233	0.025	1.72E−20	*SREBP1*,***LOX***
8*	6p12.3	6	50788778..51623864	rs6904450	A	T	−0.189	0.029	6.44E−11	***TFAP2B***,*PKHD1*
9	6q13	6	75746765..75834971	rs35523808	A	T	0.662	0.064	2.90E−25	***COL12A1***
10	8q22.1	8	95832448..95992020	rs1453379	T	C	0.156	0.025	3.32E−10	*TPS3INP1*,*CCNE2*,*INTS8*,***NDUFAF6***
11	9p23	9	13533300..13596674	rs1324175	T	C	−0.244	0.027	2.59E−19	No Gene
12	9q31.3	9	111372592..111500353	rs2417930	T	C	0.162	0.024	2.62E−11	***ACTL7B***
13	9q34.3	9	137412655..137566891	rs3118518	A	G	0.270	0.024	1.83E−28	***COL5A1***,*RXRA*
14	9q34.3	9	139830733..139866247	rs11145948	A	G	0.173	0.025	9.89E−12	***FBXW5***,*PTGDS*,*C8G*,*LCN12*
15*	10q21.1	10	55196113..55196113	rs117905623	T	C	−0.381	0.068	1.89E−08	No Gene
16*	10q26.11	10	120765171..120877372	rs658352	T	C	0.176	0.025	3.71E−12	*NANOS1*,*FAM45B*,***EIF3A***
17	11p15.5	11	721570..825777	rs7117921	T	C	0.265	0.025	1.09E−26	*CEND1*,*TALDO1*,*EPS8L2*,*PDDC1*,***PIDD***, *PNPLA2*,*RPLP2*,*SLC25A22*
18*	11q21	11	95308854..95308854	rs11021221	A	T	0.204	0.034	1.49E−09	***FAM76B***
19*	12p13.1	12	14288423..14290517	rs17340879	T	C	−0.493	0.082	1.77E−09	***GRIN2B***
20*	12q13.13	12	51754629..51756269	rs3782473	T	C	0.172	0.028	6.60E−10	***GALNT6***
21	13q14.11	13	41049191..41950539	rs2721051	T	C	0.452	0.037	5.71E-35	*MRPS31*,*MTRF1*,*NAA16*, *SLC25A15*,*ELF1*, ***FOXO1***, *WBP4*
22*	13q22.1	13	73634051..73649152	rs17285550	A	G	−0.181	0.026	2.84E−12	***KLF5***
23	15q21.2	15	51153797..51375011	rs11634895	A	G	−0.146	0.024	7.88E−10	*AP4E1*,***TNFAIP8L3***
24*	15q22.2	15	61038143..61038143	rs76194223	T	C	0.258	0.046	1.75E−08	***RORA***
25	15q22.33	15	67438586..67694780	rs12912010	T	G	−0.312	0.029	1.99E−26	*AAGAB*,*IQCH*,***SMAD3***
26	16q24.2	16	88274115..88344517	rs11117401	A	G	0.236	0.026	3.68E−20	*BANP*,***ZNF469***
27*	17p13.2	17	4824625..4997433	rs12603055	C	G	−0.234	0.031	2.23E-14	*CHRNE*,*GP1BA*,*ZFP3*,*CAMTA2*,*ENO3*,*INCA1*, ***KIF1C***, *PFN1*,*RNF167*,*SLC52A1*,*SPAG7*
28*	17p11.2	17	19619441..19653310	rs4646785	T	C	−0.197	0.029	9.01E−12	***ALDH3A1***,*SLC47A2*
29*	17q11.2	17	29883190..29889952	rs56161228	A	G	−0.210	0.033	2.70E−10	***RAB11FIP4***
30*	17q21.32	17	46328667..46645394	rs12948086	T	C	0.165	0.028	5.33E−09	*HOXB1*,*HOXB2*,*HOXB3*,***SKAP1***
31*	17q21.33	17	48244531..48269903	rs2075556	C	G	−0.191	0.032	3.35E−09	***COL1A1***,*SGCA*
32*	20p13	20	2076016..2143379	rs6106210	T	C	0.172	0.026	2.85E−11	***STK35***
33*	20q13.31	21	25357226..25357226	rs76747345	A	G	−0.545	0.080	6.53E−12	***NA***
34*	21q21.3	21	29521741..29623259	rs2143683	T	C	0.185	0.027	3.51E−12	No Gene
35*	21q22.3	21	47154348..47420667	rs142493024	A	G	0.760	0.111	9.07E−12	***COL6A1***,*PCBP3*
36*	22q11.21	22	21322888..21323369	rs756878	T	C	0.159	0.027	4.01E−09	***AIFM3***

Figure 1: 36 genes identified in the genome-wide association study of KC[165]

A 10-year longitudinal study of 369 patients in California showed that family history, gender, race and baseline corneal curvature were significantly associated with progression[132]. Li et al., (2007) reported that diagnostic KC indices such as central corneal curvature, I-S and KISA are significantly higher in normal relatives of KC patients compared to normal controls. 14% of the subjects followed in the CLEK study had a positive family history for KC[81].This finding is similar to the 10% genetic link reported by McMonnies et al., (2014). A separate study in which 150 patients with positive family history for KC were screened for KC; 14% were diagnosed with KC[30]. This finding is consistent with other figures previously reported and confirms a genetic link to KC diagnosis. Some studies suggest that the percentage of patients with KC that have at-least one relative affected too can be as high as 50% [14].

Genetic studies of KC are ongoing with the hereditary trait proposed to be autosomal dominant although a recessive mode of inheritance has not been ruled out[14]. Various mutations and genetic locations have been implicated as the cause of KC but nothing conclusive is yet to be established[14]. KC has been linked to

certain genetic disorders such as Leber congenital amaurosis (LCA), Down's syndrome and osteogenesis imperfecta[163,167,168]. The CRB1 gene has been identified as defective in LCA and was associated with a spectrum of KC presentations and thus implicated as a possible site for KC linked mutations[167]. The insightful publication by McMahon et al., (2009) looked at 16 subjects with LCA and found that 43.8% of the subjects had either KC or keratoglobus making their suggestion of a genetic link plausible. Evaluation of patients living with Down's syndrome found that 54%-60% of the subjects had astigmatism[169,170]. Although the researchers in another study did not look for KC explicitly, they reported that 39.8% of the subjects had KC[26]; it follows that in some of these refractive error cases the astigmatism may be KC-linked. It is still important to remember that most of KC cases are idiopathic and occur in patients without any family history of the condition.

2.3.5 Age

A 2012 retrospective study by Léoni-Mesplié et al. looked at 216 patients over a period of 2 years[171]. In this study the average age of diagnosis in children was 13.1±2.1 years but the youngest diagnosis occurred at 6 years of age. This is consistent with earlier publications that found that the highest rates of incidence of KC were in the younger populations[25]. In this study more than 80% of the children were classified as stage 2 KC or worse according to Krumeich's classification with 24.2% classified as stage 4 at presentation. Only 7.8% of the adults considered were classified as stage4 at diagnosis. 42.9% of the paediatric patients had ophthalmoscopic signs of keratoconus compared to 29.5% of adult patients signifying more advanced disease in the paediatric sub-group. 78.8% of these children were reported as having a significant chance of progression with at-least one stage change noted in less than 2 years. 21% were noted to have progressed within six months of diagnosis. This study demonstrated that paediatric KC is likely to be more advanced at diagnosis and changes more over a period of time compared to KC in adults. The average radius of

curvature changed by 1.98D ± 0.59 D in children compared to 0.47D ±0.28 D in adults in the two year follow up period.

A separate study which speaks to more consequential disease in children demonstrated that advanced KC was more destructive and resolved with neovascularisation in younger patients compared to adult patients[172]. This finding is supported by Ertan et al., (2008) who found that KC severity was inversely linked to age as their study showed severe KC occurred in people under the age 40 years[40]. The CLEK also linked young age to increased severity of the condition[81]. The Caucasian mean age of diagnosis is 26.5±8.5 years compared to Asians with an average age of diagnosis at 22.3 ±6.5 years[60]. Interestingly the age of diagnosis seems to be later in Caucasians compared to other ethnicities[60,81]. The Dundee University Scottish Keratoconus Study (DUSKS) reported a similar higher age of diagnosis; 24±8.9 years for Caucasians[5]. All KC stages have the potential to progress regardless of age but the disease has been shown to be more aggressive in children compared to adults.

2.3.6 Ultra violet radiation exposure

The highest incidence and prevalence of KC has been reported in the Middle East and Egypt which are predominantly characterised by clear skies and very hot dry days for majority of the year[34,35,47–50]. These conditions are synonymous with excessive UV exposure which is believed to be one of reasons for the increased prevalence of KC in the region[148,173].

The cornea is known to provide vital protection against the elements by absorbing UVB rays. Ultra violet radiation (UVR) exposure has been implicated in the generation of free radicals and active oxygen species which can initiate lipid peroxidation resulting in the formation of cytotoxic species.[148] ALDH and alcohol dehydrogenase (ADH) are corneal enzymes that play a role in the metabolism and clearance of these

cytotoxic species in the event of UVR exposure. These reactive oxygen species are known to play a role in the pathogenesis of KC[149].

UVR was clearly shown to have direct effects on the concentrations of ALDH and ADH by Downes et al., (1993). Following excessive exposure to UVR with a 302nm peak, corneal enzyme activity was shown to decrease within one day of exposure and continued to decrease to 15% of the original pre-exposure concentrations. During this period of reduced enzyme activity, the cornea is therefore vulnerable to degradation by the cytotoxic species generated by the same exposure to UVR. This was evidenced by the development of corneal haze and scarring in the affected corneas whilst control corneas remained clear and healthy in this well designed study. The ALDH and ADH levels only began to recover after day 8 with only 70% and 40%, of the pre-exposure concentrations reached respectively. Continued UV exposure would therefore be very detrimental in the long run as the cornea is unable to process reactive oxygen species in the absence of sufficient enzymes such as ALDH 3 and ADH.

UVR is predominantly absorbed by the epithelial layer[148], and when not absorbed it results in stromal swelling due to defective endothelial layer function. This also clearly demonstrates the negative effects of UVR on corneal health. Such continued and repeated distress would certainly make the cornea susceptible to ectatic disease.

2.3.7 Gender

Various studies have shown KC to be more prevalent in males than females with an average 60:40 ratio[24,163,174]. Some researchers however, have found no gender preference [25,35,37,38]. Debatably, a separate study of an adolescent population found KC to be more prevalent amongst the females (66%) compared to males (33.3%)[36]. Similarly, an Indian based study of 4711 subjects above 30 years of age found KC to be more prevalent among females than males[45]. These two studies are quite unique as both studies predominantly report a higher prevalence amongst males compared to females by varying degrees. A 5

times increased risk for developing KC in males is the highest relative risk factor reported to date [5,24,34,39–41]. Fink et al.,(2005) go a step further and suggest differences in signs and symptoms exist between genders when KC is concerned[7]. From these observations we find that gender does have some influence on the condition but is not a core irrefutable risk factor as it is likely influenced by the presence of other known risk factors for it to have an impact on the disease.

2.3.8 Visual performance

One of the main symptoms of KC is reduced visual acuity. KC patients have been shown to be myopic[45,175,176] with high astigmatism[177]. KC is known to significantly reduce visual function by affecting both visual acuity and contrast sensitivity[176]. A variable endpoint on subjective refraction has long been appreciated as a reason to investigate for the presence of KC. Variable visual acuity measurements and subjective refraction end points are characteristic of KC patients[176]. Best corrected visual acuity is reduced when measured on a low contrast chart compared to when measured on a high contrast visual acuity chart[176]. Zadnik et al., (1987) found that irregular astigmatism persists in KC patients despite optical correction with hard lenses[178]. This may explain the continued dissatisfaction with visual performance reported by KC patients. It has also been shown that the subjective refraction result can fluctuate in the presence of KC by more than 3.00D[177,179] on different days. This may explain the reduced satisfaction experienced by KC patients even with their best correction on. Auto-refraction is the least repeatable method of establishing the refractive error in the presence of KC[179,180]. The unreliability and poor repeatability of auto-refraction is more apparent in the presence of advanced KC[177].

These variations in visual performance may be due to the presence of aberrations related to the cone position[181]. In an assessment of 100 eyes, it was found that higher order aberrations up to the 6th Zernike order correlated with the severity of the disease and the location of the cone[181]. In the presence of off-axis

cones, a shift in the line of sight occurs thus reducing visual performance[181]. In a separate comparison of 80 keratoconic eyes to 81 healthy eyes, Colak et al., also reported that high order aberrations, coma and spherical aberrations were higher in the keratoconic eyes[182]. Aberrations are unwanted characteristics of optical structures that negatively affect quality of vision; therefore, it follows that visual performance is reduced in the presence of KC.

In an assessment of 126 subjects aged between 11-75 years, retinoscopy was compared to topography, tomography, biomechanical analysis and the Amsler Krumeich scale in classifying KC[183]. This well thought out evaluation found that all four methods were not comparable in classifying KC. Retinoscopy consistently identified normal eyes as did topography, tomography and biomechanical measurements. It however did not consistently identify the presence of KC. A scissors reflex is a non-uniform reflection observed in the presence of an irregular cornea. A myopic central cornea compared to a different periphery results in an 'against' movement being observed centrally and a 'with' movement being observed at the periphery; this is then termed a scissors reflex[183]. Scissors reflex occurs due to differences in optical correction over the corneal surface which are only evident in advanced disease with prominent cones and difficult to detect in early disease[183]. This is consistent with findings reported elsewhere; scissors reflex is an indicator of medium to advanced corneal ectasia [184]. Retinoscopy underestimates KC stages when compared to topography[183], it therefore would not be a good stand-alone tool for the early detection of KC. Subjective refraction is considered as the gold standard of refractive error assessment as it offers more repeatable results than auto-refraction[185]. It is therefore important that when KC is suspected, the subject undergo a detailed subjective assessment.

Contrast sensitivity has been shown to be affected in the presence of KC[186]. An evaluation of CS in normal subjects was compared to the same measurements in subjects with early KC and registered as significantly lower in the keratoconic subgroup despite both groups having good LogMar visual acuity[186]. CS

successfully differentiated normal subjects from the subjects with KC. Abnormal visual function was convincingly reported post examination of a group of KC and normal subjects. Statistically significant differences were noted in the measurement of visual acuity, refractive error, keratometric readings, thinnest corneal thickness, central corneal thickness and for some other higher order abberations[186] CS was shown to be affected earlier than VA thus making it a good variable for the early diagnosis of KC[186–188]. It therefore follows that glare sensitivity is significant in the presence of KC as reported by Pesudov et al., (2003).

2.3.9 Diet

Body nutrition has long been implicated in the development of KC. Certain nutrients are known to play a key role in maintaining the integral structure of the cornea. Vitamin D is necessary for the production and maintenance of corneal integrity including endothelial cell survival[189]. Vitamin D has also been shown to maintain the epithelial barrier function in the cornea[190]. In KC epithelial layer integrity is one of the first microscopic signs noted prior to the development of irreversible corneal changes that are typical of clinical KC[94,95]. Vitamin D also plays an anti-inflammatory and anti-microbial role in the cornea[191]such that a Vitamin D deficient diet is accompanied by corneal changes[192]. Keratoconic patients have been shown to have lower serum levels of vitamin D[189,193,194]. Research has shown that the likelihood of developing KC increases when Vitamin D blood serum concentrations are below 10ng/ml[191]. Interestingly, in the human body UV exposure is necessary for vitamin D production and utilisation of calcium. However, production of hyper reactive oxidative species and alterations in the processing of these radical species produced secondary to oxidative stress in the presence of UV radiation results in ectatic corneal diseases such as KC[191]. This shows the importance of balance; too much UV can be detrimental to the health of the cornea but too little can lead to reduced vitamin D levels which can also be detrimental to the health of the cornea.

Vitamin C also plays a key role in maintaining the health of the cornea. It is necessary for wound healing and collagen fibril synthesis. Various micro-nutrients found in the tear film and corneal layers are paramount for the corneal eco-system to thrive. The vitamin C concentration has been shown to be increased in keratoconic patients suggesting its presence is a result of an adaptive response to oxidative stress and impaired collagen synthesis and flawed cross-linking between fibrils[193]. This would also partially explain the aetiology of KC which is characterised by reduced corneal hysterisis[101,103]. Vitamin A, vitamin B9 and B12 have also been implicated in KC pathogenesis[193]. Vitamin A; similar to vitamin C, plays an important role in the structural collagen fibril networking. Interestingly, research has shown that blood serum concentrations of vitamin B9 and B12 are not altered in the presence of KC.

It then follows that nutritional cofactors of all micro-nutrients necessary for collagen fabrication and structural organisation can be considered an independent variable in the development of KC. Copper, Zinc, Selenium and Iron have been shown to be below expected levels in KC patients[194]. An analysis of the Fleischer ring; a clinical corneal sign characteristic of the condition, found ciron ions in the ring[194]. Iron is a necessary co-factor in the collagen cross-linking process. Keratoconic patients have shown lower levels of binding proteins which may explain the co-existence with copper in the Fleischer ring[195].

All these micro and macro-nutritional disturbances essentially affect the collagen production and cross-linking process leading to a weaker corneal structure susceptible to changes. This explains why the collagen-crosslinking procedure has been instrumental in the management of KC[74,75]

2.3.10 Vernal keratoconjunctivitis

KC can develop secondary to persistent VKC. As high as over a quarter of VKC patients have been shown to have clinical KC with an even higher portion found to have corneal topography abnormalities[27]. VKC is also reported to result in a KC variation that is more aggressive with faster progression[27]. In addition to causing more advanced disease, VKC patients experience a higher rate of post-surgical complications in the

management of KC. This may be due to the inflammatory nature of VKC, largely typified as an allergic reaction with varying degrees of severity characterised by the presence of immunoglobulins and other immune-active cells[196]. This suggests the need for earlier interventions in this subgroup so as to minimise the need for surgical interventions. Interestingly a recent study in Italy found a very low KC prevalence of less than 1% among 651 VKC patients aged between 7 and 23 years of age. The sizeable study applied advanced corneal assessment methods sensitive for early KC diagnosis and therefore prove that the prevalence of KC in this patient subgroup depends on the existence of other KC risk factors such as ethnicity and environment. The presence of VKC should certainly warrant further assessment as numerous studies reported clinical signs consistent with KC and topographical abnormalities in different populations ranging between 11% and 26.8%[119,197–199] The presence of corneal topography abnormalities also suggests that VKC corneal structures patients can morph into any corneal ectasia making it important for these patients to have regular corneal assessments.

In a separate study in Kenya, 31% of subjects with allergic conjunctivitis were found to have corneal topography abnormalities consistent with KC[54]. The big difference between the findings in Italy reported above and this Kenyan based study shows the importance of considering VKC along with other variables such as race and location. Two separate studies in Gambia and Nigeria also report varying degrees of KC in patients with allergic conjunctivitis, 7.9% and 1.1% respectively further highlighting the need for tailored consideration of the condition[66,200].

2.4 Research tool

A written survey; a modified Keratoconus risk investigative survey (KRIS) [201] was generated for this study. The modified KRIS had sections to capture the subject details for analysis. The survey comprised a section detailing subjects' age, ethnicity, religion and residential location. It was then followed by ten questions on personal ocular history, family ocular history, and parent's educational background which helped ascertain

social status. The ten questions also included enquiries on diet, computer use, eye rubbing and weekly UVR exposure by way of time spent in the outdoors in the sunlight. Lastly the survey had four questions enquiring on systemic conditions and atopy. It was ascertained in the literature review that the risk factors for the development of KC include age, family history, VKC, atopy, eye rubbing, UVR exposure and systemic conditions such as Down's syndrome[24,52,202–204] making this tool an appropriate instrument to determine the theoretical risk of developing KC.

A KCR score was awarded based on the total risk factors embodied by the subject along with clinical findings from an anterior segment assessment. Affluent is defined as having both parents with tertiary education. In low-resource communities, it has been shown that parents education level has great influence on achievements, success and socioeconomic standing [205,206]. Healthy is defined as eating a diet inclusive of meat, fish, fruit and vegetables at-least three times per week[207,208]. High UV exposure is defined as being outdoors an excess of 8hours/week. UV exposure in excess of 4-10hours/day has been shown to be detrimental to skin-health (34,35). High VDU use was defined as screen time in excess of 8hours/week. The American paediatric association recommends a maximum of 1 to 2hours/day of screen time and replacing screen time with outdoor activities [210–212].

2.5 Instruments

Corneal imaging has improved in leaps and bounds since the advent of refractive surgery. It continues to change in proportion to the increase in popularity of refractive surgery. Corneal topography and tomography instruments are continuously being updated to improve on accuracy of the results obtained and amount of detail we can appreciate of the corneal characteristics in each captured image. Corneal topography is the analysis of the corneal surface silhouette and corneal tomography is an analysis of the three-dimensional cross-section of the cornea[213]. As displayed in figure 2 below, topographers and

tomographers generate differing degrees of information which can complement each other to formulate a complete picture of the health of the cornea. The Topcon RT-7000 is an example of a reflection based corneal topographer that can detail corneal curvature, corneal power, dry eye assessment and corneal centre displacement. The Optovue RTVue is an example of an anterior segment optical coherence tomographer (ASOCT) that offers information on corneal pachymetry. The Optovue has been shown to slightly overestimates central corneal thickness by 7-13µm compared to the Pentacam and ultrasound pachymetry[214]. Measurements of the minimum corneal thickness were comparable to the Pentacam and ultrasound pachymetry[214].

Description	Centre displacement	Epithelial changes	Anterior surface analysis	Posterior surface analysis	Pachymetry map	Corneal Hysteresis
Reflection based topographer	√		√	√[a]		
Elevation based systems	√		√	√	√	
UHR Ultrasound		√			√	
AS OCT[b]		√[a]	√	√	√	
ORA[b]						√
Corvis ST[b]						√

[a] only available with specific models.
[b] AS OCT-Anterior segment OCT; ORA- Ocular response analyser; Corvist ST- Corneal visualisation Scheimpflug technology.

Figure 2: Table detailing corneal imaging instruments adopted from elsewhere[89]

2.6 Algorithmic approach

An algorithm is a detailing of the itemised process to be followed to solve a problem. Algorithms have been applied in medical practice as a fail-proof and standardised way of managing various conditions such as chronic pain, glaucoma, dementia; just to mention a few[215–217].Great successes have been realised by the application of diagnostic and management algorithms in daily clinical practice[218].

An algorithm for the management of clinical KC has previously been detailed elsewhere [77]. It proffers options for the management of KC with acceptable VA as the main guiding factor. A noted weakness of the algorithm is the use of 'acceptable VA' as a benchmark as this is very subjective variable. In addition, this algorithm only focuses on the management of established and advanced disease characterised by very thin corneas and scarring. It excludes the management of pre-clinical and early KC. The algorithm does not cover the diagnostic process of identifying KC. Mohadmmadpour et al., (2018) present a KC management algorithm detailing the surgical options taking corneal thickness into consideration[219]. This review also focuses on surgical management of established disease. It does not include procedures to be followed in the diagnosis of KC and management of early disease.

The development of an algorithm starts with the identification of a problem requiring a solution followed by the pattern identification around the topic of interest[220]. This important step allows for observations around a recurring phenomenon to be characterised. Once a pattern is identified one then implements a process of refining the information around the pattern, selecting the key components and identifying unique variables that enhance the process[221].

Treatment algorithms can increase access to care and standardise management protocols for conditions. This is particularly important in low resource settings where resources have to be consumed sparingly. The literature search did not yield any algorithms developed for low resource settings showing it's a novel area with much potential to be explored.

2.7 Conclusion

The prevalence of KC ranges between 0.2: 100 000 and 4790: 100 000. The lowest prevalence of KC has been reported in Europe and the highest rate recorded in the Middle East. The prevalence in Africa appears

to be under 1 000: 1000. KC is more prevalent in Asians and people of colour compared to Caucasians. To the researcher's knowledge, there are no population studies on the prevalence of KC in African countries. The prevalence studies on the African continent have been generated from high-risk populations making them non-transferable to the general population. KC risk factors include a genetic link to KC, Down's syndrome, eye rubbing, atopy, nutritional deficiencies and VKC. Visual performance is affected in the presence of KC due to reduced visual acuity, reduced contrast sensitivity and increased aberrations. Clinical instruments that detail anterior and posterior corneal stroma layers offer superior diagnostic abilities in the diagnosis of KC. Other parameters such as fluctuations in refractive error and reduced CS can also be instrumental in the early diagnosis of KC. Vogt's striae and steep keratometry are the most frequently encountered clinical signs in KC investigations. The method of evaluation has an impact on the diagnosis concluded and should therefore be considered carefully in prevalence studies.

Chapter 3: METHODOLOGY

3.1 Introduction

The aim of the study was to develop an algorithm for the identification of pre-clinical and early clinical keratoconus in children in urban Harare. The study process followed a group of subjects from the wider reaching community of primary school children in Harare that were narrowed down to a few pre-selected schools. Consenting subjects from the school were then walked through a two phase analysis which primarily screened for children at risk of developing KC then assessed the selected for the presence of clinical or pre-clinical KC.

The screening process involved the use of a questionnaire and a school-based examination routine that was guided by pre-existing knowledge of KC risk factors as detailed in literature. The school screening procedure was developed for this study and this was the first time it was applied. Subjects considered to be at risk of developing KC were then invited to get a standard comprehensive eye exam delivered at the university optometry clinic when routinely investigating for KC. This marked the end of the phase 1 analysis. Phase 2 comprised of non-routine assessments that were chosen for their abilities to identify clinical findings deemed to characterise KC suspects as detailed in literature.

This protocol evaluated the presence and severity of the risk factors of KC previously detailed in chapter 2. As the study was focusing on determining the prevalence of KC and detecting early disease, the clinical findings associated with the disease in both clinical and pre-clinical KC were researched and documented. In this chapter I shall detail the process and procedures carried out to establish an algorithm for the early detection and management of KC.

3.2 Study design

This study used a quantitative, cross sectional, analytical design.

3.3 Study site

The study site was Harare, Zimbabwe.

3.4 Study population

The study population comprised of school students aged between 6 and 12 years resident in suburban Harare.

3.5 Study sample and size

Stratified random sampling was employed to first divide the primary schools found in Harare by geographical location (North; South; East and West). One school was then randomly selected from each location. The minimum sample size (n) for a 5% level of significance calculated using Dobson's formula is:

$$n= (Z2 \times (p) \times (1-p))/\varepsilon 2$$

Where Z= the critical value for a normal distribution at 5% level of significance; p= expected prevalence of keratoconus in the target population; ε = margin of error. Hence,

n = (1.962 x (0.5) x (1-0.5))/0.052 = 424 after adjusting for 10% attrition rate.

3.6 Inclusion and exclusion criteria

Inclusion criterion:

- Children who presented completed and signed consent and assent forms
- Boys and girls who have turned 6 and have not yet turned 13 years at the time of collecting the data
- Children resident in Harare

Exclusion criterion:

- Positive history for ocular surgery and/or trauma
- Children attending a selected school but reside outside of Harare

3.7 Data collection tools

3.7.1 Objective 1: Determine the risk profile of children with keratoconus in urban Harare

- The study used the KRIS, which was modified to 14 questions specifically tailored to identify and quantify the risk factors associated with KC in urban Harare (Appendix 1a).
- A clinical demographic profile and clinical screening form that included demographic information, information on ocular history, family history, general health history, environmental considerations, visual acuity, VKC signs, corneal curvature, corneal thickness, contrast sensitivity and retinoscopy findings (Appendix 2a, 2c and 2d).
- Each known risk factor was awarded a score which was tabulated to quantify the overall risk the subject had to develop KC. A keratoconus risk (KCR) score sheet was developed to quantify the information obtained from the questionnaire and eye screening into a single KCR score that was then used to manage the subject appropriately (Table 5).

Table 3 The KCR score sheet

Parameter	Score
Positive family history of KC	3
Positive for Down Syndrome	3
Positive for eye rubbing	3
Positive for retinoscopy scissors reflex	3
Positive for vernal conjunctivitis (corneal haze, papillary reaction, limbitis)	2
VA of 6/9 or worse in at-least one eye	2
Positive for atopy	2
Positive family history of spectacle use	1
Positive for asthma/hay fever	1
Positive for itchy eyes	1

3.7. 2 Objective 2: Determine the prevalence of keratoconus in children in urban Harare, Zimbabwe

A checklist containing a list of possible clinical findings in the presence of KC was developed (Appendix 2c). One needed to have both a corneal abnormality evident on slit lamp analysis; namely Fleischer's ring, Vogt's striae, corneal scarring, Munson sign, and steep corneal curvature to be diagnosed with a keratometer.

Various KC grading scales are available for use in day to day clinical practice. The researcher chose to be guided by the Amsler-Krumeich grading scale as classification by the Amsler-Krumeich system has been shown to correlate and agree with other classification systems such as the Keratoconus severity score[222]. It is also the most appropriate for use in the study's setting, a resource constrained clinic.

The recently published ABCD grading system is a modern classification system which takes steepening of the posterior cornea into consideration in the classification of KC[22,155]. The steepening of the posterior cornea is only measurable by advanced corneal imaging methods[89] which are not readily available everywhere, making this grading system inapplicable at primary care levels within low resource settings, such as the case with the study sites. The Amsler-Krumeich grading scale (Figure 2), classifies KC into four stages by severity. In this study the researcher defined up to stage II of KC as early (mild) KC as CXL is still an option for the management of the disease at this stage and the impact on best corrected visual acuity is relatively minimal[72,75,223].

I stage	• Eccentric corneal steepening • Induced myopia and/or astigmatism <5 D • Average K value <48 D
II stage	• Induced myopia and/or astigmatism >5 D, <8 D • Average K value <53 D • No central scars • Corneal thickness >400 µm
III stage	• Induced myopia and/or astigmatism >5 D, <10 D • Average K value >53 D • No central scars • Corneal thickness 300 – 400 µm
IV stage	• Refraction not measurable • Average K value >55 D • Central scars, perforation • Corneal thickness 200 µm

Figure 3: The Amsler-Krumeich KC classification scale[223]

Previous publications also found central corneal thickness, thinnest corneal thickness and contrast sensitivity to be affected by KC[187,222–225]. Thinnest corneal thickness was reliably used to distinguish between different classes of KC by severity[222,224]. Naderan et al., (2015) report that central corneal thickness and apical corneal thickness are key parameters in distinguishing subclinical KC from clinical KC. Contrast sensitivity loss may be present even in the presence of normal Snellen visual acuity[187,223]. It is therefore an important screening tool in the event that KC is suspected but visual acuity measurements are within normal limits. Corneal volume and anterior chamber depth are only noticeable in advanced disease[222,224]

3.7.3 Objective 3: Document the pre-clinical signs of keratoconus in children identified as high risk for keratoconus

A yes or no checklist containing early signs of KC was developed (Appendix 2d). The list contained subliminal corneal changes that pre-date clinical KC signs namely changes in contrast sensitivity and as evidenced by advanced corneal imaging techniques which included topographical changes, changes in corneal thickness and the displacement of the corneal centre.

3.7.4 Objective 4: Determine the age most associated with early signs of keratoconus in children living in urban Harare

A demographics questionnaire detailing KC risk factors such as race, religion and age was used to collate this information. An analysis of the occurrence of early signs of KC was performed. Chi-square test was used to determine the association between presence of keratoconus and the age categories.

3.7.5 Objective 5: Develop an algorithmic approach for the early detection of keratoconus

The findings from objective 1-4 were collated and applied to inform and accomplish objective 5.

3.7.6 Modified KRIS questionnaire formulation

As the KRIS questionnaire was a key tool in the school screening, the table below details how the verified KRIS questionnaire was modified to suit the objectives of this study.

Table 4 Modified KRIS questionnaire[201] formulation

KRIS question investigation	Fate	Reason for exclusion
1. Establish knowledge of KC?	Kept	
2. Establish depth of knowledge of KC?	Kept	
3. Establish family history of KC?	Kept	
4. Establish climate?	Left out	Study was based in Zimbabwe so this was considered known information.
5. Establish depth of winter months in country?	Left out	Study was based in Zimbabwe so this was considered known information.
6. Establish depth of warm climate in home country?	Left out	Study was based in Zimbabwe concentrating on Zimbabwean subjects so this was considered known information.
7. Extent of sun exposure in a week?	Kept	
8. Frequency of the use of sun protection?	Kept	
9. Establishment of consanguinity?	Left out	This would be asked in the comprehensive eye exam as part of the case history
10. Father's education level?	Kept	
11. Mother's education level?	Kept	
12. Quantification of screen time?	Kept	
13. Information on home diet?	Kept	
14. Information on nutrient deficiencies?	Left out	This would be asked in the comprehensive exam as part of the case history.
15. Use of school feeding program?	Left out	There is no school feeding program in Zimbabwe.
16. Use of government assistance program?	Left out	Not relevant to our location.

17. Depth of knowledge on listed nutrients?	Left out	Information is outside the scope of this study
18. Presence of any atopic conditions?	Kept	It was however worded differently for easier completion of the question.
19. Depth of knowledge on eye conditions?	Left out	Information requested is outside the scope of this study
20. History of general systematic conditions?	Left out	Deemed insensitive by the Medicines research council of ZWE for the questionnaire so was asked in person during comprehensive eye exam.
21. Frequency of eye rubbing	Kept	
22. Severity of eye rubbing?	Left out	Information gathered is outside the latitude of this study
23. Eye frequently rubbed?	Left out	Information gathered is outside the latitude of this study
24. Modality of eye rubbing?	Left out	Information gathered is outside the latitude of this study
25. Side most used when sleeping?	Left out	Information gathered is outside the latitude of this study
26. Depth of knowledge on RGP lenses	Left out	Information gathered is inconsequential to this study
27. Information on rigid contact lense in the past?	Kept	
28. Knowledge of LASIK surgery	Left out	Information gathered is inconsequential to this study
29. Positive history of corrective refractive surgery ?	Excluded	The age bracket under consideration is not eligible for LASIK eye surgery

In addition to the included questions listed in Table 4; other relevant areas such as history of spectacle wear of the subject, history of spectacle wear in the family and history of injuries were included in the final questionnaire that was then adopted for this study.

3.8 Pilot study

3.8.1 Pilot study data collection

The pilot study was carried out at a conveniently selected primary school in Harare that was not part of the main study. A sensitisation meeting was held with the head of the school who agreed to participate in the pilot study and distribute the consent forms.

Forty consent forms and questionnaires in English and forty consent forms and questionnaires in Shona were delivered to the school a week prior to the researcher's visit. The school had three grade 7 classes and one class was randomly selected to receive the consent forms. The consent forms were to be signed the students' parents or legal guardians. The main focus of the pilot study was to test the data capturing tools, the Red Cap database and to ensure the data collection team was clear on the examination routine.

All students that had turned 13 at the time of circulating the consent forms were excluded from the study. The students each received one Shona and one English pack and advised to tell their parents to fill out what was most comfortable for them. 22 consent forms and questionnaires were returned signed and fully completed, 6 were returned with just the consent forms signed and twelve were not returned. Only the English consent forms and questionnaires had been utilised.

The 22 subjects with signed consent forms and fully completed questionnaires were screened for KC risk at the site visit. The 6 with a signed consent form only, received a general eye screening but were not included in the study.

All COVID-19 protocols were observed during this study. Everyone in the research team had received at-least one dose of a COVID-19 vaccination, wore face masks at all times and had their body temperature checked in the morning prior to commencing the data collection process. Hand sanitiser was available at every station.

The check-in desk gave the subjects an opportunity to opt in or opt out of the study by way of an assent form. All 22 subjects presented at the check in desk one at a time observing social distance guidelines and signed the assent form. They were then distributed amongst six stations for the assessments. The assessments were performed in the school hall. The examination stations were separated by 2m.

Each station was equipped with a Snellen visual acuity chart, an occluder, a pen torch, a +10DS 65mm diameter uncut lens and a Keeler streak retinoscope. The Snellen chart was stuck on a wall 3m away from the subject chair. The data collectors were previously trained third and fourth-year Optometry students from the University of Zimbabwe, they worked in pairs. The assessment involved awarding risk scores based on the answers provided in the questionnaire, the visual acuity measurement, the anterior segment assessment for the presence of VKC and retinoscopy to check for a scissors reflex and presence of a cylinder.

A total risk score greater than or equal to 5 meant the subject was considered as high risk for the presence or development of KC and therefore required a full comprehensive eye exam. A cut off point of five was logically selected based on the scores awarded to each risk factor. One needed to have at-least one high risk factor (family history, eye rubbing, scissors reflex and Down's syndrome) and any other two risk factors present to be flagged for further examination. A total risk score lower than or equal to 4 meant the subject was considered low risk for the development or presence of KC and was therefore discharged from the study.

At the end of the assessment the subjects proceeded from the assessment station to the exit desk where they received a result slip to take home which stated one of two outcomes:

- either that they had healthy eyes and no further action was required or
- they needed to come to Parirenyatwa University of Zimbabwe Optometry clinic (UZO) as they were at high risk for developing KC. Those referred to UZO were advised to notify their parents to expect a call from the research team to schedule their full eye exam.

The exit desk also served as a quality control station ensuring the forms were fully completed.

3.8.2 Pilot study results

A response rate of 55% was recorded in this pilot study. It took an average of 8 minutes for each subject to be examined from the moment they sat in the chair to the time they received a result slip to take home. The examination time ranged from 6 minutes to 12 minutes.

Three of the twenty two (14%) subjects seen were found to have a calculated risk score above 5 points and therefore considered at risk for developing KC. These 3 were invited to visit UZO for the full comprehensive exam the following week. One of the students examined was found to be at low-risk for developing KC as he only scored two points on the risk calculator but was suspected to have high myopia due to his presenting low visual acuity which had not been previously diagnosed. This student was then referred to his nearest eye unit for further care. The other 18 students were discharged as they did not need any further care. The total risk scores for the discharged students ranged from 0-2.

The 3 referred students were telephonically contacted after the school visit and scheduled a time and date for the comprehensive eye exam at UZO. They all presented at the advised time with their guardians. Following refraction, fundoscopy and a slit lamp exam they were all found to not have clinical KC and needed to be seen in the second phase of the study to investigate for the possible presence of pre-clinical KC.

Phase 2 included an anterior segment scan of the cornea to investigate for early signs of KC. As the researcher was outsourcing the anterior segment scans from a private practice, the three subjects were then scheduled in for these scans along with the rest of the study cohort. The data of the 22 students was captured in the Red Cap database. This awarded the data capturers the opportunity to trial the electronic system and offered an opportunity to amend the database.

3.8.3 Recommendations post pilot study

Following the pilot study, it was concluded that the project could proceed on the current protocol and study tools with a few amendments as detailed below;

- Consent process: The consent window was to be longer than one week to allow for more forms to be returned. An additional sensitisation opportunity through the teachers was to be utilised so as to improve the response rate. Further emphasise was placed on the importance of completing both the consent form and questionnaire.

- Questionnaire: Some answers received to certain questions during the pilot study demonstrated a lack of understanding by the parents/guardian. These questions were then removed from the questionnaire and asked during the comprehensive exam case history. In the event that some questions on the survey were not answered, the researcher was to try get the answer from the subject prior to commencing the screening. If the student failed to answer the omitted question, it was to be left blank. In the event that more than half the questionnaire was incomplete, the student was to be excluded from the study.
- Procedure: Data collection team to have an additional training session around completion of the data capturing tool as different notations were being used by different individuals as this complicated the data capturing process. The exit desk highlighted incomplete data capturing tools which then slowed down the process as the subjects had to return to the examining station for the missing data to be entered.
- The outcome options of the screening were to be amended to include a third option that addressed subjects that were found to have an eye problem not linked to KC that needs further examination by an eye care practitioner. This outcome was to be accompanied by a referral letter to the subjects nearest eye unit or preferred eye care practitioner.

The pilot also helped inform printing of study materials, with more material in English apparently needed compared to the vernacular Shona. It was overall a successful pilot study that enabled us to test the tools for objectives 1, 2 and 4. Objectives 3 and 5 require the anterior segment scans to be completed and were thus not tested in this pilot study.

3.9 Data collection process

3.9.1 Preliminary activities

- Four primary schools in Harare; one in the north, one in the south, one in the east and one in the west of the city were selected according to geographical stratification.
- Permission to visit the schools was sought and granted by the Ministry of Primary and Secondary Education and the Harare District Education office.

- The study sample included all students aged between 6 and 12 years, attending the pre-selected primary schools.
- Data collection occurred between 2 May 2021 and 31 March 2022.
- The workflow of the data collection process is displayed in Figure 3 below.

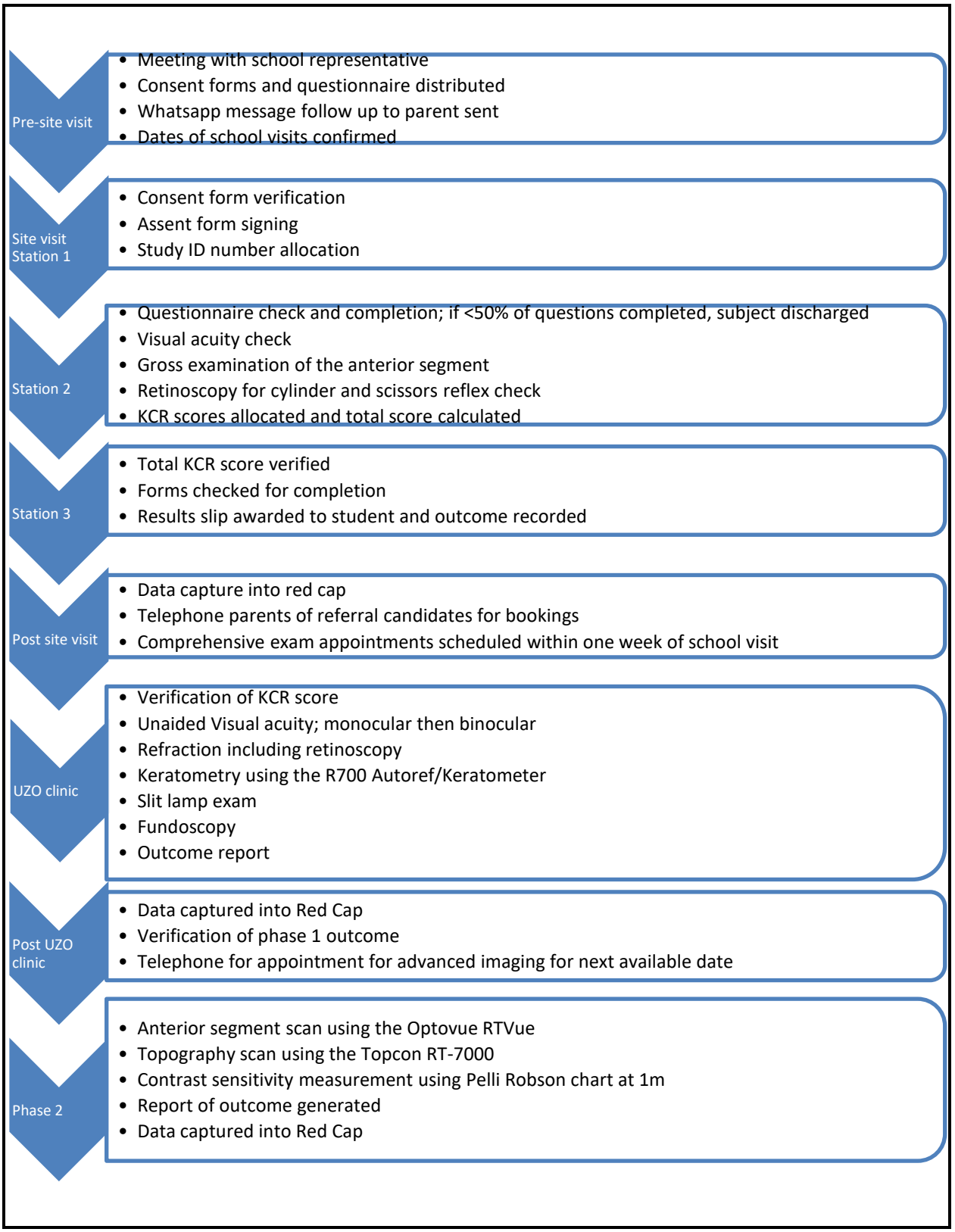


Figure 4: Data collection process flow diagram

- The first sensitisation meeting was held and written information about the study distributed to the schools one month before the scheduled school visit days. In all schools either the headmaster or deputy headmaster was engaged and once agreed on school visit dates they took custody of the literature for onward distribution to the students. The inclusion criterion was explained to the headmaster.
- The age-bracket was used as the main guiding factor for the distribution of the consent forms and questionnaires. Following the distribution of the consent forms and questionnaires, the headmaster was asked to engage the school teachers to share a previously curated text message in their WhatsApp class groups. The message briefly explained the study to the parents and shared my contact details should they need help to complete the questionnaire.
- Due to COVID-19 regulations, all government schools were practising hot sitting which meant at any school visit the researcher would encounter half the school. To overcome this, the research team visited each school on different days varied over a one month period to ensure all students with a signed consent form got the opportunity to be screened. All COVID-19 safe practice recommendations were observed throughout this study.
- Students whose parents returned signed consent forms, and who each signed an assent form in addition to a questionnaire that had at least 7 out of the 14 (50%) questions answered were assessed.
- The KRIS questionnaire was used as the basis of the questionnaire used in this study. It has a total of 29 questions but the researcher modified it and reduced the length to 14 questions as some questions as detailed in Table 6 above.
- Two training sessions for the data collection team were held, prior to the commencement of the data collection process, to standardize tools and processes used by fieldworkers in the study.

3.9.2 Phase 1

- On the screening day, the investigation commenced with the check in desk where the signed consent form was verified. Following this, the student was then offered the opportunity to opt in or opt out of the study by way of the assent form. Once the assent form was signed, the previously circulated questionnaires were

checked for completion. Incomplete questionnaires were noted at this stage and the tending examiner advised so as to complete the questionnaire first. The subjects were then awarded a study number which was entered on their data capturing tool and served as their identifier for all their paperwork.

The first step towards allocating a KCR score involved analysis of the information from the questionnaire. The answers provided were awarded risk scores as stipulated in the KCR score table (Table 5). The risk scores were entered onto the data capturing sheet (Appendix 2a). For the purposes of this study:

- *Affluent* is defined as having both parents with tertiary education.
- *Healthy* is defined as eating a diet inclusive of meat, fish, fruit and vegetables at-least three times per week.
- *High UV exposure* is defined as being outdoors an excess of 8hours/week.
- *High VDU use* is defined as screen time in excess of 8hours/week.

The findings from previous studies[29,30,123,226] were used to award each clinical sign or symptom (variables) it's weighting, taking into consideration how much they increased one's risk of getting the condition.

- A positive family history was awarded 3 points as it has the highest impact on one's risk for developing KC.
- Eye rubbing and atopy have similar values for increased risks, the researcher awarded eye rubbing a higher score of 3 compared to the 2 awarded to atopy because eye rubbing is also a symptom reported with atopic conditions. In addition, eye rubbing was awarded a higher score as it can also occur in the absence of atopy and introduces its own side effects which have been well documented as increasing the risk and severity of KC. Atopy was still included as a separate risk factor as it can also occur without eye rubbing depending on which atopic disease is present.
- Down syndrome was awarded a score of 3 although it's actual influence on risk has not been documented.
- Vernal conjunctivitis was awarded 2 points as it has been well documented that the prevalence of KC in patients with VKC is higher compared to normal controls.
- The maximum scores possible for each variable were recorded on the data capturing tool to minimise human error during the capturing process.

Following this exercise, the comprehensive eye exam was performed in the following order;

1. Monocular visual acuity was measured using a Snellen visual acuity chart starting with right eye then followed by the left eye. The Snellen visual acuity chart was stuck on a wall 3m away from the subject. The distance was measured and marked on the ground using masking tape. The masking tape was used as a check for the distance prior to commencing a new visual acuity measurement on every subject. The subject was instructed to stand with the front of their shoes touching the masking tape. The provided occluder was used to cover the eye not being tested at any given time. A visual acuity weaker than or equal to 6/9 Snellen acuity in either eye was considered reduced and awarded 2points as a risk score.
2. Retinoscopy was used to check for a scissor-reflex. The subject was asked to fixate the green line on the Snellen visual acuity chart which was 3m away. The observer used their RE to check for the scissors reflex in the subjects RE then the subjects LE was checked using the observers LE. A working distance lens was not used in this assessment. A positive finding for the scissors reflex was awarded 3 points.
3. A pen torch and a +10DS hand-held free lens were used to assess the cornea, limbus and bulbar conjunctiva for general signs of vernal conjunctivitis such as conjunctival hyperaemia, epiphora and inflamed papillae. The observer also assessed the cornea for haze and/pannus, limbitis and any other signs associated with VKC. The subject was then asked to look up and the observer would then pull down the lower lid and examine the lower tarsal conjunctiva for a papillary reaction. Lastly the subject was asked to look down, the upper lid was then checked for a papillary reaction. Any sign of VKC was awarded 2 points.
4. Lastly, the observer was asked to assess the subjects' skin for any skin rashes, eczema and past scars which could be prescribed to an atopic reaction. Additional questions around allergies were posed. Any positive findings for atopy were awarded 2 points.

The points accrued from the questionnaire responses, visual acuity measurement, retinoscopy reflex, findings from the anterior segment pen torch exam and scan for atopic reactions were added to derive a total KCR score. A combined KCR score of greater than or equal to five was considered at risk for the development of KC in this study. Those flagged as at risk were then invited to UZO for a comprehensive eye exam. Students with less than five for their total risk score were discharged. Each student was provided with a result slip to take home advising the parents

of the outcome of the screening. Those with reduced VA or any pathology detected but a risk score of less than 5 were given referral notes to visit an eye practitioner of their choice or the nearest eye unit to them.

The comprehensive clinical exam at UZO was scheduled on a separate day. All ocular examinations were completed by the same senior optometrist in the hospital. The comprehensive eye exam was completed as follows;

1. Monocular unaided visual acuity of the right eye followed by the left eye using a Snellen chart on an LED screen. The visual acuity was recorded in decimal notation.
2. Objective refraction was performed using retinoscopy and a scissors reflex noted when present.
3. Subjective refraction was performed to get the best corrected visual acuity (BCVA) of either eye. It included the use of the duochrome for spherical adjustment and the Jacksonian cross-cylinder for cylindrical power adjustment. When the visual acuity could not be improved to 1.0, a pinhole was used to ensure there was no further improvement possible. The prescription was recorded in negative cylindrical form. The BCVA was recorded in decimal notation.
4. Automated keratometry was then carried out using the R700 Autoref/Keratometer. The RE was measured first then followed with the LE. The shape and quality of the mires was also noted. The corneal curvature was recorded in mm and the dioptre power was also recorded.
5. A detailed slit lamp examination was conducted to detail any diagnostic signs of KC present. A checklist was provided and the following signs were listed as either present or absent; Vogt's striae, Munson sign, Fleischer's ring and corneal scarring.
6. Lastly fundoscopy was carried out using a handheld direct Keeler ophthalmoscope. Any abnormalities noted were recorded and forwarded to the ophthalmologist clinic for further assessment.

At the end of the exam the subject was either diagnosed with clinical KC or reported to have no clinical KC. A clinical KC diagnosis was awarded in the presence of keratometry reading greater than or equal to 45D in at least one meridian of either eye in addition to any one of the SLE signs associated with KC. The no KC category included those with pre-clinical KC/KC suspects. The exam findings were recorded on the clinical exam sheet (Appendix 2c). The no KC subjects were invited to the second phase of the study. Multiple attempts over three

months were made by telephone and text message to reach those referred but did not present for the comprehensive exam. They were then recorded as 'lost to follow up' after three calendar months.

3.9.3 Phase 2

Phase 2 of the study served to identify the pre-clinical signs of KC in the subjects at risk of developing KC that had been found to not have clinical KC after the full comprehensive exam.

The phase 2 assessments were done in a different location; The Eye Institute, a private clinic using a topographer, anterior segment OCT and a Pelli-Robson CS chart. Pre-clinical KC was awarded when two of these three assessments yielded a suspicious result.

1. Anterior segment OCT scan was done using the Optovue iVue. The RE was scanned first then followed by the LE. Only scans denoted "good" on quality were examined. The width of the narrowest part, central and thickest part of the cornea was recorded in micrometres. When the minimum corneal thickness did not coincide with the central corneal thickness it was considered to be displaced and noted. Corneal curvature less than 480µm was considered abnormal.
2. Corneal topography was performed using the Topcon RT-7000 topographer. The RE was imaged first followed by the LE. The corneal curvature for both meridians in either eye was recorded in mm along with the Dioptre equivalent. The clarity and distinctness of the mires was also noted. K readings ≥45.00D in either meridian were considered abnormal.
3. Contrast sensitivity was measured monocularly starting with the RE then concluding with the LE using a Pelli Robson CS chart placed 1meter from the subject. The eye not being assessed was covered with a handheld lollipop occluder. Log contrast of less than 1.50 was considered abnormal.

The findings of the phase 2 study were recorded on the phase 2 assessment sheet (Appendix 2d).

All data was electronically captured using the RED Cap online data management system.

3.10 Data Management

3.10.1 Data Analysis

Data was electronically captured using the RED Cap online data management system and all data analysis was carried out in STATA software package (V.16, Stata Corp, College Station, Texas, USA).

- Determine the risk profile of children with keratoconus in urban Harare

Categorical variables were expressed as frequency (percentages). Continuous variables were summarised using the mean (standard deviation) for normal data or median (inter-quartile range) for non-normal data. Histograms were plotted to check normality for continuous variables. Chi-square test was used to determine the association between KC and categorical variables. Student t-test or Mann-Whitney test were employed where appropriate to determine mean or median between KC and continuous variables.

- Determine the prevalence of keratoconus in children in urban Harare, Zimbabwe

This was determined by the number of children with clinical KC divided by the total sample under study.

- Document the pre-clinical signs of keratoconus in children identified as high risk for keratoconus

The Receiver operator characteristic (ROC) analysis was carried out to compare the sensitivity of detecting KC in different subgroups.

- Determine the age most associated with early signs of keratoconus in children living in urban Harare

Chi-square or Fisher exact test were used to determine the association between presence of KC and pre-clinical KC with the age categories.

- Assess the risk factors associated with presence of keratoconus

Log-binomial regression was used to determine the association between keratoconus and the relevant nineteen study variables. Factors associated with keratoconus at p-value < 0.05 in unadjusted univariable log-binomial regression were included in a multivariable model, to identify independent factors associated with keratoconus. Adjusted risk ratios and their 95% CIs were used as a measure of association.

- Develop an algorithmic approach for the early detection of keratoconus

Results obtained from the other objectives were applied to develop the algorithm for the early detection and management of KC.

3.10.2 Data Security

- The completed data collection reports were stored in the University of Zimbabwe Optometry department office in a lockable filing cabinet. The principal investigator is the sole holder of this key.
- The data was captured electronically using Red Cap database (https://www.project-redcap.org/).
- It will be stored for 5years then destroyed.
- All participant information was awarded a new electronically generated ID number which cannot be traced to the participant.

3.11 Ethical considerations

Ethical approval was received from the Medicines Research Council of Zimbabwe (MRCZ A/2749), the Joint research ethics committee of Parirenyatwa Hospital and the University of Zimbabwe (JREC 44/2020) and the Biomedical Research ethics committee of UKZN (BE 385/99). All letters of permission are displayed (appendix 3ai-iv). Short courses on good ethical practice were completed prior to commencement of the project (Appendix 3b). The researcher confirms that the study was conducted in accordance with Helsinki Declaration as revised in 2013.

3.12 Validity and Reliability

The construct and content validity of the KCR factor was achieved by the use of a verified KRIS questionnaire and the tabulation of known indicators for KC. A two sample t-test was performed to compare the discharge group to the referred group to ascertain validity of the screening questionnaire. The concurrent validity was determined by measuring the correlation between keratometry and diagnostic outcome by slit lamp exam. Receiver operator curves were utilised where appropriate to assess the validity and accuracy of the diagnostic variables investigated in this study. The predictive validity and reliability of the KCR score was investigated and documented using ROC curves.

3.13 Dissemination of Study Findings

1. A copy of this Thesis will be placed in the UKZN and University of ZWE libraries, for access to the academic community.
2. A summarised report of the findings was provided to the headmaster of every school assessed.
3. Articles of findings will be published in scientific journals for the eye care profession so as to share our findings and contribute towards evidence based practice in Zimbabwe.
4. A presentation will be held for the key stakeholders at the Zimbabwean Ministry of Health and Child Care and the Zimbabwean Ministry of Primary and Secondary Education. Documenting the age of onset and those at risk for this condition in our population and other similar settings will inform the public health sector of the appropriate age to introduce an eye screening program for children for the early detection of conditions such as KC.
5. The findings of this study improve access to eye care and inform best clinical practices.

3.13 Summary

The aim of this study was to develop a simple step by step process for the early diagnosis of KC. Following a successful pilot, a quantitative, cross sectional, analytical study was carried out on subjects aged between 6 and 12 years attending four pre-selected primary schools in urban Harare. Signed consent and assent forms formed part of the inclusion and exclusion criterion applied. The data collection was broken down into two phases. Phase 1 involved the use of a 14 question survey, visual acuity measurement, anterior segment assessment and retinoscopy screening. A KCR score was calculated for each subject to divide the subjects into two subgroups; one being those at risk and the other those with a low risk for the development of KC. Subjects noted to be at risk for the development of KC were invited for a full comprehensive eye exam. The eye exam further divided this subgroup into clinical KC and no clinical KC. The no clinical KC group was then invited for the second phase of the study which involved the use of topography, anterior segment OCT scan and contrast sensitivity to detail signs associated with pre-clinical KC.

CHAPTER 4: RESULTS

4.1 Introduction

Anecdotal evidence suggested that pre-pubescent children present for their first clinical examinations with advanced signs of KC and visual impairment. This hinders the practitioners' capacity to successfully manage the patient and provide good functional vision. In this chapter I will present the findings after screening and assessing pre-pubescent subjects for the risk of KC, clinical KC prevalence and the prevalence of other factors known to be present in pre-clinical KC. The protocol was divided into two phases; phase 1 looked to address objectives 1; 2 and 4 which predominantly involved the analysis of the risk factors associated with KC in urban Harare and the clinical signs of KC whilst phase 2 addressed objectives 3 and 5 that looked into pre-clinical KC signs and prevalence in subjects at risk of developing KC. The patient flow from recruitment to the end of the data collection for phase 2 is diagrammatically explained in Figure 5 below. Detailed findings from each stage are presented later in this chapter.

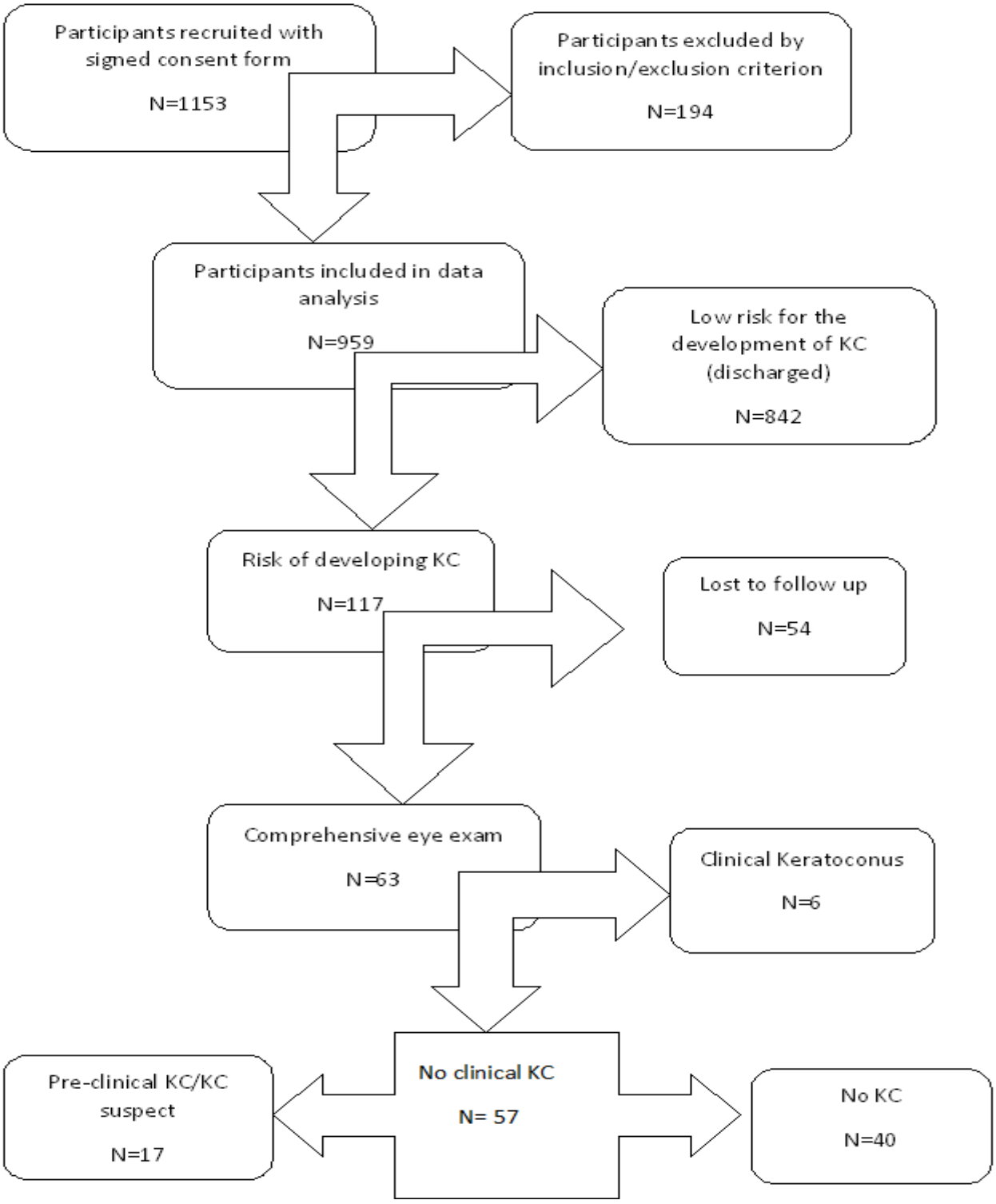


Figure 5: Subject flow chart

4.2 Demographic details

Females made up 53% of the study participants and 47% were male. The Christian religion was the dominant religion with 99% of the study participants reporting to be of Christian religion. The mean age was 9±2 years ranging between 6 to 12 years (Figure 6), with the ethnic profile being 99% of African descent and 1% of mixed ethnicity.

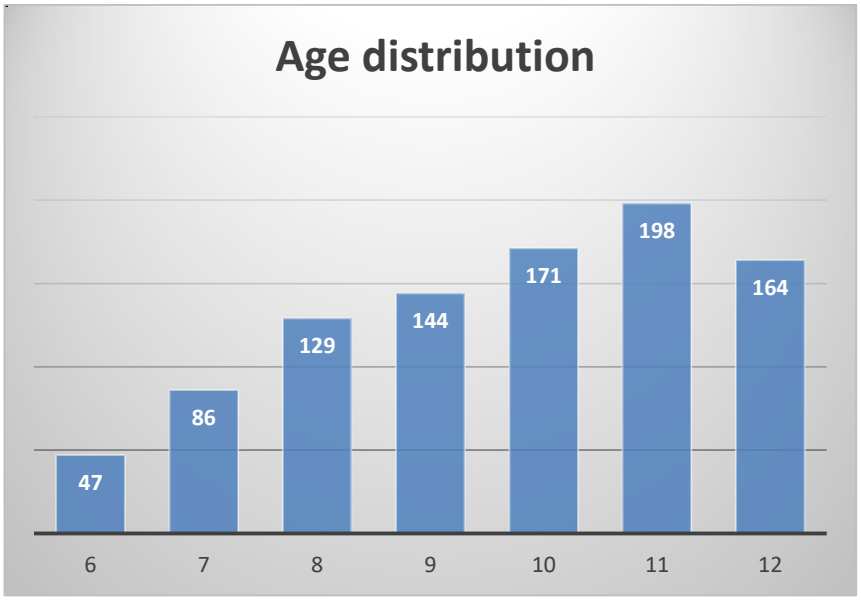


Figure 6: Age distribution of the study population

As shown in Figure 5, only 6% of the study population had a positive history for ocular injuries or surgeries; 50% reported to have high UV exposure and 43% to frequently using VDU. Only 2% reported to have used contact lenses with only 7% having ever heard of KC in the past. Using the pre-determined criteria, 82% were classified as affluent and ~85% reported having a healthy diet at home.

Table 5: Demographic details and population characteristics

Variable	Response
Gender, n (%)	
Female	502 (53%)
Religion, n (%)	

Christian	908 (99)
Other	4 (1)
Age in years, mean (SD, Range)	9 (±2; 6 - 12)
Ethnicity, n (%)	
African	918 (99)
Mixed	6 (1)
Affluent, n (%)	
Yes	656 (82)
Heard of KC, n (%)	
Yes	70 (7)
Diet, n (%)	
Healthy	804 (85)
Injuries/surgeries, n (%)	
Yes	59 (6)
UV♥ exposure, n (%)	
Yes	487 (52)
VDU♪ use, n (%)	
Yes	409 (43)
CL use in the past, n (%)	
Yes	22(2)

♪ Visual Display Unit ♥Ultra viiolet

4.2 Objective 1: Determine the risk profile of children with KC

The outcome whether someone is discharged or referred was coded into binary, 0 for one who is discharged and 1 for someone who is referred. Logistic regression analysis was conducted and the base variable is in the parenthesis. There was no statistically significant association between gender and referral outcome (*p =0.46*), 12% among both males and females had a referral outcome. There was no statistically significant association between religion and outcome *(p = 0.41)*. There was a statistically significant association between age and referral outcome *(p <0.001)*; the mean age among those with a referral outcome was 11 years compared to 9 years among those with a discharge outcome. The age distribution of the subjects diagnosed with clinical KC is displayed in Figure 7 below.

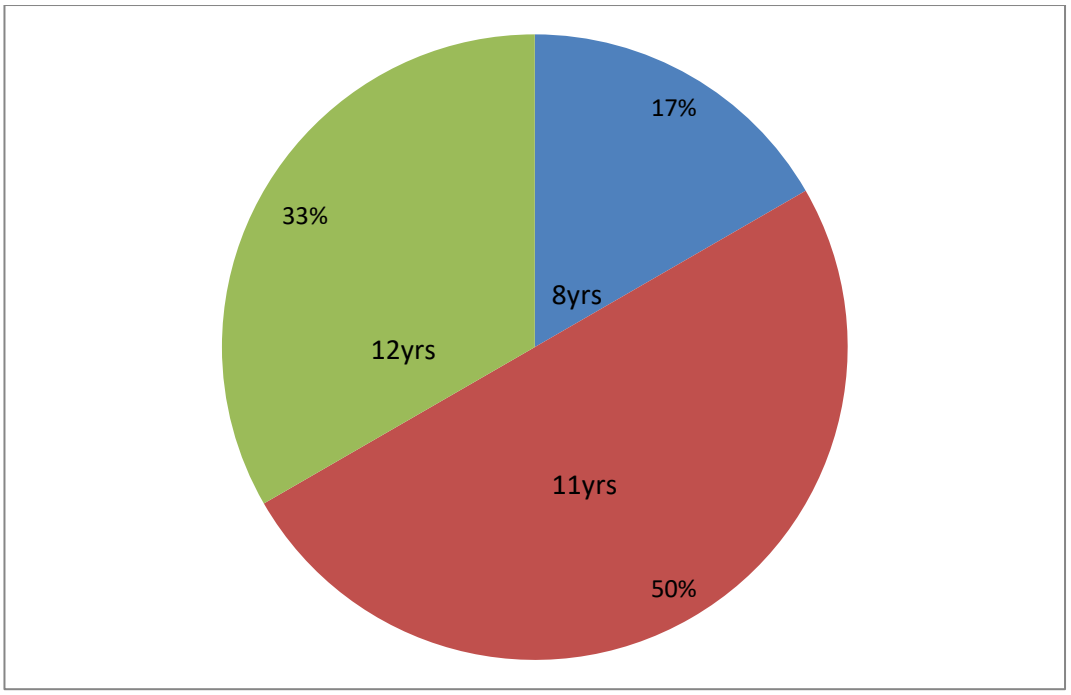


Figure 7: Age distribution of clinical KC Subjects

Results revealed in Table 6 show that there was no statistically significant association between ethnicity and outcome *(p =0.55)*, 12% of subjects among those of African ethnicity had a referral outcome compared to 17% among those of mixed ethnicity. This difference is however insignificant as both races were not equally powered. There was a statistically significant association between affluence and outcome *(p =0.04)*, 12% among those who reported to be affluent had a referral outcome compared to 7% who were less affluent. It is important to note that affluent subjects made up 82% of the total study sample. There was a statistically significant association between knowledge about KC and outcome *(p =0.015)*; 21% among those who reported to have heard of KC had a referral outcome compared to 11% who had never heard of KC.

Table 6: Association between demographic variables and the screening outcome

Variable	**Outcome**		***p-value***	***Relative risk***	***Odds ratio***
	Discharge	**Referral**			
Gender, n (%)					
Male	394 (88)	55 (12)	*0.464*	*1.00*	*0.97*
Female	439 (88)	59 (12)			
Religion, n (%)					

Christian	791 (88)	112 (12)	*0.413*	*1.17*	*2.4*
Other	3 (75)	1 (25)			
Age in years, mean (SD)	9 (2)	11 (2)	*<0.001*		
Ethnicity, n (%)					
African	801 (88)	112 (12)	*0.546*	*1.1*	*1.8*
Mixed	5 (83)	1 (17)			
Affluent, n (%)					
No	133 (93)	10 (7)	*0.040*	*1.06*	*1.89*
Yes	572 (88)	81 (12)			
Heard of KC, n (%)					
No	771 (89)	99 (11)	*0.015*	*1.13*	*2.13*
Yes	55 (79)	15 (21)			
Diet, n (%)					
Unhealthy	125 (90)	14 (10)	*0.285*	*1.03*	*1.25*
Healthy	703 (88)	98 (12)			
Injuries/surgeries, n (%)					
No	783 (89)	100 (11)	*0.017*	*1.14*	*2.19*
Yes	46 (78)	13 (22)			
UV exposure, n (%)					
No	394 (87)	60 (13)	*0.194*	*0.98*	*0.83*
Yes	430 (89)	54 (11)			
VDU exposure, n (%)					
No	469 (88)	65 (12)	*0.517*	*1.00*	*1.01*
Yes	358 (88)	49 (12)			
CL use in the past, n (%)					
No	801 (88)	110 (12)	*0.510*	*1.01*	*1.08*
Yes	19 (86)	3 (14)			
VKC♥, n (%)					
No	823(98)	82(71)	*0.000*	*2.84*	*21.33*
Yes	16(2)	34(29)			

♥Vernal keratoconjunctivitis

There was no statistically significant association between diet and outcome (p = .29); 12% among those who reported to have a healthy diet had a referral outcome and similarly 10% among those who reported to have an unhealthy diet had a referral outcome. There was a statistically significant association between injuries or surgeries status and outcome (p = .017); 22% among those who reported injuries or surgeries had a referral outcome compared to 11% among those who did not report injuries or surgeries.

VA less than 6/9 was recorded in 272 eyes giving reduced VA in 17% of the total eyes tested. The averaged unaided visual acuity (UVA) was noted to be 0.8±0.4 with a range of 0.05-1.2 in decimal notation for the 38 eyes of the subjects diagnosed with clinical and pre-clinical KC. The average BCVA was noted to be 1.0 ±0.3 with a range of 0.05-1.2 in decimal notation. The UVA spread is displayed in Figure 8 below. Cumulatively, 47% of the subjects diagnosed with either clinical KC or pre-clinical KC had presenting VA of 0.7 or weaker in decimal notation.

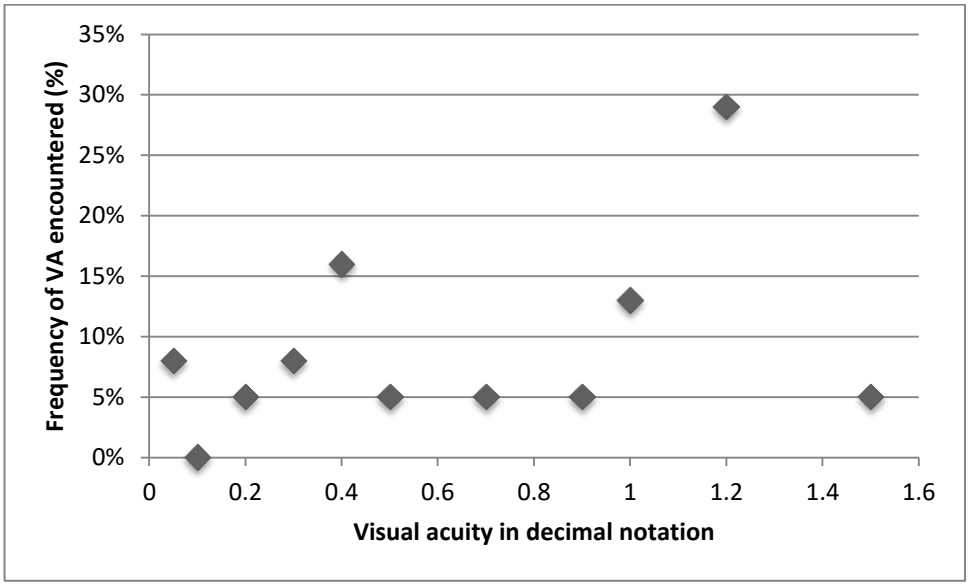


Figure 8: Graphical display of the UVA

Four percent of the overall study participants reported to have a positive family history of KC, and of these, 26% had a referral outcome. Half of the 14% of the overall study participants who were found to have reduced visual acuity in at-least one eye had a referral outcome. The majority (68%) of the ~5% of the overall study participants who were positive for active or past VKC had a referral outcome. About 4% of the overall study participants were reported to have an atopic condition affecting their skin and of these, 43% had a referral outcome. A summary of the referred subgroup is available in Figure 9 below.

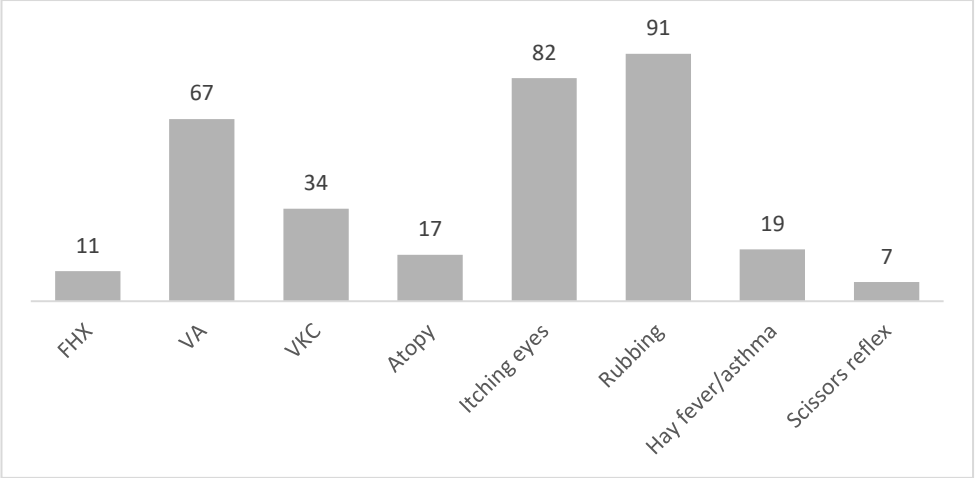


Figure 9: Number of referred subjects classified by risk factor

The two sample t-test shows a statistically significant difference between the discharged group and referred group. There was a significant difference between the discharged group (M=9.57, SD=1.85) and the referred group (M=10.23, SD=1.68); t (945) =-3.60, *p=0.0003* as shown in Table 10 and Figure 10 below.

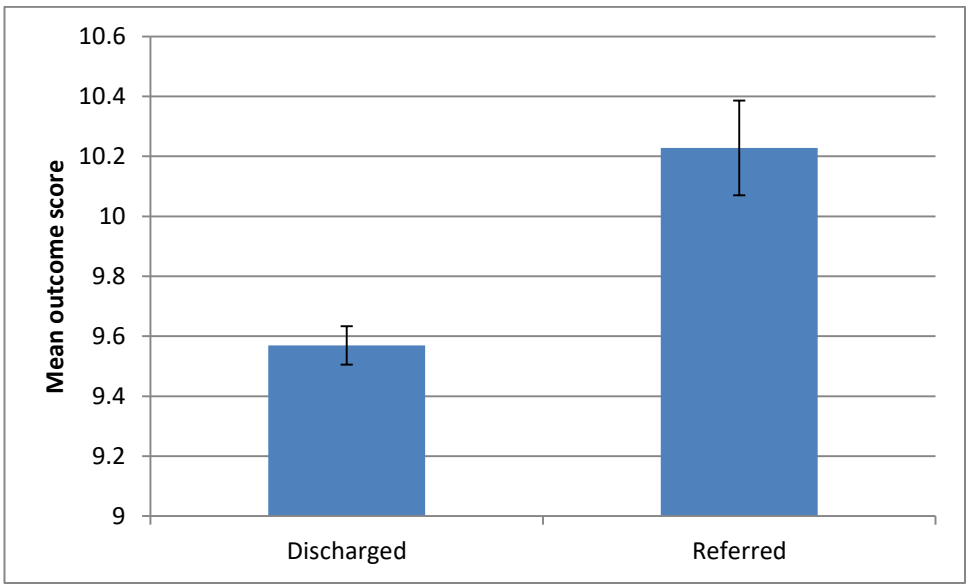


Figure 10: Graphical presentation of the two T sample test

Receiver operating characteristic (ROC) curve analysis of the 5-point cut off showed inconsistencies (Figure 11).

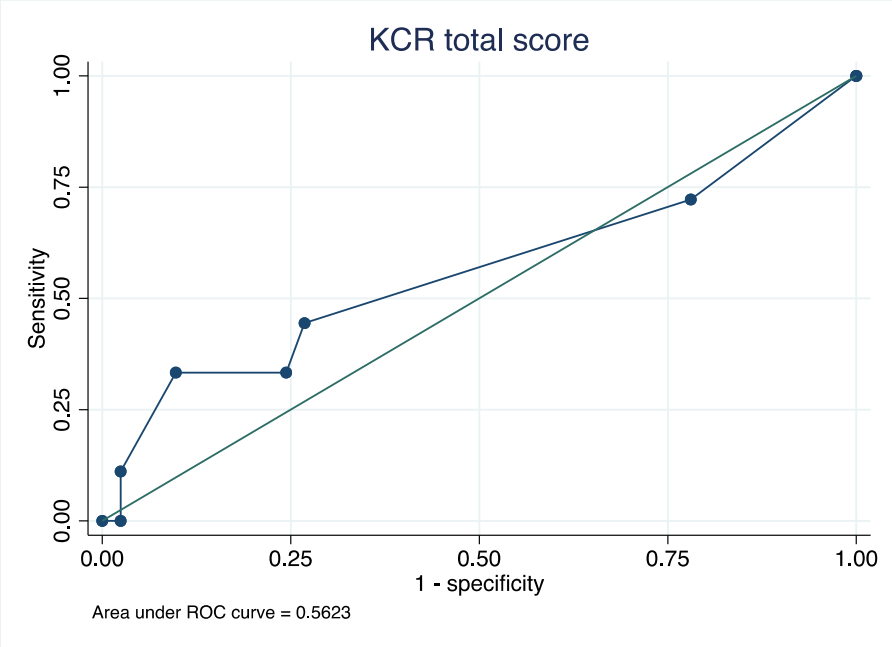


Figure 11: ROC analysis of the KCR cut off

Linear regression analysis of the cut of point as shown in Table 8 shows an improved p-value from *p=0.22* to *p=0.03* by increasing the cut-off point.

Table 7: Linear regression comparison of 5pt cut off to 9pt cut off

	Odds ratio for clinical	**95% CI**	***p-value***
Cut-off ≤5	1.22	0.89-1.69	*0.220*
Cut-off ≤ 9	4.63	1.11-19.19	*0.035*

The f-ratio value is 30.12035. The p-value is < .00001. The result is significant at p < .05

Vogt's striae were observed in all subjects with clinical KC and the Munson sign was observed in 83% of the sub-group (Table 9).

Table 8: Characteristics of the SLE findings in clinical KC subjects

Variable	**Response**
Corneal scarring n (%)	

Yes	2(33)
Age	Avg. 10±3; range 8-12
Munson sign n (%)	
Yes	5(83)
Age	Avg. 11±2; med 11; range 8-12
ir's ring n (%)	
Yes	1 (17)
Age	11
Vogt's striae n (%)	
Yes	6 (10)
Age	Avg. 10±1; med 11; range 8-12

Of the subjects found to have clinical KC; an analysis of the correlation between several factors and the outcome variable was performed. Results show that there are weak correlations between all the factors and the outcome variable. Religion and UV exposure showed a negative correlation and this is supported by the results displayed in Table 10.

Table 9: Correlation between risk factors and diagnosis of clinical KC

	Correlation coefficient	***p-value***
Gender	0.0014	*>0.05*
Religion	-0.007	*>0.05*
Affluent	0.0719	*>0.05*
Heard of kc	0.0669	*>0.05*
Health diet	0.0196	*>0.05*
Injuries surgery	0.0723	*>0.05*
UV exposure	-0.0293	*>0.05*
VDU exposure	0.0004	*>0.05*
CL use in the past	0.0084	*>0.05*

4.3 Objective 2: Determine the prevalence of KC

The prevalence of clinical KC is 630: 100 000 in children living in urban Harare. Prevalence of pre-clinical KC is 1 360:100 000. Combined prevalence of clinical and preclinical KC is 1 990:100 000 (Figure 12). Further assessment revealed that 10% (n=6) of the high-risk subgroup were found to have clinical KC.

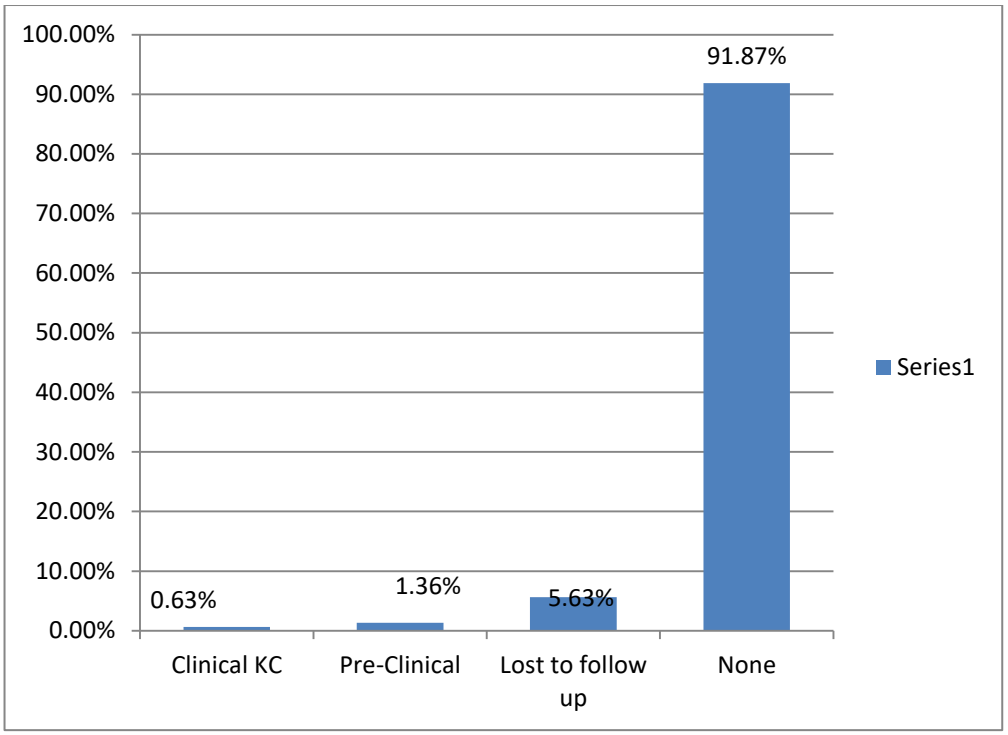


Figure 12: Prevalence of KC

4.4 Objective 3 Document the pre-clinical signs of KC in children flagged as high risk

The 117 subjects flagged as high risk accounted for 12% of the total subject population. As 54 subjects were lost to follow up, resulting in the analysis at this stage including 63 subjects (7%). In the high-risk group; 9% had a positive family history for KC, 57% had reduced visual acuity in at-least one eye, 29% had VKC, 4% had atopy, 70% had itching eyes, 78% rubbed their eyes, 16% were asthmatic and 6% had a positive scissors reflex test. Figure 13 displays the KCR scores documented in this study. The scores ranged from 0-12 with almost 50% of the subjects scoring zero. About 4% of the subjects scored above 8 points.

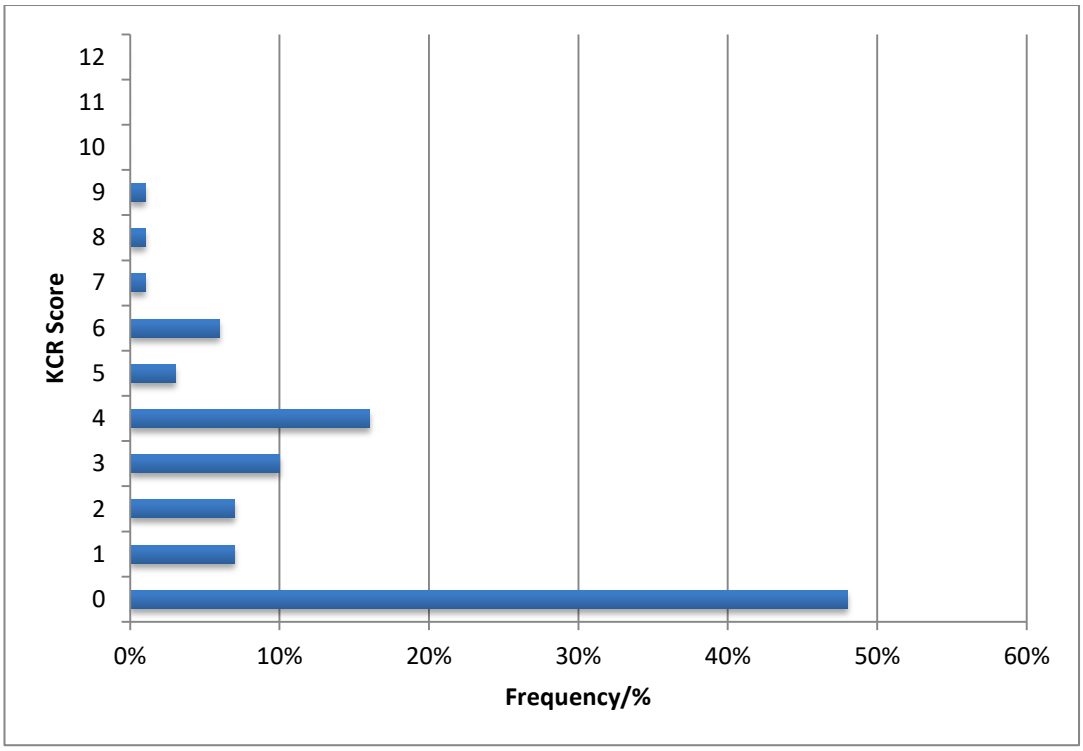


Figure 13: Distribution of KCR scores for the full study sample

The violin plot (Figure 14) shows some overlap between the healthy subjects and those with a positive KC finding in the high-risk sub-group.

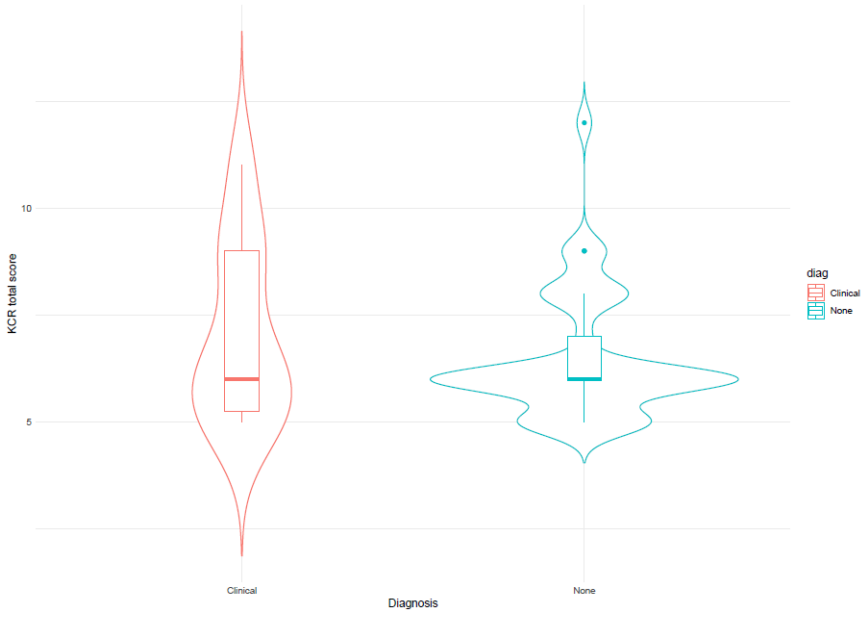


Figure 14: Violin plot display of KCR score distribution by diagnosis

The full eye exam found 9% of the high-risk group to have clinical KC, 21% were diagnosed with pre-clinical KC and 70% were clear of both clinical and pre-clinical KC at this stage as displayed in Figure 15, further highlighting the overlap noted in the violin plots above.

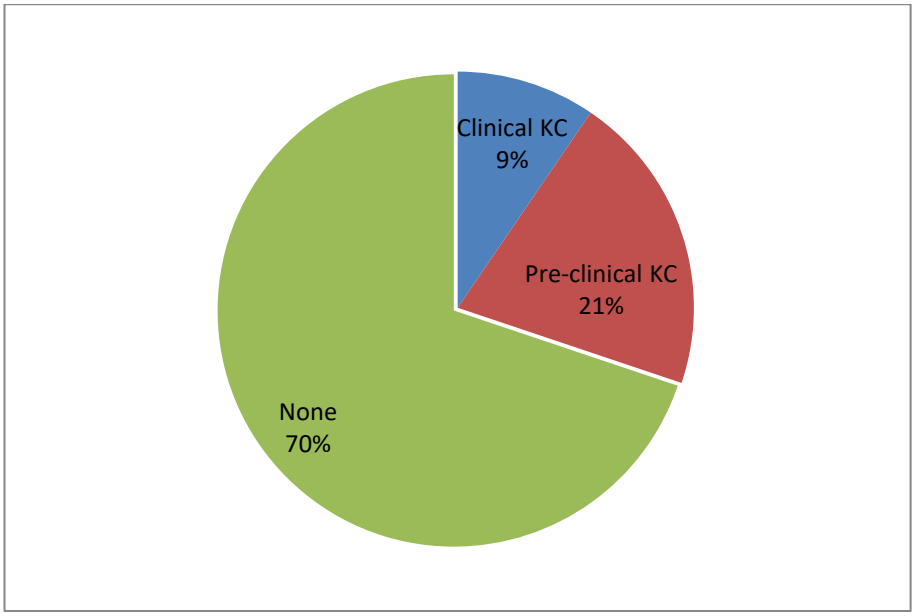


Figure 15: Display of outcomes post the clinical ocular exam of the high risk group

Table 11 details the variables encountered in the pre-clinical assessment of the high risk group (n=63).

Table 10: Pre-clinical KC signs recorded in the high-risk group

Variable	Response
Keratometry, n (%)	
D>=45D	28 (44)
Age	Avg.10±2; med 11; range 6-12
Displacement of corneal centre, n (%)	
Yes	32(54)
Age	Avg10±2; med 11; range 6-12
Anterior stroma abnormality on topography n (%)	
Yes	17 (29)
Age	Avg. 10±2; med 11; range 6-12
Variations in CCT>=100µm n (%)	
Yes	7 (12)
Age	Avg. 9±1; med 9; range 7-12
CCT<=480µm	
Yes	3 (5)
Age	Avg. 8±2; med 9; range 7-10

Reduced CS<=1.35	
Yes	16 (25)
Age	Avg. 10±2, med 10, range 6-12

Corneal curvatures >/=45D were recorded in 70% of the high-risk subjects. The second most common finding was a displaced corneal centre in 44% of the subjects examined.

The violin plots below display the difference between the keratometry results recorded for subjects diagnosed with any form of KC and those identified as having a higher risk for the development of KC.

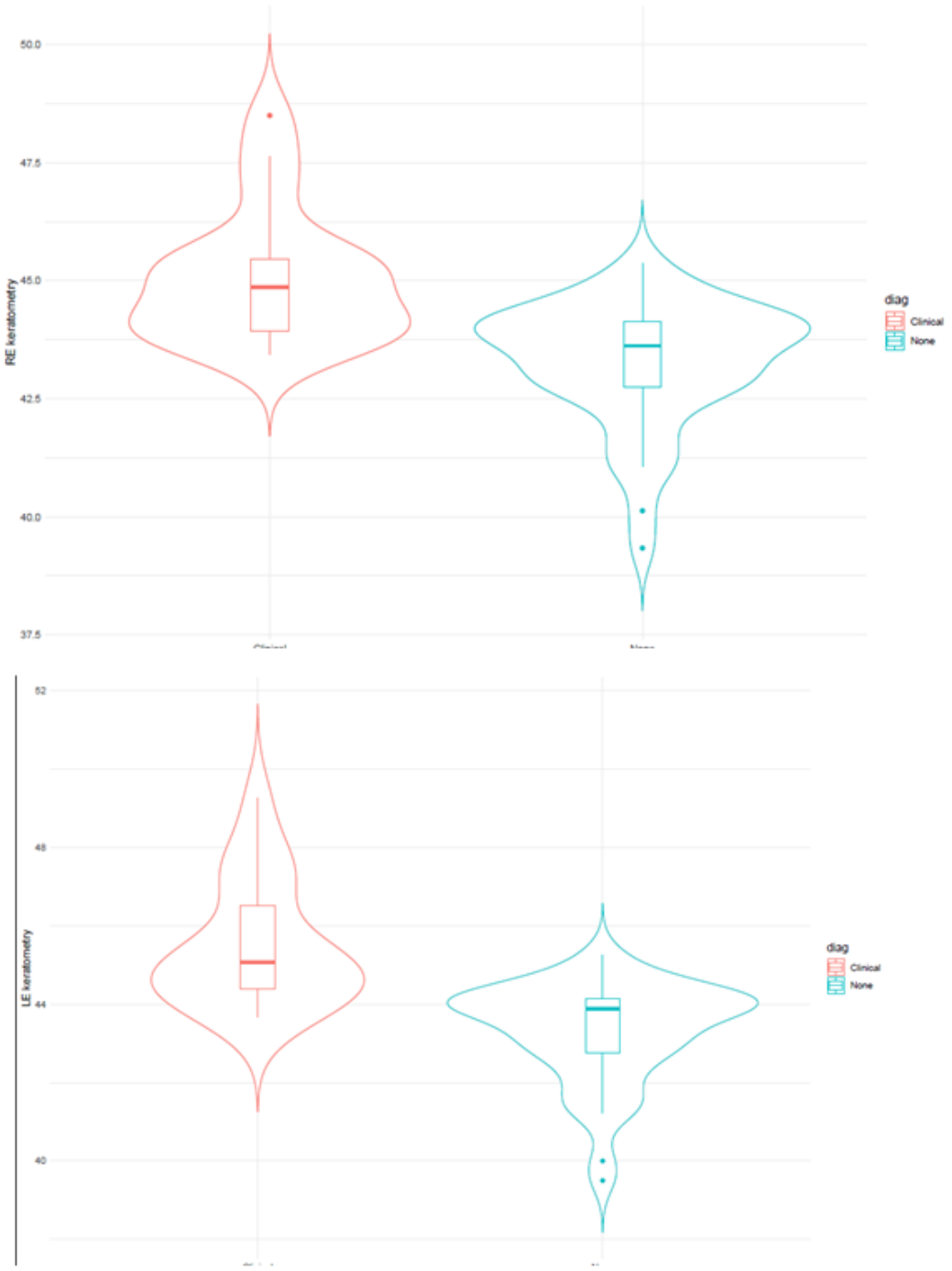


Figure 16: RE and LE violin plots showing spread of keratometry measurements as defined by final diagnosis. Clinical includes subjects with clinical KC and pre-clinical KC

The ROC curves of the keratometry measurements taken for the right eye and left eye are displayed below in figure17. The plots display good accuracy and sensitivity for the 45D cut off.

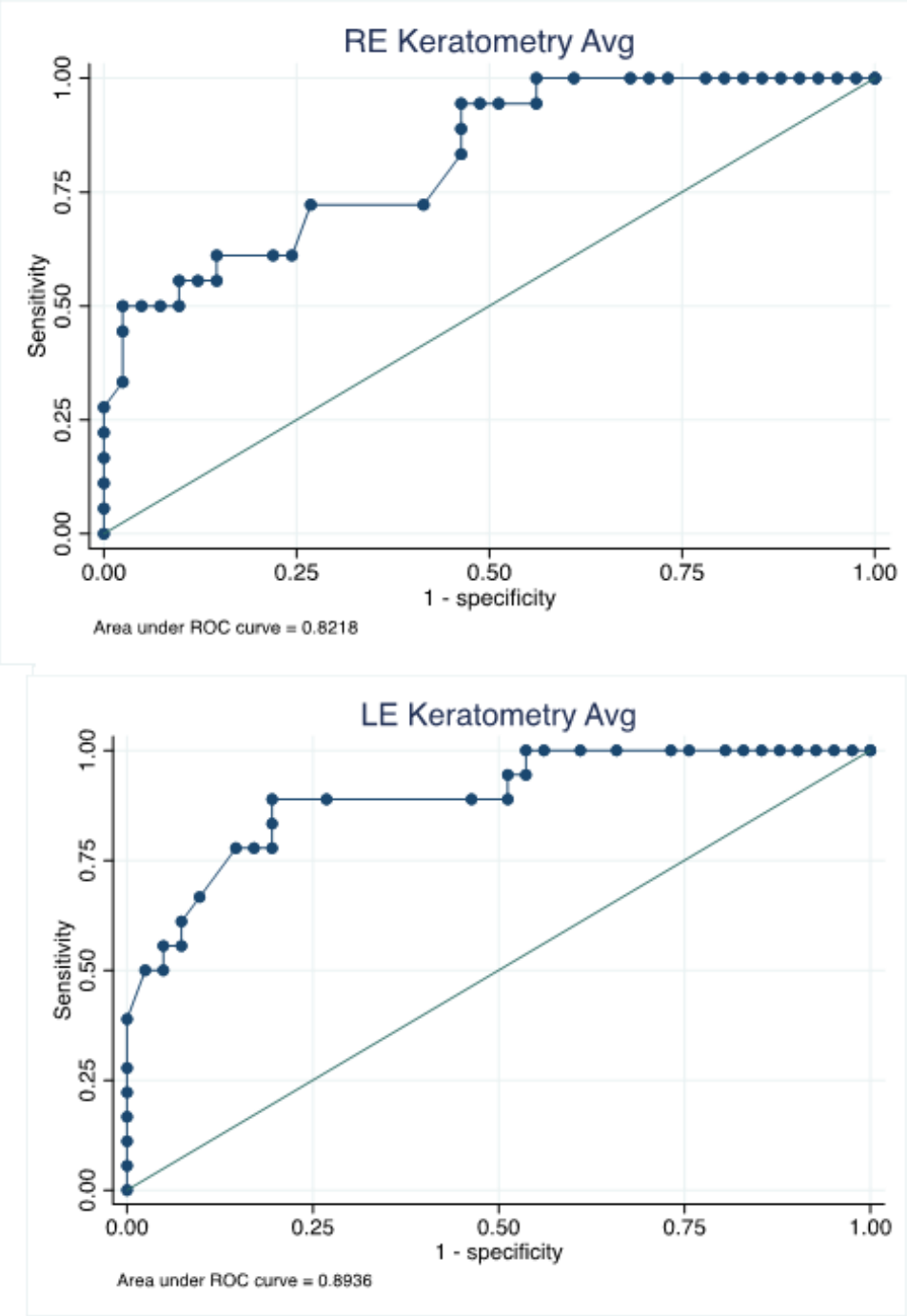


Figure 17: ROC curve analysis for the RE and LE keratometry readings for the high-risk subgroup.

Anterior surface abnormalities were present in 30% of the subjects considered to be high risk for the development of KC. Of these 30%; 65%were diagnosed with pre-clinical KC. Additional details are summarised in Figure 18.

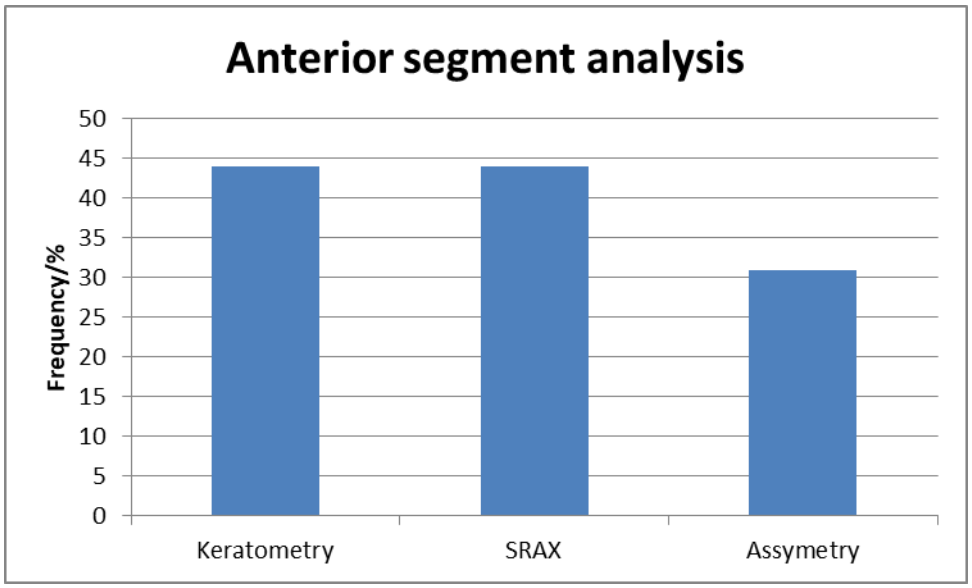


Figure 18: Corneal abnormalities detailed by anterior surface analysis using topography

The average RE and LE CCT were found to be 517±26µm and 516±25µm respectively. Minimum corneal thickness was 504±25µm and 504±24µm for the RE and LE respectively. The average difference between the thickest and thinnest point was 42±20µm for the RE and 60±19µm for the LE. Figure 19 shows the mapping of the RE along with the LE CCT measurement. It demonstrates which eye had a higher CCT for each individual and the difference between the two eyes can be visualised, very minimal insignificant differences were noted between the two eyes in majority of the subjects.

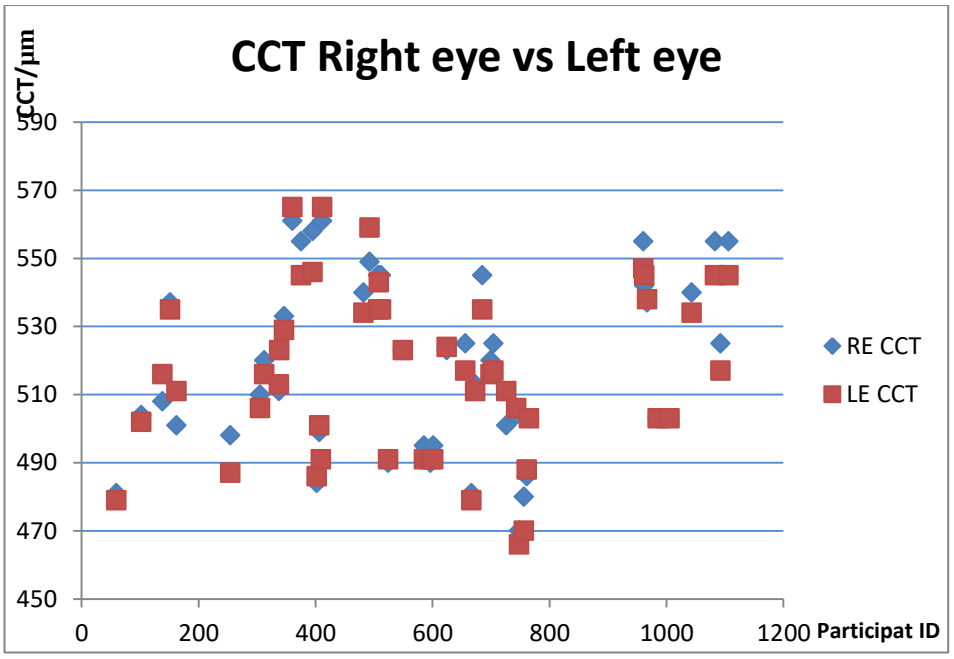


Figure 19: Distribution of CCT measurements taken

The average contrast sensitivity as measured by the Pelli Robson chart was found to be log contrast 1.50 for both the RE and LE. Reduced contrast was found in 25% of the 114 eyes assessed with an age-range of 6-12 years. Figure 20 is a display of the varied range of CS measurements taken in the investigation of pre-clinical KC in all the high-risk subjects found to not have clinical KC.

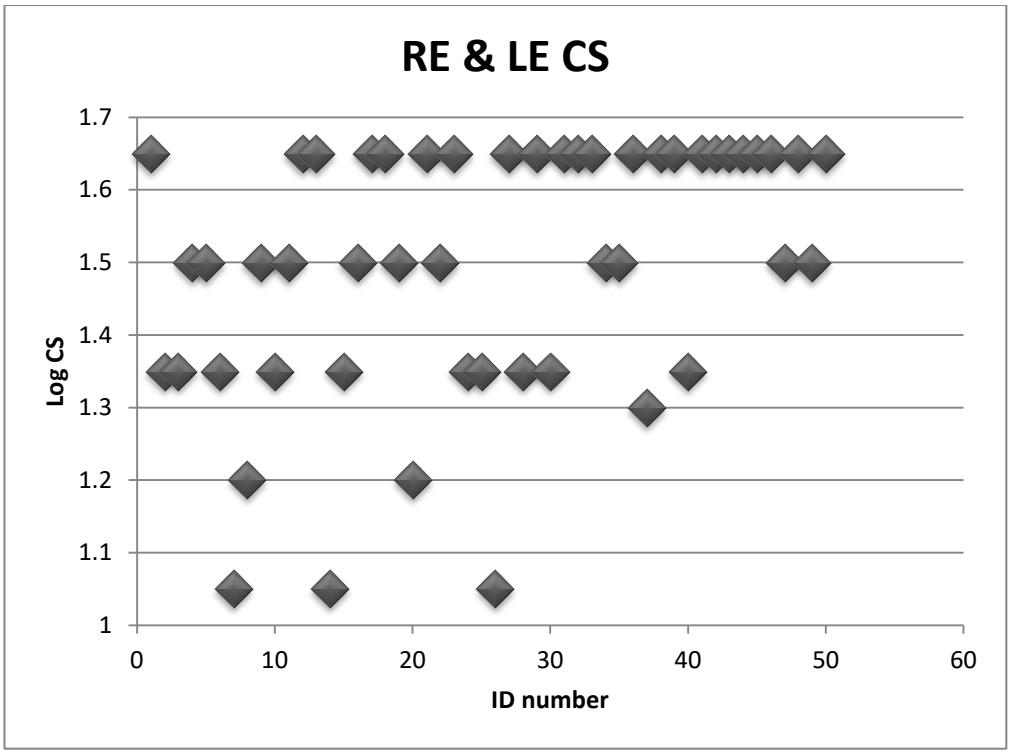


Figure 20: CS distribution for 114 eyes with an elevated risk of developing KC

Figure 21 shows the spread of CS values by diagnosis showing a similar median between subjects diagnosed with KC and those found to be healthy.

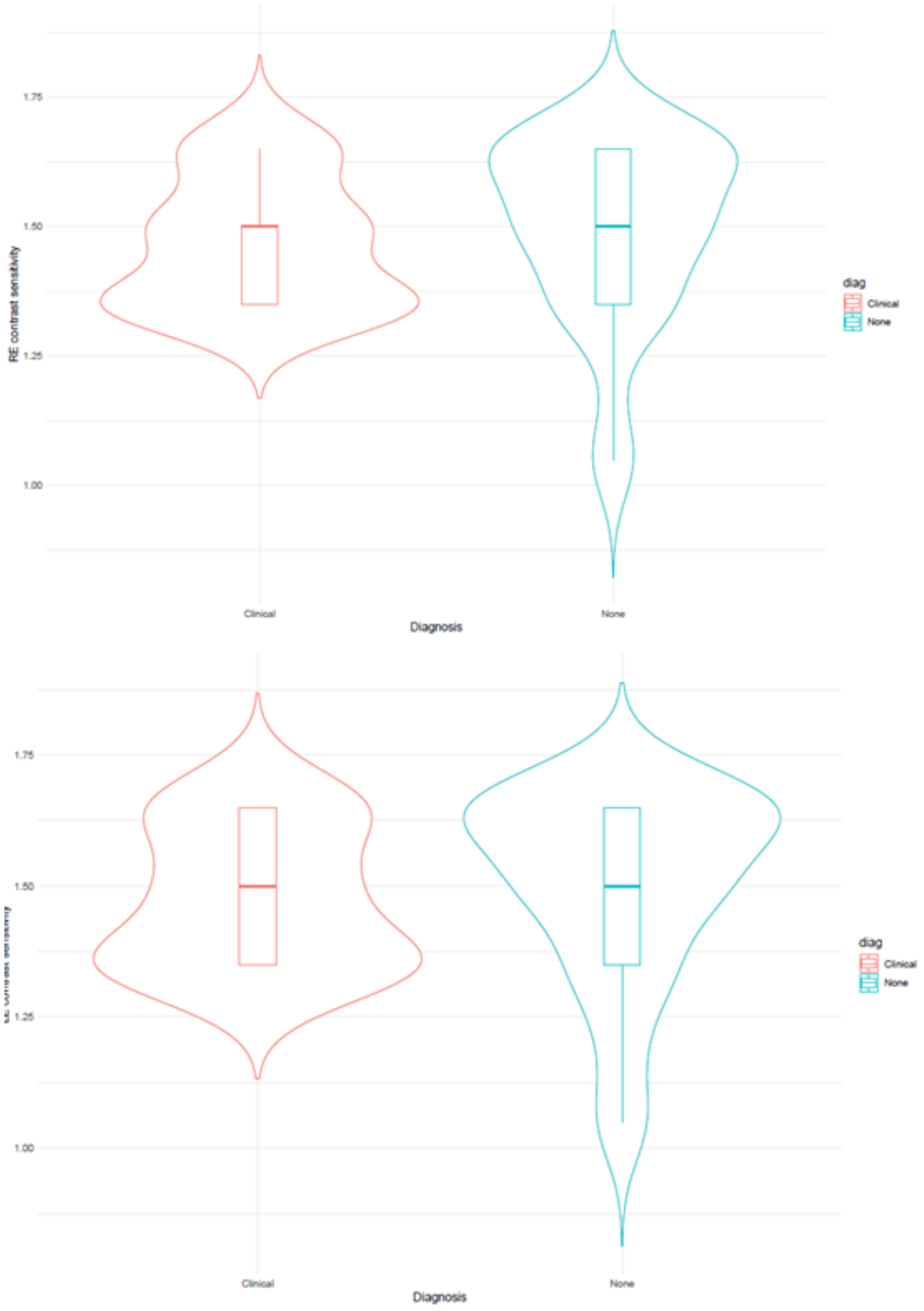


Figure 21: RE and LE CS distribution diagnosis. Clinical KC includes subjects diagnosed with pre-clinical KC.

The CS ROC curve displays inconsistencies (Figure 22).

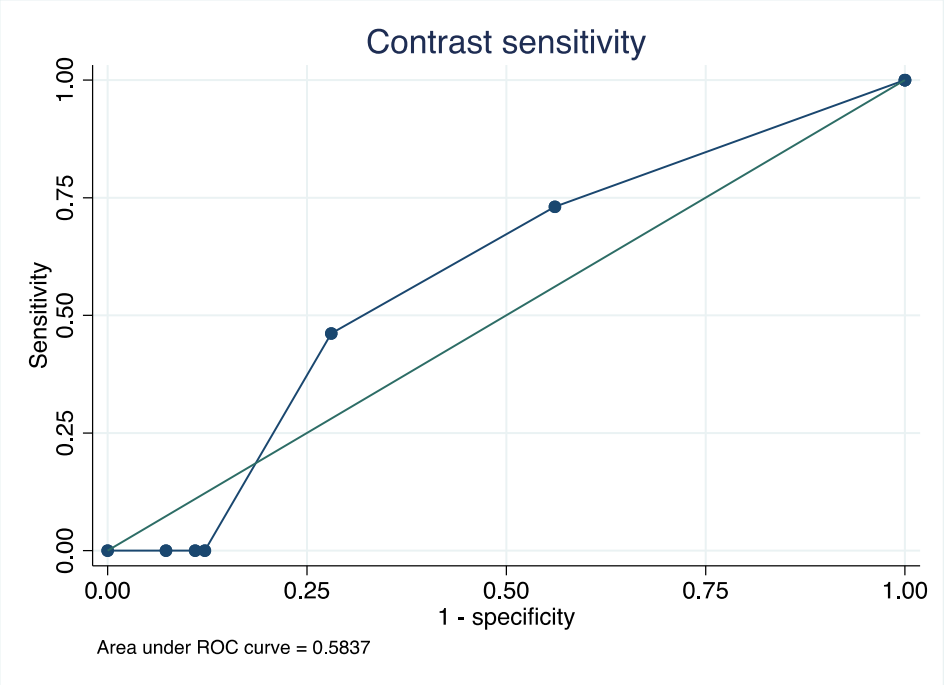


Figure 22: ROC curve for CS measurements in the investigation of preclinical KC

4.5 Objective 4: Determine the age most associated with early signs of KC in children living in urban Harare

The age range of the subgroup of subjects diagnosed with clinical and pre-clinical KC was 6-12yrs with a median of 11yrs and mean of 10.8±1.5yrs. Figure 23 below gives more information on the distribution of the subjects examined by age. The coefficient of determination is 88%.

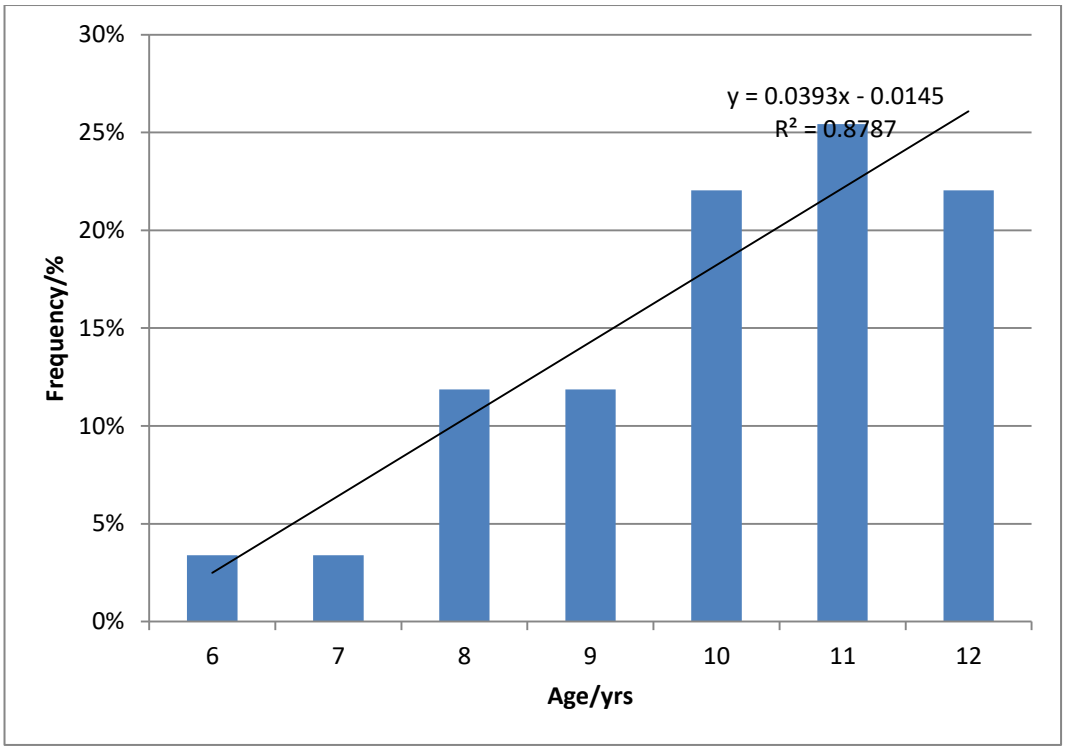


Figure 23: Age distribution of subjects at higher risk of developing KC

The final diagnosis was coded into binary with none=0 and clinical/preclinical =1 to generate the chi square age analysis. Figure 24 shows the spread of subjects diagnosed with either preclinical/clinical keratoconus by age with a coefficient r of 60%.

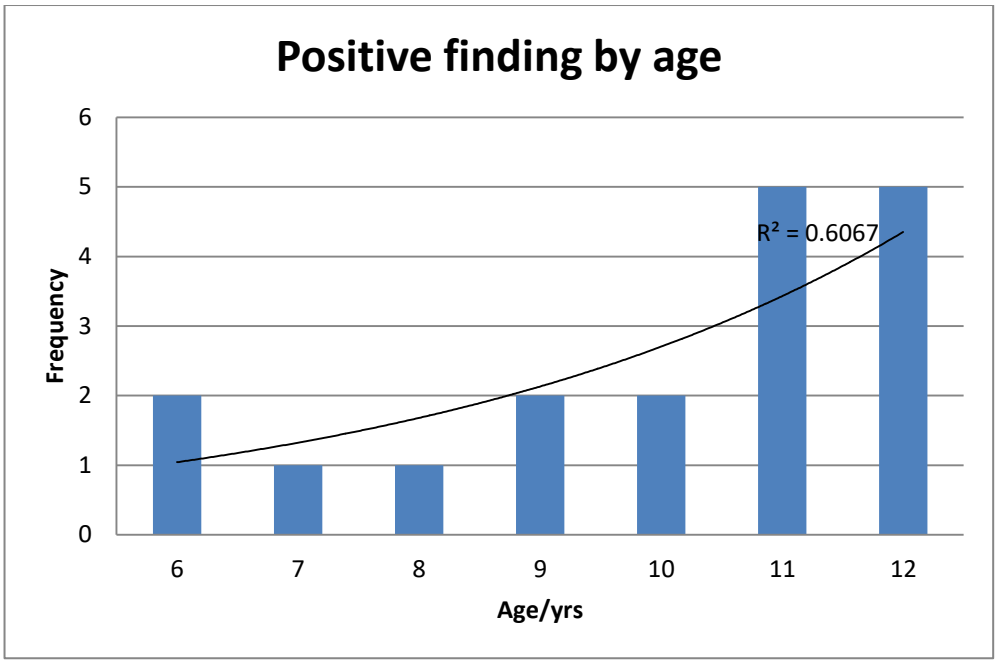


Figure 24: Age distribution of subjects with a positive diagnosis for KC

Other clinical and pre-clinical signs of KC encountered in the relevant subgroup are detailed in Figure 25. Keratometry readings >/=45D were encountered in 44% of the high-risk subjects, displaced corneal centres were found in 54% of the high-risk subjects and anterior stroma steepening was documented in 29% of the high-risk subjects. The prevalence of advanced KC signs such as corneal scarring and the Munson sign was very low.

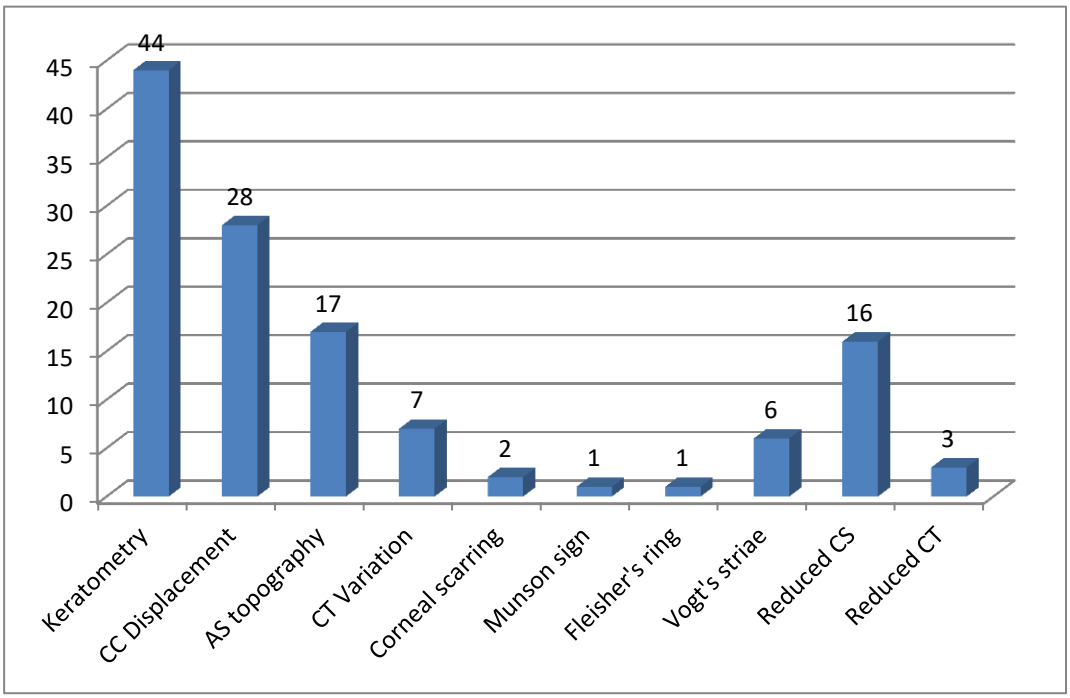


Figure 25: Clinical and pre-clinical KC signs found in the cohort

The chi square test was employed to test the null hypothesis; the prevalence of KC is not affected by age between the age of 6 and 12 years. Additional information is available in Table 12.

Table 11: Chi square analysis of age influence on diagnosis

	Yes	**No**	**TOTAL**
6-7yrs	3(1.22) [2.60]	1(2.78) [1.14]	4
8-9yrs	3(4.27) [0.38]	11 (9.73) [0.17]	14
10yrs	2(3.97) [0.97]	11 (9.03) [0.43]	13
11yrs	**5(4.58) [0.04]**	**10(10.42) [0.02]**	**15**
12yrs	5(3.97) [0.27]	8(9.03) [0.12]	13
TOTAL	18	41	59

$X^2(1; N=59) = 6.126$; $p=0.19$ therefore hypothesis is valid as $p>0.05$

4.6 Objective 5: Develop an algorithmic approach for the early detection and management of KC

4.6.1 Questionnaire analysis

The logistic regression results displayed in Table 13 below show that male children are 89% less likely to be referred for clinical testing of KC compared to females. Religion of the child was non-contributory. This may be due to the fact that majority of the subjects were Christians. Participants who had an affluent background were 74% more likely to be referred for clinical tests. Results also show that subjects who had injuries or surgery were 78% more likely to be referred for the clinical exam. Interesting to note is that subjects with high UV exposure were 87% less likely to be considered high risk for the development of KC compared to those with lower UV exposure. Results indicate that the higher VDU use subjects had 3% more chances of being considered high risk for the development of KC compared to those who had relatively low VDU use. A positive history of CL use in the past meant one had a 74% higher chance of being flagged as high risk. Ethnicity and age could not be used since 99.5% of the participants belonged to African ethnicity and all were between 6-12 years of age (Table 13).

Table 12: Logistic regression analysis of environmental factors

Factor	**Factor level**	**Odds Ratio**	**Std. Err.**	***p-value***
Gender(female)	Male	0.89	0.21	*0.64*
Religion (ATR)	ATR	1.00	-	-
	Christian	1.00	-	-
	Muslim	1.00	-	-
Affluent (no)	yes	1.74	0.65	*0.14*
Heard of kc (no)	yes	1.59	0.64	*0.25*
Health diet (no)	yes	1.85	0.72	*0.12*
Injuries/surgery (no)	yes	1.78	0.77	*0.19*
UV exposure (no)	yes	0.87	0.23	*0.60*
VDU exposure (no)	yes	1.03	0.26	*0.91*
CL use in the past (no)	yes	1.74	1.20	*0.42*

4.6.2 Other considerations for algorithmic development

The other information to be considered in the development of the algorithm include the distribution of pre-clinical signs encountered by age, the actual early signs prevalent in the young population resident in urban Harare and risk score calculating tool. This information is detailed in sections 4.2, 4.4, and 4.5 of this chapter.

4.7 Summary

A total of 1 153 subjects were recruited for this study and 959 included in the data analysis. A study sample that was largely of Christian religion and African descent aged between 6 and 12 years was evaluated. About 93% of the study sample had never heard of KC, 82% were affluent and 50% spent a lot of time outdoors. The study sample was generally healthy, reporting frequent consumption of protein, fruits and vegetables. Visual acuity was found to be reduced in 17% of the eyes tested. KCR scores recorded ranged between 0 and 12. After the screening protocol, 88% of the subjects were discharged and 12% were flagged as being at risk for the development of KC. A KCR score of 9 and above would improve the sensitivity and accuracy of the screening tool. Keratometry was a key diagnostic factor in the diagnosis of KC in this age group with the 45D cut-off employed proving to be effective. The prevalence of clinical KC by slit-lamp examination in urban Harare is 0.6%. Prevalence of pre-clinical KC is 1.4%. When pre-clinical KC is considered, the total prevalence goes up to 2% in the 6 to 12-year age group. In the high-risk sub-group; 9% had a positive family history for KC, 57% had reduced visual acuity in at-least one eye, 29% had VKC, 4% had at-least one form of atopic disease between hay-fever and eczema, 70% had itching eyes, 78% rubbed their eyes and 16% were asthmatic. The subjects diagnosed with clinical and pre-clinical KC were between 6 and 12yrs with a median of 11yrs. There was an equi-distribution of KC between males and females in this study sample although boys were less likely to be referred for the comprehensive exam.

CHAPTER 5: DISCUSSION

5.1 Introduction

Scientific research and publications, focusing on ocular conditions in the African context, are sparse in comparison to Western publications[227]. The deficit is even more evident when one factors in publications reporting on research conducted on Zimbabwean populations, with apt consideration of the resource constrained context. The dearth of eye health research that informs clinical service results in conditions like KC going undiagnosed or being ill-managed. The consequence of this is preventative visual impairment with severe impact on the quality of lives of those affected.

This study, the first of its kind in Zimbabwe, documented the prevalence of KC in primary school children in urban Harare, ascertained the risk factors for KC and characterised the clinical and pre-clinical signs associated with KC typically encountered within this selected population. The outcome of these investigations was to build on existing knowledge and literature by developing an evidence-based, comprehensive KC screening protocol. The broader expected impact is the contribution to the health system of a systematic screening routine for better detection of KC in children toward the timely management of the condition and successful minimization of visual impairment due to KC.

This chapter includes a discussion on the study findings; demographic characteristics of the population examined, prevalence of KC in primary school children of urban Harare and clinical signs found in those with clinical and pre-clinical KC as well as a recommended algorithmic process for the diagnosis and management of pre-clinical and early

5.2 Demographic details

A total of 1 153 subjects were drawn from primary school children, aged between 6 and 12 years, residing in urban Harare. Participants excluded by the inclusion/exclusion criterion were 43 leaving 959 for analysis. The female students accounted for 53% of the subjects which is reflective of the Zimbabwean population known to have more females (52%) than males by the 2022 census[228].

As expected, the Christian religion was the religion most reported, as Christianity is the main religion in Zimbabwe, with 69% of the Zimbabwean population reporting to be Christian[229]. This explains the absence of a key risk factor, consanguinity, encountered in other religious populations allowing marriage between blood relatives[230] , as Christianity does not permit inter-related marriages. However, due to changing migration patterns in much of Africa and the world at large, it is prudent for planners of KC screening programmes to always consider consanguinity when screening in schools where the children are of religious faiths that do allow inter-related marriages.

The subjects were predominantly of African ethnicity and only 1% of mixed ethnicity. This is due to the fact that the study was based in government schools which are largely populated by children from middle income African households. This is also reflective of the Zimbabwean population which is 98% African race and only 2% accounts for Indians, Caucasian, Asian and mixed race people combined[229]. Hence, the results will be an appropriate reflection of an African Zimbabwean school population and may be extrapolated to other urban school communities across the country.

The average age of the subjects was 9 years old. The age distribution graph of the study population showed an increase in the number of participants as the age increased. This may be due to the fact that the younger ages were more likely to forget to give their parents the consent forms and may have had a harder time explaining the study to their parents compared to the more senior grades. The higher grades are also more likely to actively request to participate in the study if they had a known problem with their eyes compared

to the lower grades that may not yet be aware of any vision problems present. The highest enrolment was noted in the 11 year olds as they accounted for 21% of the study population, this was four times higher in comparison to the lowest enrolment noted in the 6 year old age group, which accounted for just 5% of the total study population. The fewer 6-8-year-olds raises concern as, contrary to previous belief, research suggests that KC starts in children as young as 6 years old[156,231,232]. This variation highlights the importance of making such screening programs mandatory across the school to ensure all the children get an opportunity to be screened for conditions such as KC. Requiring the parents to choose to opt-in may exclude some students that need the care either due to a lack of knowledge and poor appreciation of the importance of such programs on the parents' part. KC information could be included in eye health awareness programmes that schools offer to parents and children.

To define the family background, presence of a medium to high level of education (Advanced level in secondary school and tertiary education) in at-least one of the parents was considered affluent. Majority of the subjects assessed (82%) were deemed to be affluent. This was further supported by the fact that 85% of the subjects reported having a healthy diet at home characterised by regular intakes of meat, fish and fruit. Frequent computer use was notable with 43% reporting to be spending more than eight hours per week on screen time. This seemed to be balanced by 50% of subjects who reported to be spending a significant amount of time outdoors in the sun. It is therefore plausible to conclude that the study population was reflective of a typical Zimbabwean family that resides in urban Harare, where the demographic profile excludes poor parental education, poor nutrition and high UV exposure from being risk factors applicable in this specific community. It is recommended that similar studies be conducted in rural areas across the country that are known to have a much lower socioeconomic profile as they may yield different risk factor data[156,226,233].

5.3 Objective 1 Determine the risk profile of children with KC

5.3.1 Gender

Equal proportions of male subjects and female subjects were flagged as high risk for the development of KC making gender an insignificant variable *(p=0.464)*. Correlation analysis of gender showed that there were weak correlations between gender and diagnosis of clinical KC *(p=0.497)*. In early years. KC was thought to affect boys more than girls[24,42,163,174]. The difference may be due to the fact that these previous studies focused on age-groups significantly higher than in this study. It was also noted by Gordon-Shaag et al., (2015) that most of the studies that reported a gender disparity were carried out in a clinical setting which may not necessarily represent the community spread. Although women are generally known to present to health care facilities more than men[234,235]; men may seek out eye care more readily than women because visual impairment linked to their distance visual acuity affects productivity and their ability to work and provide for their families.

5.3.2 Age

The age group under consideration in this study was between the ages of 6-12 years. To the researcher's knowledge, there are no studies on keratoconus exclusively focusing on candidates under the age of 12. The nearest age group found was from a study, conducted in a Mexican ophthalmology clinic[36] that focused on subjects aged 12 to 20 years, and which found that KC was more prevalent in females. However, consistent with this study's findings and studies on the African continent[204]; a study in Egypt which focused on refractive surgery patients also found no gender differences[46]. Pooled prevalence from other studies in Egypt also reported no significant association between gender and the prevalence of KC[204].

KC is said to present during the pre-pubescent years[184] and progress though life until such a time the corneal curvature ceases to change. It is for this reason the researcher chose to screen for KC so as to evaluate the presenting signs and symptoms before it results in impaired vision. Similarly, findings in this study have 11years as the mean age of the subjects considered to have an increased risk for the development of KC. This age may be falsely skewed to the right due to the increased numbers in subjects screened per age bracket that was observed as the age increased.

The average age of the subjects found to be at a reduced risk of developing KC in this study was 9 years old. The age of the subject was found to be insignificant when considering the final diagnosis of clinical KC. The age range of the subjects diagnosed with clinical KC was 8-12 years. A clinical diagnosis of KC at the age of 8 years suggests that onset predated presentation in this study as the candidate had never had their eyes tested before. An earlier age of onset also applies to the other subjects who were all diagnosed with clinical KC at 12 years old and below. These findings challenge literature that states that the age of onset is in the teenage years and early twenty's [2,23,24,204,236]. The retrospective study of subjects aged between 10 years and 20years in a Mexico clinic found the average age of presentation to be 16 years[36]. It is known that KC patients often present much later than the age of onset[42]. Patients tend to present for care when visual performance is affected typically with medium-advanced keratoconic disease[223], which may imply that in the cited studies, the age of onset was younger than the teen years reported.

Hashemi et al.,(2020) reported the presence of corneal changes consistent with KC in the younger children[232]. This study's findings are consistent with this observation. One of the limitations in this study is that it had very few subjects diagnosed with clinical KC, which hindered the confirmation of statistical significance. However, the information is still clinically important as the age of onset in Zimbabwe may be earlier than that recorded elsewhere. It is also interesting to note that the youngest subjects diagnosed with clinical KC were male. The age distribution of the subjects diagnosed with clinical KC shows the youngest

being 8 years old and 88% of the sub-group 11 years old and above. Given the nature of the condition under consideration, it would be expected that the prevalence increases with age. Further investigation, with larger sample sizes, are recommended to explore and possibly confirm this preliminary suggestion of age of KC onset varying along gender lines with males having a younger age of onset compared to females.

Additionally, valuable information on the age of onset can be further revealed by longitudinally following the subjects that were found to have pre-clinical signs of KC over the next few years. This would help ascertain how many actually develop clinical KC and to note the age of clinical conversion for better informed evidence based clinical practices. Given that the prevalence of KC is known to increase as age increases[40,172], more clinical KC cases included in the analysis over a few years will make for a more conclusive results.

5.3.3 Religion and Ethnicity

The subjects considered in this study were predominantly of Christian religion. Other religions known to be present in ZWE, albeit in lower numbers, were not considered due to lack of representation in the study. The dominant presence by Christianity explains why there was no statistically significant association between the referral outcome and religion *(p=0.413)*.

The correlation analysis on the influence of religion on the diagnosis of clinical KC showed weak correlations *(p=0.233)*, which can be due to the lack of representation of the other religions in this study. Consanguinity; which is used to describe a situation where the parents are related is a known risk factor for the development of KC[33,35,38,237]. It is particularly important to note the subjects' religion when considering the risk of developing KC, as subjects of Muslim background have been shown repeatedly[33,35,237] to have a higher predisposition for the development of KC due to the cultural acceptance of marriages between individuals with common ancestors.

It is therefore imperative that in the event that a KC screening is being carried out in a setting with a more varied distribution of religious backgrounds, the subjects' religious conviction should be taken into consideration. Subjects governed by Christian values typically frown on consanguinity such that it made the enquiry on this topic during case history difficult. It may also be considered a learning point for the development of future questionnaires to establish a more palatable way of presenting this question particularly in non-practising communities.

Ethnicity was also statistically insignificant as 12% of the African subjects were referred for a clinical exam as was 17% of the mixed-race subjects *(p=0.546)*. It was not possible to establish the true impact of ethnicity as 99% of the study subjects were of African descent. However, as the Zimbabwean population is predominantly of African heritage and KC is known to be more prevalent in people of colour, it further highlights the importance of investigating KC at community level in the country.

5.3.4 Affluence and Diet

It is widely appreciated that financial resources and worldly exposure have a strong influence on the lifestyle adopted in a family. As this study population is resident in urban Harare, parent or guardian education levels were used to differentiate them and categorize one as affluent or not. There was a statistically significant association between affluent level and the referral outcome *(p=0.040)*. Parental level of education and socioeconomic standing has been shown to influence severity of disease in KC patients due to reduced health literacy[233,238].

The affluent subgroup had 12% of the subjects flagged as high risk for the development of KC compared to the less affluent group that had 7% of the subjects referred for a comprehensive eye exam. This may be due to the fact that the affluent group was four times the size of the less affluent group. The higher percentage recorded in the more affluent group may also be due to a higher consent rate amongst this group due to a

higher level of education, better level of knowledge on general health practices and specifically eye care practices that resulted in them opting in for the study. Contrary to other studies, the level of affluence was however insignificant when it came to the diagnosis of clinical KC *(p=0.723)*, which may have been influenced by the underrepresentation in this study of parents with lower than secondary and tertiary education, a factor included in affluence determination.

Multiple servings of fruits, vegetables, meat and fish per week were used to categorise one as healthy or not. Questions on the diet helped to give the research team an idea of possible nutritional deficiencies which have been shown to influence the development of KC[191]. One particular question looked to establish red meat consumption which can be linked to iron concentration in the body[191,195]. Another question enquired on the number of times and frequency of fruit consumptions can be linked to the vitamin C concentration in the body[191]. There was no statistically significant association between a healthy diet and referral outcome. Healthy subjects had a 12% referral outcome whilst 10% of the less healthy subjects were considered at risk of developing KC. The 2% difference between the groups was not statistically significant *(p=0.285)*. This may be due to the fact that 85% of the study population was considered healthy as is typical of medium income family resident in urban Harare. Sufficient sources of iron, vitamin D, vitamin C and other such protective nutrients contributes to the health of the cornea which explains the lack of association between diet and diagnosis of clinical KC *(p=0.12)* in this study.

5.3.5 Contact lens use and mechanical abrasions

A positive history of contact lens use was previously suspected to be a contributing factor in the development of KC as it was thought that the mechanical rubbing contributed to the inflammation[150,151,239]. Only 2% of the study population reported to have used contact lenses (CL) in the past but none of them were found to have KC. Only 14% of CL users were considered high risk for the development of KC. CL

use was not a significant factor in the screened subjects *(p=0.510)*. It therefore follows that CL use did not contribute to the development of KC *(p=0.964)*. This finding is similar to that reported by Almusawi et al., (2021) who excluded use of contact lenses as a causative factor in the development of KC in a retrospective study of age and gender matched controls. Similar conclusions are reported elsewhere[152].

A separate retrospective study by Macsai et al., (1990) failed to unreservedly distance CL use from the development or progression of KC therefore called it a circumstantial cause. Many KC patients have had to use CL for visual improvement making it impossible to rule out CL contribution to the progression of the disease. In addition, one cannot unreservedly exclude CL as a causative factor as research has found that KC appears to present later in CL users suggesting the use of CLs plays a role in its development[151]. It is worth noting that CL uptake remains very low in Zimbabwe due to affordability and accessibility constraints and should CL play a role, albeit minimal; it is therefore not expected that the use of CLs currently in the local market to significantly increase the occurrence of the condition.

About 6% of the study group had a positive history of incidences such as ocular injuries or surgeries. Of this 6%, 22% were considered high risk for the development of KC and this was statistically significant *(p=0.017)*. A small percentage of the female subjects (5%) reported a history of injuries or surgeries to the eyes. Interestingly, once in the high risk subgroup a history of injuries and surgeries was insignificant to the development of KC *(p=0.388)* as 50% of the subjects diagnosed with KC did not have a history of injuries or surgeries to the eyes. This is consistent with findings reported in other studies where past ocular injuries and surgeries were found to be insignificant in the development of KC.[38] It has been reported that ocular surgeries would have to significantly penetrate the cornea into the deeper stromal layers to cause a corneal ectasia [10,113,115,240] and it therefore follows that superficial corneal injuries would not contribute to the development of KC.

CL use and past ocular injuries and surgeries were found to be contributing factors in subjects considered to be high risk for the development of KC in other studies which included older subjects but insignificant in the development of KC in this age group. The researcher proposes that the factors be considered if older age groups are being evaluated as the effects may change as the subjects get older.

5.3.6 Atopy, asthma and hay fever

In this study atopy was described as a skin irregularity and was considered separately to asthma and hay fever which are actually atopic conditions by definition. This was done to consider the various forms of atopy in their own right as experience has shown that they affect ocular structures differently although they can co-exist. Atopy was reported in 4% of the study participants with 43% of these subjects being marked as high risk. Atopy was awarded a risk score of 2 meaning it had to co-exist with other KC risk factors for the subject to be considered as having a risk for the development of KC. As a standalone variable atopy was insignificant in the development of KC possibly due to it being uncommon in the population considered.

Asthma and hay fever were noted in 5% of the study population. Atopic conditions were of low prevalence in this study population. An earlier study on paediatric patients of similar background presenting for allergen testing in Zimbabwe had highlighted eczema and asthma as the most prevalent forms of atopy in the population[241]. The fact that both variations were not a prevalent symptom reported by the subjects suggests that atopic conditions are not a risk factor to worry about in the paediatric urban population in Harare. This may be due to absence of environmental aggressors for these conditions which may be prevalent in a different environment.

5.3.7 Vernal keratoconjunctivitis

Just 5% of the study cohort was positive for VKC. This was similar to findings detailed in a Rwandan study that reported 4% VKC prevalence in school aged children[28]. The majority (68%) of these subjects with VKC had a referral outcome and 50% of them had clinical KC. It would have been interesting to see how many of them had abnormal tomography maps which could mean that KC may develop at a later stage. This analysis was however outside the scope of the study, but would be a good follow-up study. VKC was awarded a risk score of 2 in the researcher's analysis, meaning it had to coexist with at-least one other variable as previous research has shown that VKC alone does not result in KC.

A study in Nigeria found keratopathy in 1.1% of patients with allergic conjunctivitis[200]. This finding however contradicts the findings in Kenya that report a higher KC prevalence of 31% in VKC patients[54]. This variation may be due to differing age-groups as this particular study focused on subjects under the age of 12 and the Kenyan study included participants up to 24 years old. By the nature of the condition, KC prevalence increases with age; we would therefore expect to see an increase in the prevalence of KC in the group as age increases. Despite VKC being one of the top five symptoms noted in the high risk group, it had no discernible effects on the diagnosis of clinical KC as 50% did not have clinical KC. The low prevalence of KC in this study limited the statistical significance of the enquiry. A 50% prevalence of clinical KC among VKC subjects would be the highest value reported to date compared to other studies in different locations[66,130,198,199]. A larger sample size would be needed to verify this finding. Additionally, as the study population considered in this study is very young, we would expect an increase in this value as the subjects get older and pre-clinical signs progress.

5.3.8 Itchy eyes and eye rubbing

Itchy eyes were reported by 35% of the study population and similarly 31% reported frequent eye rubbing. Eye rubbing was awarded a risk score of 3 and itchy eyes a risk score of 1 guided by the risk profile generated from literature[152,242]. The slightly lower percentage of eye rubbing may be explained by the fact that some subjects do experience itchy eyes but do not rub as frequently and hence the disparity. Interestingly, 82% of the eye-rubbing subgroup was classified as high risk whilst 92% of the subjects with itchy eyes were flagged. The difference can be explained by the difference in risk scores awarded. Both variables had no effect on referral outcome although they were the two most frequently reported symptoms in the study. This is probably due to the fact that other ocular conditions manifest as itchy eyes needing rubbing such as dry eyes and therefore this common symptom is not a good indicator for KC in this subgroup. Additionally, these activities may become more consequential as the subjects get older as it is the repetitive nature of the eye rubbing that has been shown to be problematic[142,242] It should still be considered when investigating for KC given the overwhelming literature that links eye rubbing to the development of KC[142,150,152,242].

5.3.9 UV exposure and VDU use

Approximately half the study group reported high UV exposure whilst just over 40% reported high screen time. Just over 10% of both subgroups were flagged for further exams with both variables having no statistically significant association with the outcome. The subjects diagnosed with clinical KC reported to spend a lot of time outdoors with just 17% reporting low UV exposures. This finding is to be expected as previous studies suggest that high UV exposure leads to the production of reactive oxidative species that are detrimental to the health of the cornea[148,149]. The weak correlation coefficient reported for UV exposure in the study's data analysis can be due to the small sample size which would generate inconsistent results.

VDU usage is less common in the 6-12 year old age bracket compared to the working class. Computer use is reported to be associated with increased eye rubbing due to a higher prevalence of dry eyes among computer users[243]. The researcher therefore proposes that it be not considered as a standalone variable in the investigation of KC in school children as there is no research, to the researcher's knowledge, that found that it affects the development or progression of KC. Considering eye-rubbing will indirectly include this variable.

5.3.10 Visual acuity and spectacle wear

Visual acuity (VA) remains a key component of any screening program due to its accessibility, ease of interpretation and is delegation savvy making it an easy to deliver task even in the absence of expert human resources. The study used 6/9 Snellen acuity as the cut-off line. Although 6/12 is universally accepted as a safe cut-off point when considering visual acuity and impact on functionality, the study went one line better so as to identify any candidates with early onset disease[244]. Presenting visual acuity was reduced in 17% of the eyes examined, a finding consistent with a Malawian based study in a similar population that also employed a 6/9 cut off and found reduced VA in 13% of the subjects[245]. Similarly, a Qatar based school screening program found reduced visual acuity in 17% of the 99 661 pupils assessed although they used a more stringent cut off of 6/6[246]. This finding speaks to the possibility of undiagnosed refractive errors in the subjects screened.

Reduced visual acuity was the third highest risk factor noted in the subjects that were classed as high risk for the development of KC. Only 14% of those with reduced presenting visual acuity were flagged as high risk for KC development, showing that the remaining 86% had reduced vision for other reasons needing further attention. Reduced visual acuity in children may be due to uncorrected refractive errors, retinal pathologies, congenital cataracts and glaucoma [88,245,247,248]. Visual impairment has been shown to have a

significant detrimental effect on the mental health of the children living with the problem[249]. This finding highlights the need for a national school screening program to identify and manage all causes of impaired vision. Zimbabwe does not currently have a mandatory school screening program for eye care.

Of the subjects diagnosed with either clinical KC or pre-clinical KC, 47% had a presenting VA of 0.7 or weaker. Right eye (RE) visual acuity and Left eye (LE) visual acuity were considered separately. This shows that VA remains a very useful screening tool but using VA alone would have over-estimated the number of subjects at risk of developing KC and also excluded some subjects needing to be investigated further. The use of the questionnaire in combination with on-site retinoscopic scissors reflex assessments helped make the screening routine more specific

The level of VA measured ranged between 6/120 and 6/5 with an average of 6/7.5 ± 3 lines showing that a sizeable portion of the flagged students were already struggling with their visual performance. The study awarded reduced VA a risk score of 2 as visual acuity and fluctuations in refractive error are amongst the signs of KC[176,177,179]. Cumulatively almost 50% of the students flagged for further care had reduced presenting VA. This highlights the importance of considering other variables in addition to visual acuity when carrying out a visual screening program. If the study had considered VA alone; as most school screening programs do, it would have overlooked 50% of the subjects that needed further care as they would have been excluded by the adopted VA cut off. There was no gender preference noted and all of the subjects diagnosed with clinical KC had reduced VA.

As both KC and refractive errors have a genetic influence on them, history of spectacle use among the immediate family was investigated. A positive history of spectacle wear was reported in just 1.5% of the participants whilst 50% of the subjects diagnosed with clinical KC reported having a family member that wears spectacles.

5.3.11 Family history and knowledge of KC

Just 4% of the study population reported to have a positive history of KC and 7% stated they had knowledge of the condition. As these two variables are co-dependent, they will be combined for this discussion. Both values are very low and show the need of improved health education practices around eye care. From the 4% of subjects that had a positive family history, we can infer that KC is indeed present in the Harare community and further investigations on prevalence need to be done to ascertain the true extent of the problem. The researcher believes the 3% that did not have a positive family history but knew of KC had someone in their network that did have the condition as it is very unlikely to be general knowledge.

Of the 7% that had heard of KC, 21% were referred as being at an increased risk for KC development whilst only 1% of those with a positive family history (1 in 4) were considered high risk for the development of KC. This is consistent with findings reported by Tuft et al., (2012) in a twins study, they reported that KC was present in 28% of the immediate relatives when dizygotic and monozygotic families were combined[161]. A positive family history of KC was awarded a risk score of 3 on this study's risk factor scale. Three was the highest score possible for a single variable and despite this making up more than 50% of the necessary total to warrant a full exam, only a small portion of these subjects were considered high risk. This shows that the scoring system did not skew the referral outcomes.

There was a statistically significant *(p=.015)* association between knowledge of KC and referral outcome. Only 11% of the subjects that were not familiar with KC had a referral outcome. As knowledge of a condition in its own right is not expected to affect the probability of you developing this condition, this 10% difference in the result is interesting. It may be due to malingering whereby one can relate to a particular sign or symptom just because they are familiar with the said symptoms which would have resulted in false positives amongst the knowledgeable group. Malingering is not an uncommon

phenomenon in paediatric patients[250] and brings forward the importance of following the questionnaire with an actual exam to ascertain the true risk of developing KC.

Positive family history has been repeatedly shown to significantly increase the risk of developing KC[24,79,150,202]. Interestingly in this study, it was excluded as a causative factor with a negative correlation coefficient as none of the subjects diagnosed with clinical KC had a reported positive family history for the condition. This finding supports the notion that a genetic inclination requires an environmental trigger for KC to develop[42,150]. It also explains why not everyone with a positive family history of KC develops the condition. Increased risk does not mean one will definitely have the condition but rather should be used as a tool to guide lifestyle choices to minimise chances of developing the condition.

5.3.12 Referred vs Discharged subgroup

A two sample t-test was performed to compare the discharge group to the referred group to ascertain validity of the screening questionnaire. The two sample t test score of -3.5974 shows that the referred group is not comparable to the discharged group *(p=0.0003)* on 95% CI. The null hypothesis that there is no difference between the two groups is therefore rejected and therefore shows the questionnaire successfully segmented the subjects as desired. On graphical presentation the error bars do not overlap at all showing a significant difference between the two means. This confirms that this study's questionnaire and brief exam successfully differentiated and grouped candidates as was intended.

The total risk score cut-off was logically set to 5points for this study considering the characterisation of various risk factors detailed in literature[156,202,204,226]. On ROC curve plot analysing this cut off point showed inconsistencies as the curve dipped under the classifier line in some parts. The graph was also low with the highest curve noted at 0.56 showing low specificity for the desired diagnosis. This was also supported by the fact that the majority of the subjects flagged as high risk for the development of KC were then found to

be healthy post the comprehensive assessments. Linear regression analysis of the 5-point cut-off also shows statistically insignificant performance *(p=0.2).* Amending the cut off score to 9 improves accuracy and specificity as the ROC curve displayed below (Figure 26) for the 9point cut off stays above the classifier line. The linear regression analysis shows improved significance, with a p value of *0.04* and increased odds ratio of 4.63. The researcher therefore concludes that the 5-point cut-off used in the study was too low and recommend an upward revision to 9 points for future applications of this screening tool.

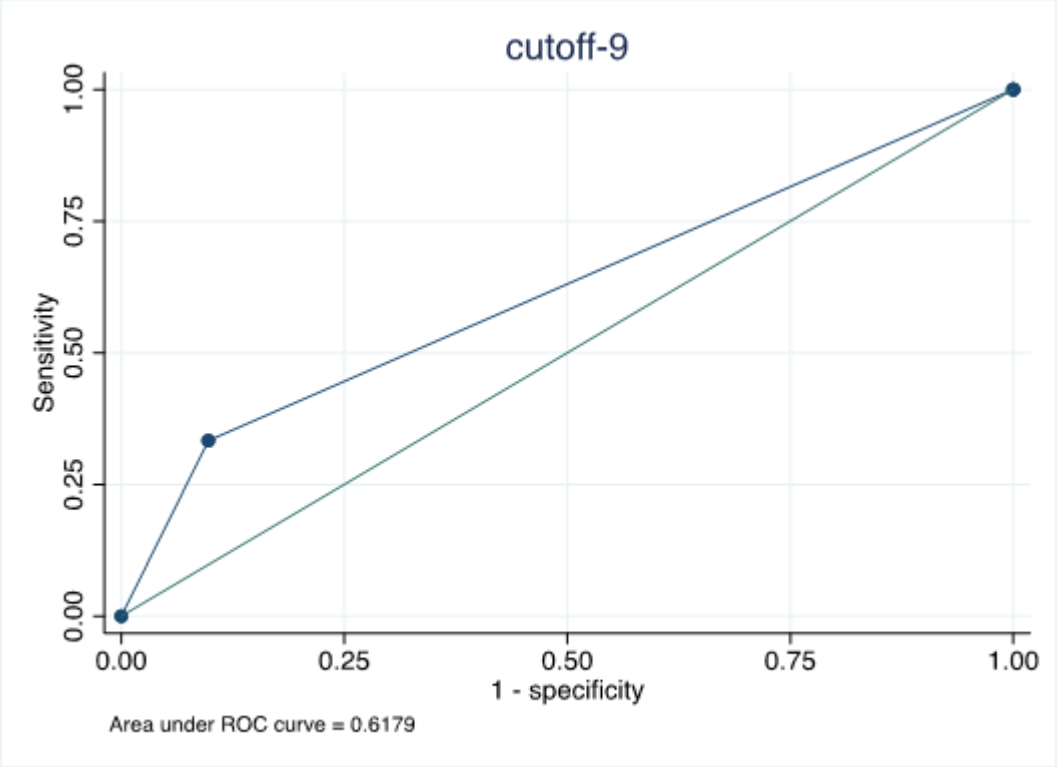


Figure 26: ROC curve of KCR cut off of >/=9

Vogt's striae, corneal scarring and Munson sign were the only clinical signs observed on slit lamp examination in this study. Vogt's striae were the most prevalent finding, which is to be expected in early disease. However, due to the small number of participants found to have clinical KC, very weak correlations were found between the risk factors under investigation and final diagnosis. A larger group of subjects pre-diagnosed with clinical KC would need to be evaluated to ascertain the true relationship between these variables; gender, religion, diet, UV exposure and CL use, and the prevalence of KC.

5.4 Objective 2: Prevalence of KC in children in urban Harare

The prevalence of clinical KC was found to be 630:100 000. This is a relatively low prevalence reported to date on the African continent. This may be due to the fact that this was the first in community investigation of KC, to the researcher's knowledge, whereas hospital-based studies found significantly higher prevalences[35,204]. It is also the first study to specifically consider the young 6-12 year age group. This study finding is comparable to the prevalence value reported in Gambia of 900:100 000 found in subjects with allergic conjunctivitis[66]. The difference may be explained by the different age-groups considered; the Gambia study sample went up to the age of 15 years whilst this particular study capped at 12 years. Allergic conjunctivitis has been shown to increase the risk of developing KC[198,199,251]. In addition, the fact that the subjects in the Gambian study had already been diagnosed with allergic conjunctivitis makes the study sample in Gambia a high risk sample which would also explain the slightly higher prevalence reported in Gambia. A hospital based Kenyan study reported a KC prevalence of 10% when diagnosed based on clinical findings alone, 14.6% when diagnosis is based on keratometry and 30.9% when the diagnosis is based on Topography[54]. The higher prevalence reported in this study may be due to the higher risk subjects being assessed.

The study's prevalence finding is comparable to an Italian study that assessed subjects 18-25 years of age and found a prevalence of 750:100 000[51]. Although the study populations under evaluation are quite different, it is worth noting the similarities as the environmental variables experienced in Italy of a warm climate are similar to those experienced in Zimbabwe. An American based study by Hoffstetter et al., (1959) also found a prevalence of 600:100 000 which is comparable to this study's findings. They also used keratometry measurements as a key diagnostic tool albeit in an older population. Prevalence values reported elsewhere around the globe are lower, as seen in the Asia Pacific region, possibly due to religion

and ethnicity differences[224]. Interestingly, this study's finding is higher than the prevalence 0f 440:100 000 reported in a Nigerian study[59]. This may be because the Nigerian study evaluated subjects with visual impairment and hence may have under estimated the prevalence of KC, as those with mild-medium KC, which is still correctable by standard optical aids, may have been overlooked in their study.

The study defined clinical KC as having keratometry readings>/=45D in either meridian of either eye and at least one slit lamp sign associated with KC such as Vogt's striae, Fleisher's ring, Munson sign and the Rizutti sign. The 45D cut-off may be considered low but the study intentionally set this cut-off as it was focusing on a young population that is likely to have early disease that is then characterised by mild steepening of the corneal curvature. Research has shown that advanced corneal assessment techniques that detail the corneal structure at a deeper level and not just superficially are more sensitive to the presence of KC and result in an increased prevalence of KC[54,89,251,252]. Using advanced imaging techniques and a 48D cut off, prevalence of KC was found to be between 40-960:100 000[58,253]. In similar fashion, we would expect the prevalence of KC to be higher than reported, should more advanced corneal imaging techniques, such as corneal tomography with posterior stroma imaging capabilities be employed. Unfortunately, such instruments were not available at the researcher's disposal for this study.

In this study the researcher described preclinical KC as having keratometry readings>/=45D and the presence of two other signs characteristic of pre-clinical KC such as reduced CS, displaced corneal centre, reduced CT and variations in CT across the cornea. The prevalence of preclinical KC was found to be 1.36% (1 360:100 000). Ideally this corneal assessment should have been done with the use of a corneal tomographer that can detail the posterior corneal surface, which is key in the earliest diagnosis of pre-clinical KC[16,89,155]. This analysis would probably see this prevalence value increase but unfortunately, there was no access to a device with such capabilities for this study. It is worthwhile noting the usefulness of

simple accessible tests such as the CS chart (Figure 27) and corneal pachymetry measuring devices that can be utilised in the absence of advanced corneal imaging techniques.

Figure 27 Pelli Robson CS chart

The combined prevalence of KC in this urban population is 2% (2 000:100 000). This confirms the anecdotal claims of a high incidence of KC being encountered in Harare eye care hospitals. That said, this study's findings are significantly lower than the prevalence values reported in Egypt that range between 1700 and 34 000:100 000[46–50]. This can be explained by the differing demographic qualities of the

populations under consideration. The Egyptian population is largely Arabic and practices consanguineous marriages that are known to increase the risk of KC. In addition, all the studies in Egypt used advanced corneal imaging devices which are known to be more sensitive to KC diagnosis compared to the slit lamp exam and would therefore report higher prevalence values compared to us. Environmental differences, such as UV exposure[202,226], may also explain the higher prevalence in Egypt.

This particular study is the first study, to the researcher's knowledge, to establish the prevalence of KC in Harare. Investing in advanced clinical instruments and implementing a school screening programs would go a long way in managing this condition. Until such investments are made in the purchase to more advanced diagnostic equipment such as ocular coherence tomographers, practitioners may utilise the resources they have at hand to proactively screen for KC and manage it accordingly to minimise the occurrence of potentially blinding events such as corneal hydrops if undetected.

5.5 Objective 3: Document preclinical signs of KC in children identified as high risk for KC development

Out of the 117 subjects that had a referral outcome, 46% were lost to follow up leaving us with a modest 63 subjects for this analysis. Of these 63; 6 (9.5%) subjects were diagnosed with clinical KC leaving 57 for the phase 2 part of the study. Ideally a larger sample size would have provided a stronger analysis statistically but the information obtained is still very useful. The most frequently reported symptoms were eye-rubbing, itchy eyes, reduced VA, presence of VKC and asthma, but in this section, focus shall be on the findings of the comprehensive exam and additional tests employed in the investigation of pre-clinical KC.

The violin plots (Figure 14) clearly show some overlap between the healthy subjects and those with a positive clinical diagnosis. To illicit useful information from the data gathered, for this objective the study focused on the signs of KC found in subjects considered to be at risk for the development of KC. The sub-group of the study population considered for this evaluation all underwent the phase 2 investigations for

pre-clinical KC. In the investigation for pre-clinical KC, six parameters were explored namely corneal curvature, location of corneal centre, topography, pachymetry map, central corneal thickness and contrast sensitivity.

5.5.1 Corneal curvature

Corneal keratometry measurements: Keratometry readings remain one of the most reliable and repeatable ways of characterising the cornea regardless of method used to obtain the measurement[89,254–256]. Forty four percent of the subjects had >/=45D with the youngest subject noted to be 6 years old. This was the second most prevalent finding in the presence of pre-clinical KC. Corneal curvature less than 48D classifies the condition as Grade 1 by the AmslerKrumeich scale.

An analysis of corneal curvature in 5 559 subjects, aged 6-12 years old, in Iran showed that the average corneal power is 43.5±1.96D with it being 0.82D steeper in girls than boys[231]. These values are comparable to this study's findings. A similar study in an older population found an average corneal power of 42.98D and 43.98D in the flattest and steepest meridians respectively[257]. This shows that the cornea becomes significantly flatter in adult life in the absence of disease. Paediatric studies report very steep corneas at birth; average 47.5D that flatten by the age of 5 years to an average of 45.50D in normal eyes[258,259] In this study, it was found that mildly-steep keratometry readings of 45D in either meridian were a popular finding consistent with the aforementioned findings. A corneal curvature of 45D therefore did not make for a good differentiating factor. However, Zhao et al., (2020) successfully diagnosed subclinical KC with a cut-off point of K>46.5D in an older population, ranging between 17-40 years, using the Orbscan topographer[260]. The researcher adopted similar parameters but reduced the cut-off to 45D as the subjects were younger. For increased sensitivity, corneal curvature had to be identified along with two other signs characteristic of KC to warrant a diagnosis of pre-clinical KC. Corneal curvature can be steep for other reasons such as corneal

astigmatism, myopia and paediatric cataracts[231,257,259,261] and so a finding of steep corneal curvature should be considered along with other clinical information for an accurate diagnosis.

The violin plots show distinct differences between the clinical group (preclinical KC combined with clinical KC) and the healthy subjects when corneal curvature is considered (Figure 16). This shows that the 45D cut off employed in this study was effective. The median values and the box plots in the clinical group do not overlap with the healthy group. The ROC curves for both the RE and LE (figure17) further show that the 45D value was a good cut off as the curve stays above the classifier line at all times and has a good degree of sensitivity displayed (0.89).

5.5.2 Topography

Anterior surface analysis was carried out using the Topcon RT 7000 topographer. Fig 28 is an example of the images obtained for analysis. Topography offers a more detailed anterior surface analysis over keratometry allowing for early diagnosis of KC[89,100,262–266] . Information on corneal curvature variations across the 6-8mm diameter analysis, skewed radial axis values and asymmetry between the two eyes are all identifiable on topography. These variables are important in the diagnosis of early KC such that any instrumentation with such abilities would be superior to keratometry alone in the investigation of KC[89] and hence the need for topography assessment in addition to the keratometry measurements taken in phase 1. Keratometry alone has been shown to be accurate in differentiating advanced KC from normal eyes but not normal eyes from early KC[267].

The anterior surface classification in this study involved separating the subjects into two subgroups; normal and abnormal. Abnormal anterior surface was defined as having at-least two signs characteristic of KC such as K readings above 45D in either meridian, skewed topography patterns, asymmetry between the two eyes and corneal astigmatism >1D. A longitudinal study of 778 subjects with form frustè KC highlighted these clinical signs as prevalent amongst the subjects that progressed from normal to clinical

KC[132,268]. Figure 28 is an actual map taken during the study, included here to demonstrate the information used for anterior surface analysis.

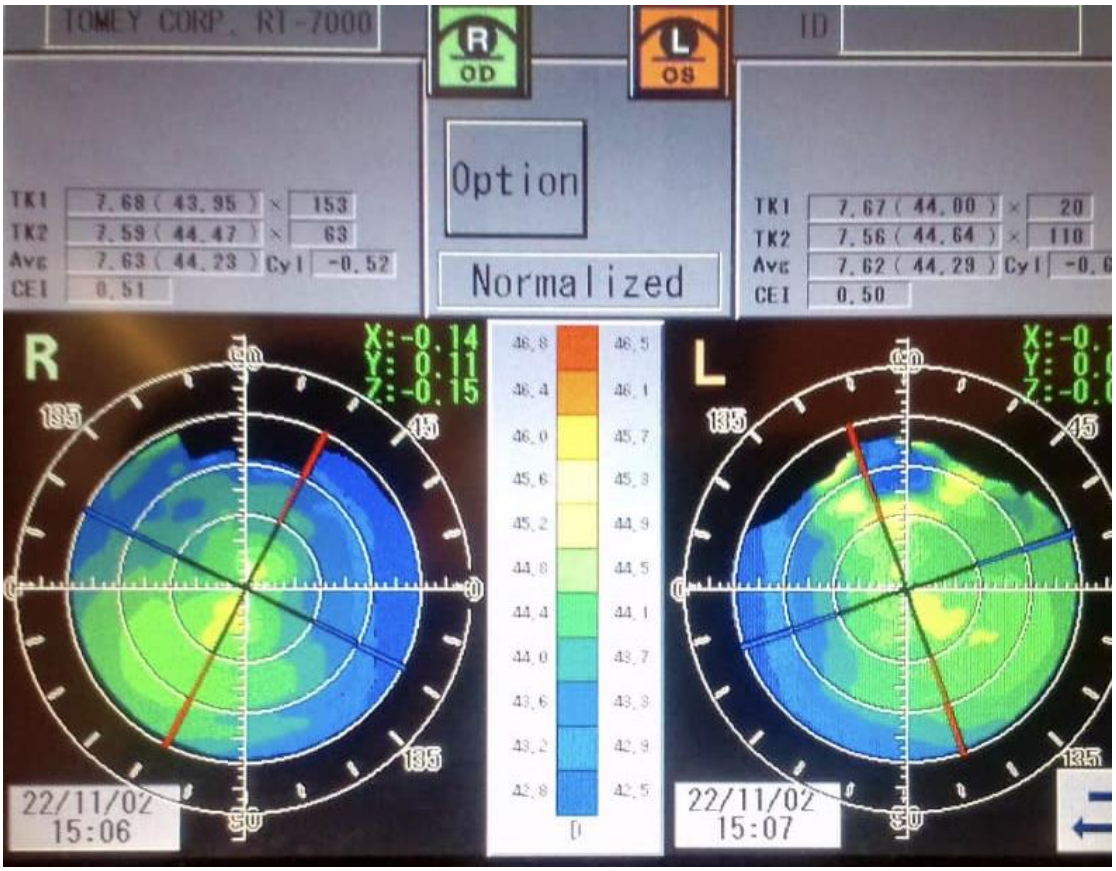


Figure 28 Topography maps of a patient being investigated for preclinical KC

Amongst the 57 high risk subjects that had topographical map analysis, 44% were found to have skewed diagrams; steep keratometry was noted in 44% of the subjects and 31% had corneal asymmetry between their two eyes and 19% had all three. A population based study of 442 randomly selected individuals reported corneal steepening as the most frequent abnormality encountered followed by skewed diagrams as was seen in this study as well[269]. However research has also shown that emmetropic eyes can have an asymmetric bow tie pattern[270] thus illustrating the need to consider all topographical analysis findings; radial axis and corneal astigmatism, in conjunction with the patterns. Consistent with this, the researcher

encountered a subset of subjects that displayed asymmetric bowties but had corneal curvatures flatter than 45D.

The average age of the subjects with an abnormal anterior surface was 10±2 years. A longitudinal study following how these young subjects progress over time would yield very useful information. It may follow that by the time the subject displays corneal power of 45D when older, having advanced from flatter readings, they would need to be managed differently if compared with a control group that advances from a naturally steep cornea that is normal when considered against a normative database.

After taking all parameters into consideration, 29% of the subjects were classified as having abnormal anterior surface and of these 65% were diagnosed with pre-clinical KC. The high prevalence of pre-clinical KC in subjects with anterior surface abnormalities shows that it is a significant factor useful tool in the identification of early KC when additional information such as corneal thickness and pachymetry mapping is considered in addition to corneal curvature[271,272].

5.5.3 Location of corneal centre

Corneal centre displacement is said to be present when the corneal centre and the thinnest part of the cornea do not coincide and the corneal centre appears displaced on a corneal pachymetry map[16,271,273,274] as seen on anterior surface corneal tomography using the Optovue anterior segment analyser. In this study, the corneal centre was found to be displaced in 54% of the subjects with an average age of 10±2 ranging from 6 to 12 years. The ability to document the location of the corneal centre makes corneal pachymetry maps clinically superior to ultrasound spot pachymetry[16,272,275]

One of the early signs of KC is the displacement of the corneal centre which then progresses to the infero nasally displaced cone in advanced disease[93,276]. In this study, the researcher was not able to document the cone location and magnitude index (CLMI) that has been shown to be sensitive in the diagnosis of KC including subclinical KC. The instruments at the researcher's disposal did not have this ability due to lack

of the appropriate software, hence only considered the location of the corneal centre as highlighted on the pachymetry map. The displacement of the thinnest corneal location has been documented in pre-clinical KC[92,129,273,277]. However, as was seen with keratometry, corneal centre displacement was present in over half the subjects examined. This is consistent with an earlier study that documented corneal centre displacement in over 90% of the subjects[278]. Similarly, this finding was largely inconsequential in the study by Liu et al., (1999), just as also observed. This illustrates the need to consider these parameters along with other clinical findings for an accurate diagnosis.

5.5.4 Pachymetry map and central corneal thickness

Qin et al (2011) investigated the accuracy of diagnosing KC based on a pachymetry map analysis and concluded that pachymetry map analysis was reliable in the screening for KC. Although their study would have benefitted from a larger sample size to make the outcomes more statistically relevant, the observations yielded very useful information and were reproduced by a separate study that concluded that tomography acquired pachymetry analysis could be utilised in the investigation of preclinical KC[16,274]. Similarly Kendrick et al., (2019) report that the use of a pachymetry map is more sensitive to the diagnosis of KC compared to using CCT alone[279,280]. In this study the researcher evaluated pachymetry maps generated from the Optovue ASOCT as shown below and confirmed this finding.

In addition to central thickness the researcher documented the minimal corneal thickness for each and the maximum corneal thickness for each eye. There was also comparison of the inferior corneal thickness to the superior corneal thickness for asymmetry. The researcher again compared the RE pachymetry map to the LE pachymetry map. Previous research has shown that variations in inter-corneal thickness that are greater than 23.2µm are only normal in less than 5% of the population making it a good parameter to

consider in the diagnosis of disease[281]. All the inter-corneal differences encountered in this study were less than 23.2µm confirming the rarity. We would expect this difference to be wider in the presence of KC.

A difference in corneal thickness between the thinnest and thickest point greater than 100µm is highly suggestive of KC[104] and a range of 60-100µm should be investigated further[90,280]. The range between the thinnest and thickest point encountered in this study was 23-91µm. The corneas that had a wide range were found to have thicker peripheries rather than a thicker corneal centre.

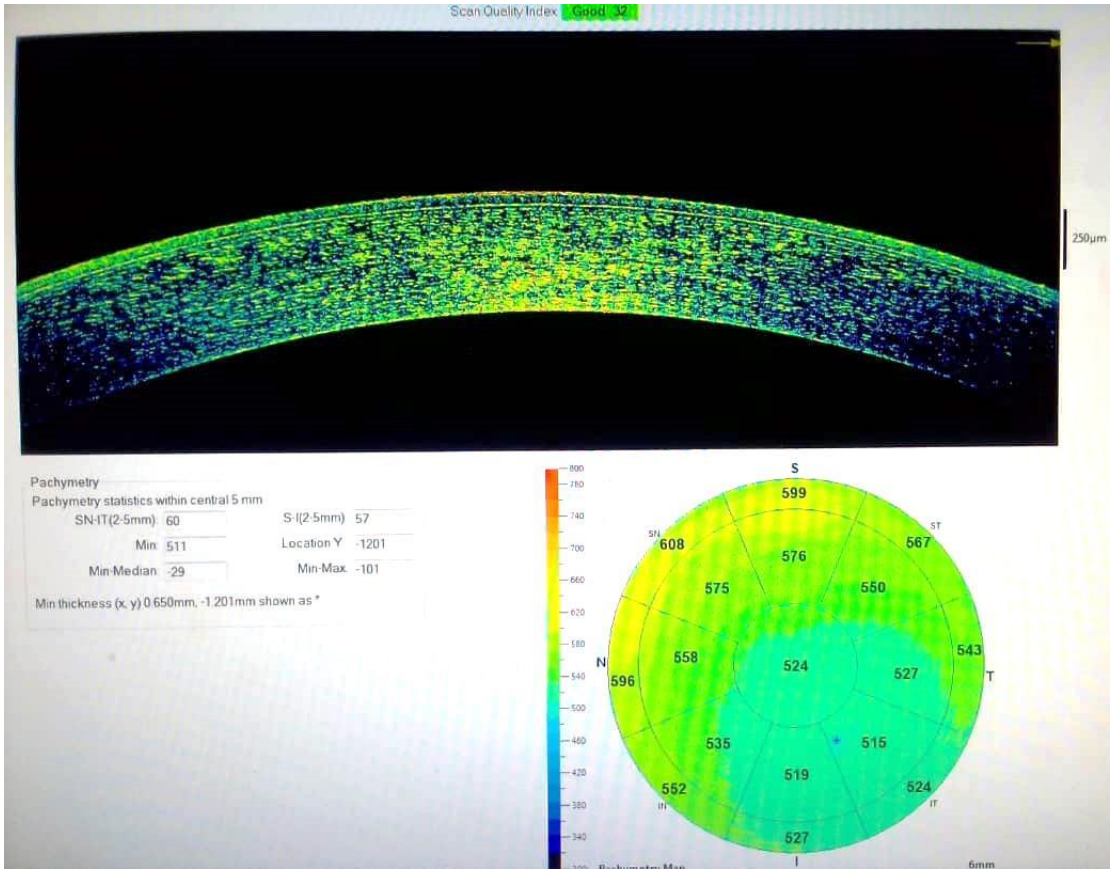


Figure 29 Corneal pachymetry map showing an IS irregularity and corneal centre displacement (*)

A normal CCT is 537±30µm in both adults and children [23,282,283]. The finding of an average CCT of 518±25µm shows that the CCT measurements in this subgroup were generally lower than expected. This may be due to the fact that the population was largely of Africa descent and research has shown Africans

have a CCT lower than the average in other races[284,285]. In an analysis of over 1100 subjects made up of 58% females, the average CCT was found to be 529µm which is comparable to the study's finding[284]. In an analysis of KC patients, Li et al., (2009) found an average corneal thickness of 491µm with a minimum average thickness of 452µm. It has been shown that pachymetry measurements are consistently lower in subjects with pre-clinical KC[225,271,286]. Corneal thickness should therefore be considered with ethnicity in mind as the CCT can be reduced due to one's race or due to pathology. This further illustrates the importance of considering the pachymetry map and not just the CCT.

CCT was below the 480µm cut-off applied in this study in just 5% (n=3) of the participants. When pachymetry maps were taken into consideration, additional subjects with suspicious pachymetry findings were identified although they had CCT>480µm; allowing for them to be identified and managed accordingly. Pachymetry abnormalities; inferior: superior variations and a variation in corneal thickness greater than 60µm were highlighted in an additional 15% of the subjects thus showing an increase in diagnostic sensitivity realised by the use of pachymetry maps.

5.5.5 Contrast Sensitivity (CS)

A number of studies have evaluated CS or put forward contrast sensitivity as a screening parameter for KC using different charts such as the Vistech chart, the Regan multi-contrast visual acuity chart , the Pelli Robson CS chart, vertical Gabor patches and horizontal sinusoidal bars[186,188,223,223,287–290,290]. The average CS measured in this group was log contrast 1.50 with a range of log1.05-1.65. CS may be reduced for a number of reasons including ocular pathology such as dry eye, refractive error, systemic diseases, such as multiple sclerosis, and toxic retinopathy[291]; making a clinical exam necessary to establish the root cause. The subjects at risk for developing KC displayed low contrast sensitivity loss, this is consistent with findings reported elsewhere where they reported a CS level of 1.10 in subjects with KC[290]. The age range of those with reduced CS was 7-10 years and it was easily measured using the Pelli Robson chart. CS

would be a great screening tool as it can be delegated to school nurses, community nurses and trained vision screeners. In addition, it can be dispensed at any school going age and the Pelli Robson charts are readily accessible and affordable. It was a useful parameter in the characterisation of the cornea and facilitated the detection of early disease.

5.6 Objective 4: Determine the age most associated with early signs of KC in children living in urban Harare

From analysis of the KCR score it was established that more than 50% of the high-risk population were 10 years and above. This may have been affected by the distribution of the subjects in the study sample as the higher age brackets had higher representation in the study. The proportion of variance is 88% suggesting a strong relationship between risk and age. One would then expect that the age then most associated with most signs associated with early signs of KC is between the ages of 10-12 years. The most common signs of early KC observed in this age group were corneal centre displacement, steep keratometry readings, reduced contrast sensitivity, abnormal corneal topography maps and reduced contrast sensitivity. The study's findings are consistent with pre-clinical signs of KC reported elsewhere[225,260,292].

Clinical signs such as Vogt's striae, corneal scarring and Fleisher's ring were not commonly sighted in this age group although they are documented in literature as the earlier slit lamp signs[1,2,184,293]. Previous publications describe Vogt's striae as the most commonly encountered clinical sign in KC patients[154,226,294]. As the 6-12 year-old age group examined in this study is mostly associated with very early diseases, only Vogt's striae were observed a few times. Vogt's striae are said to be characteristics of distressed collagen bundles[295] and this is therefore only evident in established disease and are a result of progression from pre-clinical to clinical.

The Chi-square test was used to establish the presence of a relationship between age and diagnosis. The result showed a statistically insignificant relationship as *(p=0.19).* The null hypothesis; KC prevalence is

not affected by age in the 6-12 year category is therefore true, no effect of age was observed showing that generally speaking the proportion of subjects that had preclinical or clinical KC did not differ by age. Interesting to note that when each individual age bracket is considered on its own merits, the 11 year-olds show a statistically significant relationship between age and diagnosis *(p=0.02)*. The age of 11 may be the age where marked changes are noted and pre-clinical KC progresses to clinical. This suggests that under the age of 12 all ages should be awarded the same amount of attention and be screened for early signs of KC.

5.7 Objective 5 Develop an algorithmic approach for the early detection and management of KC

In the development of a diagnostic algorithm, it is important to ensure that the included steps are sensitive to the condition being targeted to minimise false positives as this can have a negative impact on resources. It is also important to ensure the algorithm is palatable to a varied audience for easier adaptation and implementation. Aatila et al., (2021) detail a four-step process that is best adopted in the development of an algorithm. The four steps applied are feature selection, data reprocessing, filters and wrapper methods[221].

5.7.1 Methodology

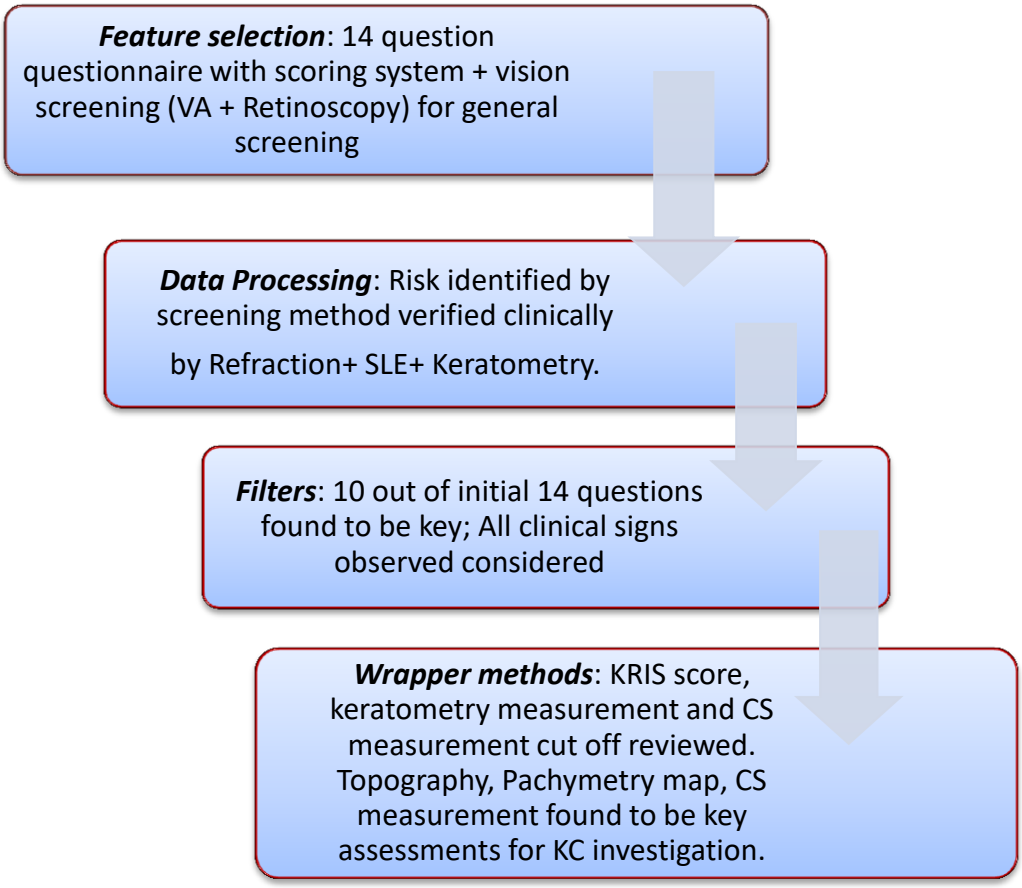
Feature selection involves the strategic and informed selection of key variables to be focused on. Data processing involves the considering of the information gathered from the feature selection step to ensure relevance of parameters being considered. Filters are employed to eliminate repetitive steps or tasks in the process to make for a more streamlined process. Lastly wrapper methods compliment the feature selection by assigning value to the variables so that the variables with the least influence are excluded. Table 14 details how each step was addressed in this study to establish the algorithm for early detection and management of KC. Readily accessible tests were selected to allow for communities in low-income countries, with few human resources and challenges with accessing advanced clinical instruments, to also employ the generated tools to timeously identify children, either at risk for or already, with early KC.

Table 13: Four step application for the development of an algorithm

Step	Description
1. Feature selection	An extensive literature review was carried out to establish known KC risk factors and their effect on the occurrence of the disease. This led to the development of the adapted KRIS questionnaire
2. Data processing	Following the application of the questionnaire to screen the general population for those at risk of developing KC, specific tests were employed to ascertain the true chance of developing KC based on clinical findings. Both phase 1 and phase 2 of the study aimed to ascertain the clinical assessments that reliably identified the subjects at risk of developing KC.
3. Filters	The tests applied at each stage were evaluated and relevance determined via statistical analysis. The key examinations were then identified.
4. Wrapper methods	A strategically engineered risk scoring system was developed and applied to the screening procedure which involved the use of the questionnaire and a few tests. Statistical analysis then allowed for the identification of the key questions and tests to be included in the algorithm.

5.7.2 Algorithm development

The flow chart below diagrammatically demonstrates the process applied in curating the algorithm. The adapted KRIS score cut-off was interrogated and a score of 9 was found to be the most sensitive and accurate when screening for clinical and preclinical KC.



Following the aforementioned considerations, the algorithm below (Figure 30) was developed for the early detection and management of KC. The marking scheme for the yes/no questionnaire the study proposes and scoring system to be adopted is displayed below (Table15)

Table 14: Modified KRIS Questionnaire and scoring system

	KCR score calculator	Yes/No	Score if yes	Actual score
1.	Is there a positive family history for KC?		3	
2.	Does the subject have Down Syndrome		3	
3.	Are the subjects' parents related?		3	

4.	Does the subject frequently rub their eyes?		3	
5.	Is there a scissors reflex on retinoscopy?		3	
6.	Is there an active or past vernal conjunctivitis (corneal haze, papillary reaction, limbitis)?		3	
7.	Is the measured VA 6/9 or worse in at-least one eye?		2	
8.	Is there a sign of atopic disease? (Eczema, hay fever)		2	
9.	Is the patient asthmatic?		1	
10.	Does the subject complain of itchy eyes?		1	
	TOTAL			

The questions in Table 15 above are to be used for screening the general population for the risk of developing KC. A score of 9 was found to minimise false positives which may clog up the referral system but sensitive enough to identify those likely to have or develop KC. The flow diagram displayed in Figure 30 shows the management of the subjects once a risk score has been calculated

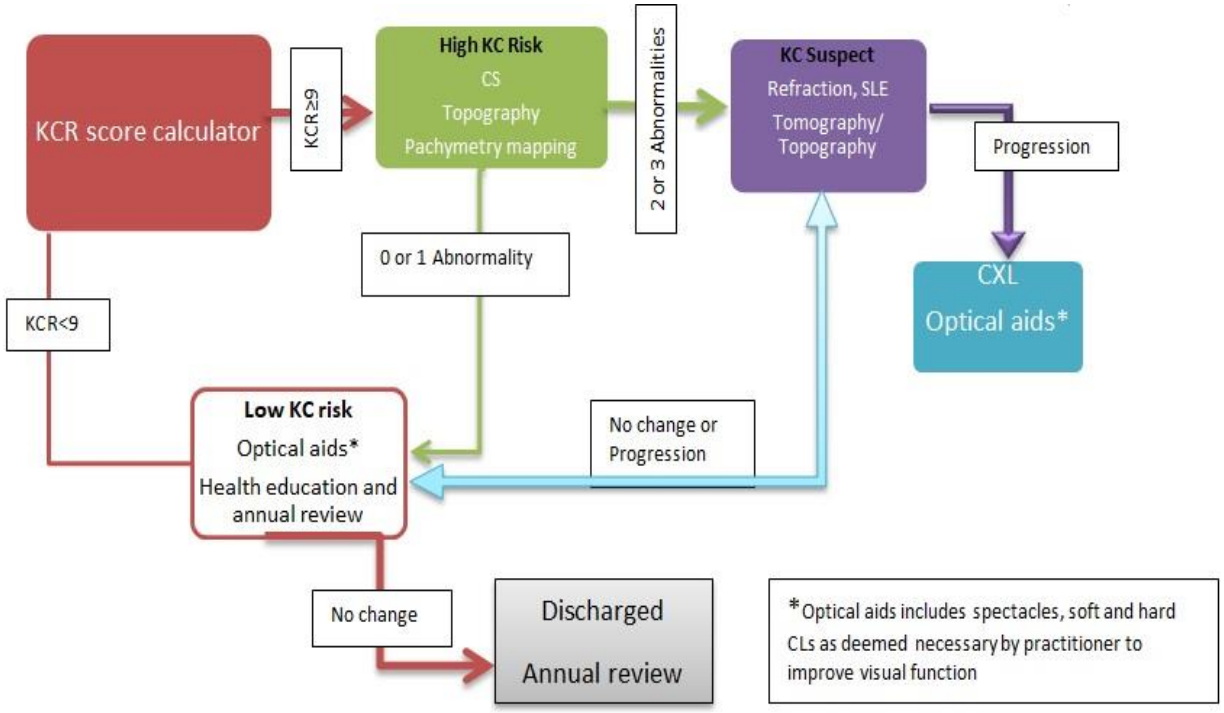


Figure 30: Algorithm for the detection and diagnosis of early KC

The questions dropped from the screening survey were found to either be insignificant in occurrence in the study population or found to be uniformly spread between those with KC and those without.

5.8 Conclusion

A good sized study sample of children resident in urban Harare aged between 6 and 12 years attending primary school were successfully screened for the presence of preclinical KC signs and clinical KC. The adapted KRIS questionnaire utilised proved successful as a primary school tool in segregating the high risk subjects from the general cohort. KC is a multifactorial disease that seems to have different triggers in different ethnic populations, existing in different environments. Risk factors that should be considered in children currently resident in urban Harare aged between 6 and 12 years include age of subject, degree of affluence, knowledge of KC, active or positive history of VKC, frequent eye rubbing, high UV exposure and reduced visual acuity. Full effectivity for the screening of KC was achieved by the addition of carefully selected clinical tests. Combining the questionnaire results with VA improved the sensitivity of the screening regiment compared to VA screenings alone. All variables investigated to establish the risk profile for KC were warranted by literature. Some questions and tests proved to be more effective in separating the normal from the targets in this sample, they were not all equal. Despite the lack of sophisticated diagnostic equipment such as tomographers, topography, pachymetry maps, contrast sensitivity and a slit-lamp examination were key in diagnosing preclinical and clinical KC. As this lower-cost equipment is more easily accessible in resource-constrained contexts, their usefulness in detecting KC early and preventing visual impairment later must be considered. KC has potential to be a significant non-communicable disease problem as the prevalence of 600:100 000 is expected to be higher in older population groups. The study was able to show the importance of tailored community eye screening and diagnostic processes for schoolchildren in a low-cost context. An informed process for the development of an algorithm for the detection, diagnosis and management of KC was employed and an algorithm successfully generated.

Chapter 6 CONCLUSION

6.1 Introduction

Anecdotal evidence proffers that pre-pubescent children present for their first clinical examinations with advanced signs of KC and visual impairment that can no-longer be corrected with readily accessible optical aids. In addition to the negative impact on the lives of the affected children, it also hinders the practitioner's capacity to successfully manage the patient and provide good functional vision, often resulting in visual impairment. The study set out to verify this observation and to provide a potential solution to the problem that is the late presentation of young subjects with KC resident in Harare. Through a set of key questions that were answered, this chapter highlights the key findings related to the profile, prevalence and risk factors of KC in urban Harare among children aged 6 to 12 years and infers what it means as a public health consideration. Recommendations on the variables to be considered in the screening for KC, highlighting the value of a screening regiment and the clinical tests to be employed for the early detection of KC in urban Harare are made. Additionally, an intervention plan is presented to ensure early access to care, promote continued care and minimise visual impairment due to KC. The chapter concludes with the study limitations and key recommendations that are informed by the empirical data

6.2 Key Research findings

6.2.1 What are the risk and clinical profiles of early keratoconic patients?

KC was found to be gender-neutral amongst the study population. The risk of developing KC was higher in the 11 year-old age group but on actual diagnosis of KC age did not influence the outcome. The age range of subjects diagnosed with clinical KC was 8-12 years and the subjects diagnosed with pre-clinical KC

ranged from 6-12 years old. The study population was predominantly of African ethnicity which supports other findings that people of colour have been shown to have a higher occurrence of KC[41,296]. Contact lens use and past ocular injuries were prevalent amongst subjects considered to be high risk for the development of KC, although they had no bearing on final diagnosis. In previous research studies contact lens use has been shown to increase the risk of developing KC[151,239] so, although these subjects did not get diagnosed with KC they would need to be monitored as they get older.

Just 5% of the study cohort was positive for VKC yet, the majority of them were flagged as high risk for KC and 50% of the subjects diagnosed with KC had VKC showing a strong influence of VKC on final diagnosis. Similarly, eye rubbing and itchy eyes were common symptoms amongst the subjects found to have clinical KC. This finding is consistent with other reported studies[66,200,251]

Reduced presenting visual acuity was found in all the subjects diagnosed with clinical KC. Of the subjects diagnosed with either clinical KC or pre-clinical KC, 47% had a presenting VA of 0.7 or weaker. This shows that visual acuity may continue to be normal in over 50% of the subjects with early KC.

A positive family history for KC has been reported as a significant risk factor for the development of KC[161,162,204]. However, in this study none of the subjects diagnosed with clinical KC had a positive family history although 1 in 4 subjects with a positive family history had been flagged as high risk. Atopic conditions were rare in the study population; being reported in just 4% of the study population. Atopic conditions increased the chances of being flagged as high risk but did not have a bearing on diagnosis either. This suggests that these risk factors are inconsequential in the younger population but have an impact on disease development or progression later in life.

The 6-12 year old children in urban Harare are 53% female and 47% male, 99% of African ethnicity and Christian background. The majority of the study population were from an affluent background, consuming a healthy diet, and spending an equal amount of time on the computer as they did outdoors in the sun.

Taking the above findings into consideration, the odds of having KC are increased if the child is aged between 8 and 12 years and of African ethnicity, regardless of gender. They may have VKC, reduced VA, complain of itchy eyes and frequently rub their eyes. They are likely to be of Christian religion, from an affluent background, have a healthy diet and spend a lot of time in the sun.

6.2.2 What is the prevalence of KC amongst children between the ages of 6 and 12 years in urban Harare?

The prevalence of clinical keratoconus amongst of pre-pubescent children attending primary school in urban Harare was found to be 0.63% (630: 100 000) and all of these were newly diagnosed in this project. A third of them had advanced clinical KC, characterised by steep corneal curvature and corneal scarring. Researchers were no longer able to correct this subgroup to a best corrected visual acuity of 6/6 with spectacles, substantiating the observations that had been put forward by clinicians in primary eye care. In addition, the prevalence of pre-clinical KC was found to be 1.36% (1 360:100 000). These study findings are lower compared to other studies reported in Africa but the researcher believes that this is because the study population is significantly younger than the age-brackets considered elsewhere[54,66] and this has a strong bearing on KC prevalence as it increases with age. This study is also the first community-based study in Harare, Zimbabwe, and would therefore offer the true prevalence of KC. Many other prevalence studies reported in the literature were hospital-based[46–48,54] and investigated high-risk groups[54,66,200] which would explain the differences when compared to this study. In addition, demographic differences between this study's population and other studies would explain the difference in values reported. Egypt-based studies report prevalence values at-least three times the value this study found[46–50]. Similarly, prevalence of KC reported in India is significantly higher than this study's finding.[45]

This study finding is significantly higher than values reported in parts of Europe that range between 0.2 and 250:100 000[6,56,64,68–71,296]. All of the study samples in Europe were characterised by predominantly

Caucasian populations that reside in cooler climates, which would explain the discrepancy when compared to this particular study's sample, thus confirming higher KC prevalence amongst people of colour.

6.2.3 Does corneal tomography detect keratoconus earlier than keratometry in the urban population of Harare between the ages of 6 and 12 years?

The answer is in the affirmative. Using the keratometry cut-off of 45D, 28 subjects with a normal slit lamp exam were identified. Out of these 28, 46% were found to have pre-clinical KC. A corneal evaluation looking into key corneal parameters facilitated a deeper corneal assessment compared to keratometry allowing for the earlier detection of KC, findings consistent with other documented research[16,89,111,274,297]. Corneal surface analysis allowed for a number of useful parameters in addition to corneal curvature such as skewed radial axis, information on inter-eye-asymmetry and a figurative presentation of corneal centre displacement. Central corneal displacement was consistently identified on evaluation of the pachymetry map generated on anterior surface tomography, offering additional information on central corneal thickness.

Normal central corneal thickness average is about 540µm and a thickness less than 480µm is considered thin[111,120,298,299]. Corneal tomography allows for corneal thickness analysis across the corneal diameter for variations in corneal thickness and corneal centre location that are also key in the diagnosis of pre-clinical KC in this study. As found in other studies[120,274,300], comparison of the inferior corneal thickness to the superior corneal thickness also showed consistent variations in the KC suspects seen in this study population which were not evident in the healthy subjects. Courtesy of this additional information generated by corneal tomography, the study concludes that KC is detected earlier by tomography compared to when using keratometry alone.

6.2.4 What is the relationship between age and clinical signs of KC in children under the age of 12 years resident in urban Harare?

Corneal keratometry measurements >/=45D were reported in 44% of the subjects with the youngest subject noted to be 6 years old. These findings tie in with findings from an analysis of corneal curvature in subjects in the same age bracket in Iran that showed that the average corneal power is 43.5±1.96D[231].Vogt's striae were the most prevalent slit lamp sign, with the youngest subject with a positive finding being 8 years of age. This finding is consistent with the fact that Vogt's striae are one of the early clinical signs of KC evident on slit lamp exam[293,295]. Corneal scarring was observed in 33% of the cases diagnosed with clinical KC, with the youngest subject being 8 years old. Fleisher's ring are amongst the more rarely observed clinical signs evident in medium to advanced disease[301,302], and similarly was noted in just one 11 year old study subject.

In this age group, signs consistent with pre-clinical KC were more evident than slit lamp signs. Reduced corneal thickness was observed in 14% of the assessed subjects with the youngest subject being 6years old. In people of African ethnicity, corneal thickness is naturally relatively low when compared to other races[285]. The fact that 14% of the subjects assessed had relatively thin corneas should be considered along other clinical signs of KC. Corneal centre displacement was reported in over 50% of the subjects assessed of all ages. This shows that the observation would need to be localised and quantified to be relevant in KC diagnosis. Central corneal displacements to the inferior variations in corneal pachymetry maps were noted in 12% of the subjects all aged between 8 and 12 years.

In conclusion, the age range of 8 to 12 years contained the highest incidence of clinical signs associated with KC. Clinicians would need to focus on findings consistent with pre-clinical KC rather than slit lamp exam signs of KC as this could result in under diagnosis and late diagnosis of the disease.

6.3 Significance of the study

6.3.1 Policy change

This study confirmed the occurrence of KC in Harare but in addition documented undiagnosed visual problems in school going children in Harare. Current practice generally involves children presenting for their first ever clinical examinations with advanced signs of keratoconus amongst other eye conditions and visual impairment that can no-longer be corrected with spectacles as was found in this study. To address the late presentation, the study will advocate for policy change so that a school screening program is mandated by law at multiple milestones in a child's schooling years.

In Zimbabwe it is currently not mandatory for a child to have their eyes checked before enrolling for school or getting a drivers licence at the age of 16 years. These are two noteworthy opportunities for the general population to receive eye checks that can save sight. Late presentation hinders eye-care practitioners' capacity to successfully help the patients and provide good functional vision with optical devices, as many would need direct referral for surgical options. In addition, timely diagnosis is necessary as some loss of sight is irreversible when discovered later in life, such as amblyopia or field loss due to glaucoma. Hence, there is a need, within this resource constrained context, to proactively implement appropriate strategies for early detection of KC and other eye conditions. A primary school screening program will lead to the early diagnosis of eye conditions and enable those affected to be successfully managed with relatively affordable, accessible options before becoming visually impaired. Successful strategies may ultimately reduce the contribution of KC and other eye conditions to the prevalence of preventable blindness in Zimbabwe and other similar resource settings.

6.3.2 New knowledge

This study is the first of its kind in Zimbabwe to document the prevalence of KC. To the researcher's knowledge, it is the first study in Africa to consider subjects aged between 6 and 12 years of age and detail prevalence of KC, pre-clinical KC, corneal curvature and corneal thickness in this age bracket. It is arguably the first study to develop a keratoconus screening regiment and risk score calculator which can be adopted with minimal resources. A number of electronic algorithms are available in advanced clinical devices for the early detection of KC but are inaccessible in low resource settings and require expertise to interpret. The KCR calculator tool and VA measurement can be used to screen the general population for KC at any given age. This study also unearthed valuable information on the use of contrast sensitivity measurement as a tool in the investigation of KC. The study's findings also put forward clinical practice changes on the management of children being treated with VKC in Zimbabwe for their management to include routine screening for KC in addition to the management of their symptoms.

The findings of this study suggest the need for a literature update to include figures on the prevalence of KC in the age group considered. It is also important to note that KC has been documented to have an age of onset in the teenage years in existing literature but evidence gathered shows clinicians should consider KC as a differential in pre-pubescent children as well.

6.3.3 Human resource deficit addressed

The findings of this study highlight the need for vision screeners to identify those in need at community level. It also showed the need for primary eye care practitioners (optometrists) to manage the patients identified by the vision screening program and also highlighted the need for ophthalmologists to manage the patients with advanced disease that were seen to be as young as 8 years old.

Bourne et al., (2021) estimate that 90% of visual impaired people live in low-middle income countries[85]; which includes Zimbabwe, the Southern African country within which this study was based. Zimbabwe has a high rate of unemployment with 40% of the population living off $2/day[86]. According to the International Agency for the Prevention of Blindness (IAPB), the Southern African region is well below the recommended number of eye care professionals required to service the population[87]. Zimbabwe has a population of 17million people who are serviced by approximately 40 ophthalmologists and 60 optometrists. The WHO recommends 4 surgeons per million in population and 20 optometrist per million in population[87]. By this recommendation Zimbabwe should have a minimum of 68 ophthalmologists and 340 optometrists, the country is hugely under serviced. The country therefore needs more resources channelled to the two universities that train optometrists. As they only have an intake of 20 students/year combined, it will take a long time to meet the human resource needs with this current intake. The school of ophthalmology also requires the same intervention to increase intake from the current 5 students/year so as to capacitate the public health sector with the appropriate numbers of human resources to meet the needs highlighted.

6.3.4 Eye unit capacitation

In addition to addressing the human resource needs detailed above, the existing eye units need to be capacitated to be able to offer timely interventions. This study confirmed the superiority of corneal tomography over keratometry. In the public sector hospitals, devices that carry out corneal keratometry are readily accessible but not a single eye unit has an OCT machine, let alone one with the ability to image the anterior surface. The public sector patients have to outsource these imaging facilities from the private sector and, as the prices are often inhibitive, it leaves many of these patients without access to the services they need.

Even as a practising clinician in Harare, I struggled to gain access to a facility that had a tomographer with anterior surface imaging abilities. In this quest, I learnt that only two private clinics had tomographers with the ability to assess the posterior stroma. These instruments are superior to generalised anterior segment tomography and would be prudent for the earliest diagnosis and management of KC patients. One can only imagine how difficult it is for an average civilian to have such a scan done; once again highlighting the need for such instruments to be readily available in the public sector.

6.3.5 Health promotion and education

The survey circulated at the beginning of the screening routine showed that only 7% of the total population considered had heard of the condition KC. The number of subjects that left some questions blank particularly on contact lens use and history of spectacle wear showed that there was very little knowledge on these topics. Majority of the students examined were having their eyes checked for the first time in their lives. This goes to show that there is very little awareness around eye care and associated topics. Health education on the importance of eye examinations, how frequent they should occur and general information on eye conditions in the community was found to be lacking. This would need to be addressed for best practices to be adopted in day to day leaving to compliment the adjustments that can be made at policy level.

6.4 Study limitations

The following list details some of the study limitations of this project;

- Sample selection: the majority of the study sample was of African ethnicity and Christian religion. The Zimbabwean population is predominantly of African ethnicity and generally follow Christianity, but it does have other races and religions as well not represented in the study sample considered. This therefore limits the span of the generalisations that can be made from the findings.

A follow-up study recruiting subjects from private primary schools will most likely have a better representation of all religions and races.

- Subject distribution by age: the 6-8 year old age group was poorly represented in this study. This makes it a challenge to characterise KC risk factors and signs of disease in this age-group with statistical significance.
- Demography: selected study population excluded low-income subjects, those from rural communities, other races and religions found in Zimbabwe, therefore the findings cannot be extrapolated to these communities.
- Time constraints: Carrying out the data collection during the era of COVID-19 with so many restrictions on access to schools made it impossible to visit the schools as often as the researcher would have wanted. This affected recruitment as children were learning from home for the best part of the study's data collection time-period. A follow-up study in the current post-COVID-19 era will allow for better subject recruitment.
- Instrumentation: adaptations had to be made for the diagnosis of pre-clinical KC due to the unavailability of ASOCT for easier diagnosis of pre-clinical KC. One step diagnosis of pre-clinical KC with an ASOCT scan required 3 separate tests to reproduce. It would solidify the findings if those identified as pre-clinical KC subjects could be verified by an ASOCT scan with abilities to analyse the posterior stroma.
- Questionnaire: the scoring system on the KCR calculator is a novel system that would benefit from being verified against an established diagnostic instrument.
- Insufficient sample size: the sub-group diagnosed with clinical KC had a few subjects. This was a challenge for the researcher to analyse and accurately characterise KC in the Zimbabwean population with statistically significant observations. A follow-up hospital based study of patients presenting with clinical KC would allow for a larger sample selection and better observations to

characterise clinical KC in the Zimbabwean population. The small age-group represented in the clinical KC group cannot be generalised to the older population affected by the condition.

- Lack of previous research: the literature review for the African context of KC yielded very little results as there are not many publications from the region on the topic. No publications on pre-clinical KC were available at all. The few studies found were significantly different demographically, making it a challenge to compare.
- Lack of normative data: there is no normative database of parameters such as contrast sensitivity or corneal thickness for the 6-12 year-old African population that the researcher knows of. This would have helped validate the figures measured in this study and facilitated the diagnostic process.
- Budgetary constraints: The extra resources and routine testing necessary for COVID-19 safe practices as detailed by the Ministry of Health and WHO recommendations significantly affected the study's budget, which in-turn affected the number of trips the researcher could make to the schools. A similar study carried out without COVID-19 limitations would probably yield more information from an even larger study sample.

6.5 Recommendations

1. There is imperative need for policy change by the Ministry of primary and secondary education in Zimbabwe to make vision-screening programmes in primary schools mandatory upon children commencing school at that level and at one other opportunity prior to their reaching puberty.
2. It would be important to have publications in scientific journals to update the eye-care fraternity on this study's findings on the prevalence of KC, early onset of KC and the recommendation on the adoption of an easy screening regiment for the early diagnosis and management of KC.
3. The Ministry of tertiary education in collaboration with the Ministry of Health and Child Care should increase the training capacity of universities for eye-care practitioners to address the HR gap prevailing in Zimbabwe's healthcare facilities.
4. The Ministry of Health and Child Care must consider investing in private/public partnerships to facilitate the procurement of advanced diagnostic equipment as dictated by current technology for earlier diagnosis of disease and improved long-term prognosis.
5. The Ministry of Health and Child Care should take the lead in the delivery of routine public awareness campaigns on the importance of regular eye examinations, interventions available as well as give information via health education media broadcasts on eye-care conditions encountered in the community.
6. Children being treated for VKC in Zimbabwe should be routinely screened for KC.
7. Future research in the following areas will help enrich literature and evidence-based clinical practice in Zimbabwe;
    i. Generating detailed normative data on parameters such as contrast sensitivity and corneal thickness for the African paediatric population.
    ii. Documenting the prevalence of KC in an older-age bracket to ascertain the true burden of KC in Zimbabwe including characterisation of the refractive errors encountered.

iii. Profiling the risk factors and clinical findings associated with clinical and pre-clinical KC in the 6-8 year-old age group in a larger study sample to compliment the findings from this study so as to detail a full picture of early KC in the paediatric population of urban Harare.

iv. Documenting the prevalence of pre-clinical KC as detected by corneal tomography in a wider age-bracket, which will help establish whether KC is a future public health concern in eyecare.

v. Researching to validate the KCR score calculator as a screening tool for KC against diagnosis by a corneal tomographer with posterior stroma imaging capabilities.

vi. Undertaking a longitudinal study to follow up on the subjects diagnosed with pre-clinical KC in this study to document how many progress to clinical KC over the next ten years as well as to identify the age and time one takes to progress from pre-clinical KC to clinical KC.

vii. Undertaking a follow up study on the family members of the subjects diagnosed with clinical KC in this study to establish genetic link and prevalence amongst family members.

viii. Carrying out a similar study to this one in rural schools to consider lower socio-economic settings to ascertain the validity of poor nutrition and lower affluence as risk factors for KC in the Zimbabwean population.

ix. Carrying out a similar study to this one in more racially diverse schools to consider ethnicity and religious influence on KC in the Zimbabwean population.

x. The development of a simple app that details the algorithm and a step by step procedure from first encounter with a possible patient till the various exit points as detailed in the algorithm developed for easier distribution around the world. This will allow for easy access to the app and minimise effects of human error in delivering the algorithm.

6.5 Conclusion

The early detection and management algorithm will allow for the timely diagnosis of KC and in turn offer improved prognosis as the earlier management of the condition will be possible with all treatment options still viable. Collagen cross-linking has been proven to manage KC by slowing down progression and toughening the cornea, thus minimising the need for corneal transplants[75]. The standard Dresden protocol requires a minimum corneal thickness of 400µm excluding the epithelium[75,303,304] to ensure the endothelium stays healthy post-procedure and for best outcome. In the African population; that the study showed to have relatively thinner corneas, the window for safe procedures is narrow as KC affects the stromal thickness. Earlier detection will ensure CXL can be utilised before the cornea becomes too thin and the procedure unsafe. The algorithm for the early detection and management of KC will also allow for CXL to be actioned in a timely manner minimising the need for the more complicated and relatively less successful corneal transplants. This in turn will address the need for donor corneas that are not readily accessible in Zimbabwe.

Minimising progression to visual impairment will improve the quality of life for patients diagnosed with KC. The BCVA of normal levels will be achievable with the use of readily available optical aids enabling the patients to continue with life without any disadvantages as a result of KC. The Sustainable Development Goals (SDGs) 2030 agenda includes goals on poverty reduction, good health and well-being, quality education and reduced inequalities as part of the seventeen goals. Reducing the prevalence of visual impairment and allowing patients with KC to lead a normal life will directly and indirectly impact on the achievement of all the aforementioned SDGs. In addition, the recommendations above will benefit the general community at large by increasing access to eye care and improving the quality of eye care services available in the public health sector thus reducing the prevalence of preventable blindness in the world at large.

This study has achieved the objectives it set out to achieve by establishing the prevalence of clinical and pre-clinical KC in the Harare paediatric population and detailing the risk profile of the children in urban Harare and developing a screening and management regiment for KC. It will contribute to literature, improve the detection of KC and promote evidence based clinical practice in eye care.

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APPENDICES

Appendix 1a KC demographics and screening survey

MODIFIED KERATOCONUS RISK INVESTIGATIVE SURVEY (KRIS)

Thank you for taking the time to complete this KERATOCONUS RISK INVESTIGATIVE SURVEY.

Please feel free to provide additional details/requests at the end of the survey if you feel that the questions did not adequately cover your specific case.

THANK YOU!

Today's date	[Click or tap here to pick a date]
Country	[Country]
Province	
City	
Name	[Full name]
Age	
Race	**African** **Indian** **Coloured** **White** **Other** _____
Ethnic/Tribal Group	
Home Language	
Religion	
Contact information	[Contact information]

SECTION A: SOCIO-DEMOGRAPHIC INFORMATION

1.

GENDER	
MALE	
FEMALE	

2. Have you heard of the eye condition called Keratoconus?

Yes	
No	

3. **Has anyone in your family been diagnosed with keratoconus?**

No one	
Mother	
Father	
Brother/sister	
Cousin	

4. **Do you live in a country where the climate is mostly hot or cold?**

Climate	
Hot climate	
Cold climate	

5. **Are your parents blood relatives/related to each other (Consanguinity)?**

1st cousins	
2nd cousins	
Distant relatives	
Not related	

6. **Father's highest level of education?**

HIGHEST LEVEL OF EDUCATION	
JUNIOR/PRIMARY SCHOOL	
SECONDARY SCHOOL	
TERTIARY	

7. **Mother's highest level of education?**

HIGHEST LEVEL OF EDUCATION	
JUNIOR/PRIMARY SCHOOL	
SECONDARY SCHOOL	
TERTIARY	

8. **How many hours, on average <u>per week,</u> do you spend outside in the sunlight?**

HOURS	
LESS THAN 8 HOURS	
8-24 HOURS	
>24 HOURS	

9. How many hours, on average <u>per week</u>, do you spend doing near tasks (reading/using your cell phone/computer games)?

HOURS	
LESS THAN 8 HOURS	
8-24 HOURS	
>24 HOURS	

10. Tick the foods that you eat at least twice a week?

Fish/Chicken	
Red Meat	
Eggs	
Beans	
Milk	
Rice/Pap/Pasta/Bread	
Vegetables	
Fruit	

SECTION B: CLINICAL PROFILE

11. Do you have any of the following atopic diseases?

ATOPIC DISEASES	
Eczema (skin rash)	
Hay fever	
Vernal Keratoconjunctivitis (VKC)	
Asthma	

Food allergies	

12. How often do you rub your eyes?

EYE RUBBING FREQUENCY	
Never	
Occasionally	
Regularly	

13. Do you/have you worn rigid contact lenses?

Yes	
No	

14. Have you had LASIK eye surgery previously?

Yes	
No	

THANK YOU FOR PARTICIPATING IN THE SURVEY

Appendix 1b Consent form

P.O. Box A178
Avondale
Harare
Zimbabwe
Telephone: 263-4-791631
Email: primaryhealth9@gmail.com

UNIVERSITY OF ZIMBABWE Department Of Primary Health Care Sciences

27 October 2021

PHASE I PARENT/GUARDIAN INFORMED CONSENT

PROTOCOL TITLE: Development of an early detection model for Keratoconus
NAME OF RESEARCHER: Ms Lynett E Masiwa
PHONE: +263 773 596 419

PROJECT DESCRIPTION Keratoconus (KC) is a condition which shows changes in the clear front part of the eye (cornea). The condition changes the shape, thickness and how the eye works resulting in very poor eye sight. KC is believed to affect children 12years and above and requires a thorough eye exam to be diagnosed. The risk of developing KC increases in the presence of a positive family history for the condition, certain skin problems, itchy eyes and other conditions that affect joints. This study looks to explain KC if seen in our population and our

communities so as to come up with suitable management plans to minimise the number of people that end up blind due to KC.

YOUR RIGHTS: Before you decide whether or not to let your child voluntarily participate in this study, as the parent/guardian you must understand its purpose, how it may help your child, the risks to your child, and what is expected of your child. This process is called informed consent. **PURPOSE OF RESEARCH STUDY:** To establish a way to find the disease early before it affects vision. To document the commonness of KC in children aged between 6-12years that reside in urban Harare. Determine the age it starts and identify the signs, symptoms and common findings among children found to have KC in urban Harare.

PROCEDURES INVOLVED IN THE STUDY: A team of health care providers that look after eyes will visit your child's school. The children will be asked to complete a short questionnaire pertaining to their general health, ocular history and family history of ocular conditions. Should they not be sure about any answers we will telephone the parent/guardian for information. They will also get a quick eye screening at their school. This initial screening and form completion shall be known as Phase I. Your child will only be requested to participate in phase II if they have a chance of developing KC. We expect it to take less than five minutes for each child to complete the questionnaire and another five minutes for the eye screening. No extra tests/exams will be carried out in addition to those highlighted above.

DISCOMFORTS AND RISKS: None expected.

POTENTIAL BENEFITS: The study is intended to document the commonness and identify the early features of KC in Zimbabwean children then utilise these to develop a way of finding it earlier (early detection model). The early detection model will then contribute towards the diagnosis and management of KC. Early detection will result in early treatment therefore minimise the numbers of children that end up with poor vision due to KC. The results will also be used to lobby the Ministry of Health and Child welfare to put the necessary systems in place for mandatory eye screening of children.

STUDY WITH DRAWAL You may choose not to let your student enter the study or withdraw from the study at any time without loss of benefits entitled to you.

CONFIDENTIALITY OF RECORDS: All the data collected is recorded anonymously and will not be distributed to third parties unless mentioned on this form. **PROBLEMS/QUESTIONS** Please ask questions about this research or consent now. If you have any question in future please ask Ms Masiwa on lemasiwa@gmail.com or +263 773596419.

AUTHORIZATION

I have read this paper about the study or it was read to me. I understand the possible risks and

benefits of this study. I know being in this study is voluntary. I choose for my child to be in this study. I know I can stop my child from being in the study at any point and I will not lose any benefits entitled to me. I will get a copy of this consent form. (Initial all the previous pages of the consent form)

_____

Parent/Guardian Signature Date

_____

Parent/Guardian Name (Printed)

_____

Researcher Signature Date

_____

Witness Signature Date

Appendix 1c Assent form

P.O. Box A178
Avondale
Harare
Zimbabwe
Telephone: 263-4-791631
Email: primaryhealth9@gmail.com

UNIVERSITY OF ZIMBABWE Department of Primary Health Care Sciences

ASSENT FORM ENGLISH

Hie there

My name is Lynett Masiwa. We are doing a study to learn about children's eyes and a condition called Keratoconus. We are asking you to help because we don't know very much about the condition in children staying in Harare.

If you agree to be in our study, we are going to ask you some questions about your eyes and your family. We want to know if they bother you at times. For example, we will ask you if they get itchy sometimes. We will also ask you to let us check your eyes.

You can ask questions about this study at any time. If you decide at any time not to finish, you can ask us to stop. There are no right or wrong answers for the questions we ask and there is no bad ending because this is not a test.

By signing this paper, it means that you have read it and that you want to be in the study. If you don't want to be in the study, don't sign this paper. Being in the study is up to you, and no one will be upset if you don't sign this paper or if you change your mind later.

Your signature: _____ Date _____

Your printed name: _____ Date _____

Researcher's signature: _____ Date _____

Printed name of Researcher: _____ Date _____

Appendix 2a KCR data collection sheet

KERATOCONUS SCREENING DATA RECORDING SHEET

DATE _____ DATA COLLECTOR _____

KEY	YES	NO
	√	**X**

SUBJECT NUMBER _____

Demographics

Gender (M/F)	Religion	Age	Ethnicity	AFFLUENT(Y/N)	KNOW OF KC	DIET (Healthy or not)	Injuries/Surgery (Y/N)	UV exposure≥ (Y/N	VDU≥8hrs/week (Y/N)	CL use in the past (Y/N)

Phase 1

	FHX	VA		VKC	DOWN SYND.	ATOPY	ITCHY EYES	RUBBING	HAY FEVER/ ASTHMA	SCISSORS REFLEX
Possible score	**3**	**2** If 6/9or less		**2**	**3**	**2**	**1**	**3**	**1**	**3**
Comment		RE	LE							
Actual score										

TOTAL SCORE: _____

OUTCOME:

1. REFER FOR FULL CONSULTATION IF SCORE ≥ 5 ☐

2. DISCHARGED IF SCORE <5 ☐

Appendix 2b School screening feedback

School screening student feedback sheet

Surname: _____ First Name: _____

School: _____

D.O.B _____ Grade: _____

School visual screening report

- Vision: Within normal limits ☐
- Vision: Below expected level ☐
- Low chance of developing Keratoconus ☐
- Higher chance of developing Keratoconus ☐

If the screening showed that your child's vision is below expected levels and that they have a higher chance of developing keratoconus (2 ticks); please come to the school on the date provided with your child where transport to Parirenyatwa University of Zimbabwe Optometry Clinic where an eye exam will be provided free of charge.

If your form only has one tick for below expected level, please visit your nearest eye unit or Optometrist or Ophthalmologist for further care.

If vision is within normal limits, no further care is required.

It is encouraged to get young children's eyes checked at-least once every year until they are adults. Adults should get their eyes checked at-least once every two years.

Signed: _____ Date: _____

Lynett E Masiwa (Optometrist)

Appendix 2c Clinical exam recording sheet

Phase 1 CLINICAL EXAMINATION RECORD SHEET

Risk factor Score: _____

Record # _____

Gender _____ Age _____

Refraction result

RE	Unaided VA	PRESCRIPTION	BCVA	Near print
LE				

KC linked sign (in either eye)	Present	Absent
Parents related?		
Diagnosed with down syndrome/osteogenesis imperfecta?		
Vogt's striae		
Fleisher's ring		
Munson Sign		
Corneal scarring		
Keratometry D≥ 45D R.E V H L.E V H		

Diagnosis (Circle one) Clinical KC No Clinical KC detected Management _____

Practitioner _____

Appendix 2d Phase 2 Data collection tool

CANDIDATE NUMBER_____

Risk factor score _____ **Gender/ Age _____**

	Central Corneal thickness/ µm	Min corneal thickness/µm	Max corneal thickness/µm	Displacement of Corneal centre Y/N	Variations in CCT 100≥µm Y/N	Anterior stroma steepening on topo Y/N	Contrast Sensitivity	Preclinical KC (Y/N)
RE								
LE								

Appendix 3a(i) Biomedical Research ethics committee

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

29 July 2020

Ms LE Masiwa (219058746)
School of Health Sciences
College of Health Sciences
lemasiwa@gmail.com

Dear Ms Masiwa

Protocol: An algorithmic approach to the early detection of Keratoconus
Degree: PhD
BREC Ref No: BE385/19

RECERTIFICATION APPLICATION APPROVAL NOTICE

Approved:	**26 July 2020**
Expiration of Ethical Approval:	**25 July 2021**

I wish to advise you that your application for recertification received on 25 July 2020 for the above study has been **noted and approved** by a subcommittee of the Biomedical Research Ethics Committee (BREC).The start and end dates of this period are indicated above.

If any modifications or adverse events occur in the project before your next scheduled review, you must submit them to BREC for review. Except in emergency situations, no change to the protocol may be implemented until you have received written BREC approval for the change.

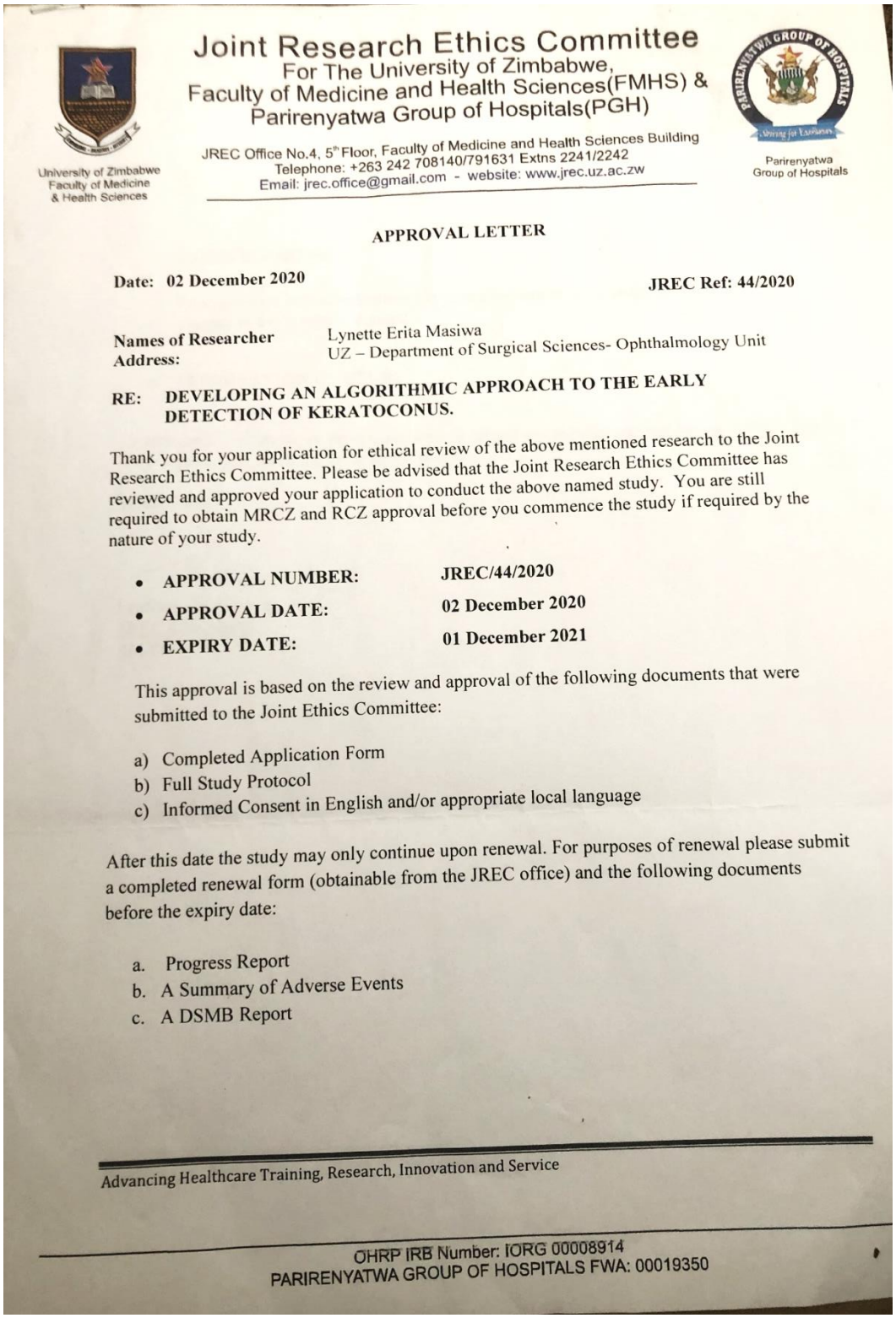
The committee will be notified of the above approval at its next meeting to be held on 08 September 2020.

Yours sincerely

[redacted]

Ms A Marimuthu
(for) Prof D Wassenaar
Chair: Biomedical Research Ethics Committee

Appendix 3a(ii) Joint research ethics clearance



University of Zimbabwe
Faculty of Medicine
& Health Sciences

Joint Research Ethics Committee
For The University of Zimbabwe,
Faculty of Medicine and Health Sciences(FMHS) &
Parirenyatwa Group of Hospitals(PGH)

JREC Office No.4, 5th Floor, Faculty of Medicine and Health Sciences Building
Telephone: +263 242 708140/791631 Extns 2241/2242
Email: jrec.office@gmail.com - website: www.jrec.uz.ac.zw

Parirenyatwa
Group of Hospitals

APPROVAL LETTER

Date: 02 December 2020 **JREC Ref: 44/2020**

Names of Researcher Lynette Erita Masiwa
Address: UZ – Department of Surgical Sciences- Ophthalmology Unit

RE: DEVELOPING AN ALGORITHMIC APPROACH TO THE EARLY DETECTION OF KERATOCONUS.

Thank you for your application for ethical review of the above mentioned research to the Joint Research Ethics Committee. Please be advised that the Joint Research Ethics Committee has reviewed and approved your application to conduct the above named study. You are still required to obtain MRCZ and RCZ approval before you commence the study if required by the nature of your study.

- **APPROVAL NUMBER:** **JREC/44/2020**
- **APPROVAL DATE:** **02 December 2020**
- **EXPIRY DATE:** **01 December 2021**

This approval is based on the review and approval of the following documents that were submitted to the Joint Ethics Committee:

a) Completed Application Form
b) Full Study Protocol
c) Informed Consent in English and/or appropriate local language

After this date the study may only continue upon renewal. For purposes of renewal please submit a completed renewal form (obtainable from the JREC office) and the following documents before the expiry date:

a. Progress Report
b. A Summary of Adverse Events
c. A DSMB Report

Advancing Healthcare Training, Research, Innovation and Service

OHRP IRB Number: IORG 00008914
PARIRENYATWA GROUP OF HOSPITALS FWA: 00019350

Appendix 3a(iii) Medical research council of Zimbabwe

Telephone: 08644072773/791193
E-mail: mrcz@mrcz.org.zw
Website: http://www.mrcz.org.zw

Medical Research Council of Zimbabwe
Josiah Tungogara / Mazowe Street
P. O. Box CY 573
Causeway
Harare

APPROVAL

MRCZ/A/2749 **13 October, 2021**

Ms Lynett Musiwa
243 Enterprise Road
The Grange
P.O Chisipite
Harare

RE: - Developing an algorithmic approach for the early detection of Keratoconus

Thank you for the application for review of research activity that you submitted to the Medical Research Council of Zimbabwe (MRCZ). Please be advised that the Medical Research Council of Zimbabwe has **reviewed** and **approved** your application to conduct the above titled study.

This approval is based on the review and approval of the following documents that were submitted to MRCZ for review: -

a) Completed MRCZ Application Form 101
b) Protocol
c) Informed Consent Form (English and Shona
d) Assent Form (English and Shona)
e) Data Collection Tools

- **APPROVAL NUMBER** : **MRCZ/A/2749**

This number should be used on all correspondence, consent forms and documents as appropriate.

- **TYPE OF MEETING** : **Full Board**
- **MEETING DATE** : **26 August, 2021**
- **APPROVAL DATE** : **13 October, 2021**
- **EXPIRATION DATE** : **12 October, 2022**

After this date, this project may only commence upon renewal. For purposes of renewal, a progress report on a standard form obtainable from the MRCZ Offices should be submitted three months before the expiration date for continuing review.

- **SERIOUS ADVERSE EVENT REPORTING:** All serious problems having to do with subject safety must be reported to the Institutional Ethical Review Committee (IERC) as well as the MRCZ within 3 working days using standard forms obtainable from the MRCZ Offices or website.
- **MODIFICATIONS:** Prior MRCZ and IERC approval using standard forms obtainable from the MRCZ Offices is required before implementing any changes in the Protocol (including changes in the consent documents).
- **TERMINATION OF STUDY:** On termination of a study, a report has to be submitted to the MRCZ using standard forms obtainable from the MRCZ Offices or website.
- **QUESTIONS:** Please contact the MRCZ on Telephone No. (0242) 791193/08644073772 or by e-mail on mrcz@mrcz.org.zw

Other

- Please be reminded to send in copies of your research results for our records as well as for Health Research Database.
- You're also encouraged to submit electronic copies of your publications in peer-reviewed journals that may emanate from this study.
- In addition to this approval, all clinical trials involving drugs, devices and biologics (including other studies focusing on registered drugs) require approval of Medicines Control Authority of Zimbabwe (MCAZ) before commencement.

Yours Faithfully

[redacted]

MRCZ SECRETARIAT
FOR CHAIRPERSON
MEDICAL RESEARCH COUNCIL OF ZIMBABWE

MEDICAL RESEARCH COUNCIL OF ZIMBABWE
2021 -10- 13
APPROVED

PROMOTING THE ETHICAL CONDUCT OF HEALTH RESEARCH

Appendix 3a (iv) Ministry of primary and secondary education clearance

All communications should be addressed to "The Secretary for Primary & Secondary Education"
Telephone: 794895
Telegraphic Address: "EDUCATION"

ZIMBABWE

Reference: C/426/3/
Ministry of Primary and Secondary Education
P.O Box CY 121
Causeway
HARARE

4 November 2020

Lynett E. Maslwa
School of Health Sciences
P. O. Box A78
Avondale
Zimbabwe

Re: **PERMISSION TO VISIT HARARE METROPOLITAN PROVINCE FOR RESEARCH: NORTHERN CENTRAL DISTRICT: NORTH PARK; DAVID LIVINGSTONE AND BLACKSTON AND WARREN PARK MABELREIGN DISTRICT: WARREN PARK 2 PRIMARY SCHOOLS**

Reference is made to your application to visit schools to collect data for research purposes at the above mentioned schools in Harare Metropolitan Province on the research title:

"DEVELOPMENT OF AN ALGORITHMIC APPROACH FOR THE EARLY DETECTION OF KERATOCONUS"

Permission is hereby granted. However, you are required to liaise with the Provincial Education Director Harare Metropolitan Province who is responsible for the schools which you want to involve in your research. You should ensure that your research work does not disrupt the normal operations of the school. Where students are involved, parental consent is required.

You are also required to provide a copy of your final report to the Secretary for Primary and Secondary Education.

[redacted]
T. Thabela (Mrs)
SECRETARY FOR PRIMARY AND SECONDARY EDUCATION

PERMANENT SECRETARY
MINISTRY OF PRIMARY AND SECONDARY EDUCATION
10 NOV 2020
P.O. BOX CY 121, CAUSEWAY
HARARE, ZIMBABWE

Appendix 3b Research ethics certification

TRREE

Zertifikat
Certificat
Certificado
Certificate

Promouvoir les plus hauts standards éthiques dans la protection des participants à la recherche biomédicale
Promoting the highest ethical standards in the protection of biomedical research participants

Clinical Trials Centre
The University of Hong Kong

Certificat de formation - Training Certificate

Ce document atteste que - this document certifies that

Lynett Masiwa

a complété avec succès - has successfully completed

Introduction to Research Ethics

du programme de formation TRREE en évaluation éthique de la recherche
of the TRREE training programme in research ethics evaluation

[redacted]

Release Date: 2018/12/31

CID : 5ZNVQsWW2X

Professeur Dominique Sprumont
Coordinateur TRREE Coordinator

FMH Continuing Education Program (5 Credits)
Programme de Formation continue (5 Crédits)

Foederatio Pharmaceutica Helvetiae FPH Programmes de formation continue
Continuing Education Programme
Programmes de formation continue

Ce programme est soutenu par - This program is supported by :
European and Developing Countries Clinical Trials Partnership (EDCTP) (www.edctp.org) - Swiss National Science Foundation (www.snf.ch) - Canadian Institutes of Health Research (http://www.cihr-irsc.gc.ca/e/2891.html) - Swiss Academy of Medical Science (SAMS/ASSM/SAMW) (www.samw.ch) - Commission for Research Partnerships with Developing Countries (www.kfpe.ch)

[RIEV : 20170310]

TRREE

Zertifikat
Certificat
Certificado
Certificate

Promouvoir les plus hauts standards éthiques dans la protection des participants à la recherche biomédicale
Promoting the highest ethical standards in the protection of biomedical research participants

Clinical Trials Centre
The University of Hong Kong

Certificat de formation - Training Certificate

Ce document atteste que - this document certifies that

Lynett Masiwa

a complété avec succès - has successfully completed

South Africa

du programme de formation TRREE en évaluation éthique de la recherche
of the TRREE training programme in research ethics evaluation

[redacted]

Release Date: 2018/12/31

CID : jVdD25TRQw

Professeur Dominique Sprumont
Coordinateur TRREE Coordinator

FMH Continuing Education Program (5 Credits)
Programme de Formation continue (5 Crédits)

Foederatio Pharmaceutica Helvetiae FPH Programmes de formation continue
Continuing Education Programme
Programmes de formation continue

Ce programme est soutenu par - This program is supported by :
European and Developing Countries Clinical Trials Partnership (EDCTP) (www.edctp.org) - Swiss National Science Foundation (www.snf.ch) - Canadian Institutes of Health Research (http://www.cihr-irsc.gc.ca/e/2891.html) - Swiss Academy of Medical Science (SAMS/ASSM/SAMW) (www.samw.ch) - Commission for Research Partnerships with Developing Countries (www.kfpe.ch)

[RIEV : 20170310]

Published: Review

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of Optometry

www.journalofoptometry.org

REVIEW

A review of corneal imaging methods for the early diagnosis of pre-clinical Keratoconus

Lynett Erita Masiwa° *, Vanessa Moodley [b]

^ *Department of Ophthalmology, University of Zimbabwe, College of Health* Sciences, *P. O. Box A178, Avondale, Harare, Zimbabwe*

[b] *School o/ Health Sciences, Department of Optometry*, University *of KwaZulu Natal, Durban, South Africa*

Received 26 July 2019; accepted 9 November 2019

Corneal imaging; Pre-CU n\Cal keratocoilus; Topography; Tomography; Keratoconus

Abstract ***Background:*** Keratoconus (KC) is a corneal ectasia characterised by steepening corneal curva- ture, changes in refractive error and corneal thickness that result in visual impairment. Early signs of KC Include displacement of the thinnest part of the corner from the central position, changes in the corneal epithelial layer cell distribution, variations in the anterior corneal astig matism/posterior corneal astigmatism relationship and a variation in corneal thickness. It 's important that we review the corneal imaging methods for the diagnosis of preclinical KC. ***Method.*** ' An online literature search was carried out on PubMed. Only publications detailing corneal assessment procedures were cons idered for this review and any publication on instru- ments that did not generate KC predictability indices were also excluded from the review. The 308 publJcations were reviewed.

Discussion: Corneal assessment techniques, with the ability to characterise both the anterior and posterior corneal surfaces, are invaluable in the diagnosis of pre-clinical KC. Reflection based and elevation-based corneal imaging sysLeits should be used in conjunction with other assessments such as higher order aberration measurlng systems to improve sensitivity and reliability in the diagnosis of pre-clinical KC. Ultra h1gh resolution ultrasound can detect pre-clinical KC. The ability to asses both the epithelium and endothelium makes anterior surface optical coherence tomography a superior technique for pre-clinical KC diagnosis. There is a positive correlation between central corneal thickness and corneal hysteresis. Corneal biomechan cs should be considered in conjunction with other corneal assessments in the diagnosis of pre-clinical KC.

Submitted for consideration: Screening for Keratoconus in a low resource setting

Abstract

Background: Keratoconus (KC) is the most documented corneal ectasia. Symptoms of KC include blurred vision, photophobia, glare, and frequent refractive error changes. The diagnosis of KC involves identification of corneal signs, refraction, and corneal structure imaging. The prevalence of KC ranges between 0.4 per 100 000 to 4 790 depending on geographical location and ethnicity. Anecdotal evidence suggests a higher occurrence of KC in Harare. The diagnosis of KC should occur early so that affected can be successfully managed with relatively affordable, accessible options before becoming visually impaired.

Method: Written consent and assent was obtained from subjects. A modified KRIS questionnaire was used to collate demographic information, general and ocular history of the subjects. Visual acuity was measured using Snellen charts. A scoring system was then used to award a risk score which resulted in either referral to the optometry unit for a full eye exam when considered high risk or discharge when considered low risk for KC. A full exam included refraction, keratometry, slit lamp exam, and fundoscopy.

Results: 1153 subjects aged between 6yrs and 12yrs were seen; 53% females and of African ethnicity. Prevalence of KC was found to be 626/100000. Reduced VA in at least one eye, positive family history for KC, VKC, itching eyes, and eye rubbing were the most influential risk factors encountered in this study group.

Discussion: Various KC risk factors were encountered in the community. The prevalence of KC is relatively high in primary school children in Harare.

Conclusion: Prevalence of KC in Harare is 626/100 000. School aged children stand to benefit from the early screening of KC.

Submitted for consideration: Corneal thickness and contrast sensitivity measurements in 6-12year KC suspects in Harare

ABSTRACT

Background Central corneal thickness (CCT), thinnest corneal thickness and contrast sensitivity are affected by Keratoconus. Thinnest corneal thickness was reliably used to distinguish between different classes of KC by severity. Central corneal thickness and apical corneal thickness are key parameters in distinguishing subclinical KC from clinical KC. Contrast sensitivity loss may be present even in the presence of normal Snellen visual acuity.

Method This study used a quantitative, cross sectional, analytical design. School students aged between 6 and 12 years resident in suburban Harare were initially screened for keratoconus (KC).CS was measured used Pelli Robson CS chart and CCT measured used Optovue iVue OCT.

Results 63 Subjects aged 6-12years were examined. Average CCT of 517±25µm and an average CS of log contrast 1.50 with a range of log1.05-1.65 were found.

Discussion The CCT measurements in this subgroup were generally lower than expected. The subjects at risk for developing KC displayed low contrast sensitivity loss.

Conclusion CCT and CS measurement offer valuable information for the characterisation of the cornea and diagnosis of ocular pathology. Average CCT measures lower in children of African ethnicity.

Submitted for consideration: Development of an algorithm for the early detection of Keratoconus

Abstract

Background: Many eye care providers in low resource settings do not have access to advanced technology but continue to offer services in challenging circumstances. It is in light of this that we developed an algorithmic approach for the early detection and management of KC in a low resource setting. In the development of a diagnostic algorithm, it is important to ensure that the included steps are sensitive to the condition being targeted to minimise false positives as this can have a negative impact on resources. It is also important to ensure the algorithm is palatable to a varied audience for easier adaptation and implementation.

Method: A four step process was applied in the development of the algorithm; feature selection, data reprocessing, filtering and wrapper methods,

Discussion: The algorithm was developed for the early detection and management of KC in low resource settings where corneal tomography is not readily accessible. The marking scheme for a yes/no questionnaire is proposed along with the scoring. The algorithm can be used to screen the general population for the risk of developing KC. Those found to be at high risk for developing KC can then be examined and managed accordingly.

Conclusion: The algorithm for the early detection and management of KC is a useful tool for the early detection of KC which will improve on prognosis.