Evaluation of Keratoconus Prevalence Among College-Aged Students at a Large University Setting

Thesis

Presented in Partial Fulfillment of the Requirements for the Degree Master of Science in the Graduate School of The Ohio State University

By

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Abstract

Purpose: The primary objective of this study is to determine the prevalence of keratoconus within the target population, as well as investigate a possible prevalence rate for keratoconus suspects. A secondary objective of this study is to explore if topographic indices other than those typically used to identify keratoconus show significant differences when comparing normal, suspicious, and keratoconic eyes.

Methods: A retrospective study design was completed to analyze previously collected data from a Marco OPD Scan-III device in order to evaluate the eyes of a population of undergraduate and graduate students attending college in a large university setting. Subjective clinical assessment of topography data combined with objective criteria (Kmax, I-S index, SRAX index) application were utilized to classify subjects into pre-determined groups. The final total count for each category was 35 keratoconus, 5 pellucid marginal degeneration, 72 keratoconus suspects, and 6,152 normal when considering only right eye data.

Results: The prevalence of keratoconus for this sample is 0.63% or 630 per 100,000 persons (95% CI: 0.46% - 0.85%). The median (IQR) age for the total sample population is 26.02 (22.68 – 28.66) years. There were 3,986 (63.7%) female subjects and 2,273

(36.3%) male subjects used for the final population analysis. ANOVA analysis with post hoc multiple comparisons reveled there was a significant difference between all possible group combinations for the variables $SimK_2$, corneal eccentricity, corneal RMS, total corneal coma HOA, refractive cylinder power, and AST.

Conclusions: The prevalence of keratoconus in this study population is greater than the most recently reported global prevalence rate. Improved reliability of prevalence reporting can potentially lead to better detection of patients with keratoconus, and earlier detection will improve how eye care professionals manage the condition and monitor for disease progression.

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Vita

Dr. Madison Roth graduated with her Bachelor of Science in Health and Rehabilitation Sciences with a minor in Biology from The Ohio State University in 2019. She then went on to obtain her Doctor of Optometry degree from The OSU College of Optometry in 2023 where she graduated first in her class. Upon graduation, Dr. Roth continued her education at OSU by enrolling in a two-year Advanced Practice Fellowship with a specialty in Cornea and Contact Lenses. Dr. Roth is a member of the Ohio Optometric Association, the American Optometric Association, and the American Academy of Optometry. She is currently working towards earning her Fellowship to the American Academy of Optometry. Her passions include fitting a variety of specialty contact lenses and contributing to optometric research projects relating to myopia control and innovation in contact lenses.

Publications

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Fields of Study

Major Field: Vision Science

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Chapter 1. Introduction

Derived from the Greek words ‘kéras,’ meaning cornea, and ‘cōnus,’ meaning cone, keratoconus is a corneal ectasia defined as non-inflammatory thinning of the corneal stroma that progresses over time.[1] This degeneration leads to an irregular corneal shape commonly characterized by protrusion of the central or paracentral cornea, frequently concentrated inferiorly, which causes impairments to vision. These corneal changes result in blurry and distorted vision that is not fully correctable with traditional spectacle correction. Additionally, keratoconus is a bilateral disease that often presents asymmetrically. Studies have determined that for individuals with keratoconus in one eye the second eye has a 50% chance of developing the condition within sixteen years from onset.[1] This ectasia affects men and women equally and can be found in people of all ethnicities. Epidemiological studies indicate substantial variation in the global prevalence and incidence of this condition with the lowest rates occurring in Caucasians and the highest rates occurring in individuals of Middle Eastern and Asian descent.[2]

The severity of keratoconus is often classified by the clinical ocular signs a patient exhibits and the associated symptoms these pathological changes produce. Prior to the onset of clinical signs, histopathological changes that affect the corneal epithelium, Bowman’s layer, and anterior stroma can be observed.[3] In keratoconus, the cellular uniformity of the basal epithelium becomes compromised and breakdown of the

proteoglycan matrix surrounding stromal collagen leads to progressive degeneration of the cornea's structural integrity.[1,3,4] These anatomical changes result in visual symptoms that present in the second or third decade of life, commonly during puberty, and progress until the fourth decade. However, some cases of keratoconus have been observed in younger and older individuals, and earlier onset is typically associated with faster progression of clinical signs and symptoms.[5]

The true etiology of keratoconus is unknown despite intensive research efforts. Previously, it was accepted to be a non-inflammatory condition; however, several studies have found an association between keratoconus and elevated levels of inflammatory mediators.[3] Patients with keratoconus also have increased oxidative stress marker levels and decreased protective antioxidant levels which may play a role in disease progression.[6] Understanding of the true pathophysiology of this disease has proven difficult as there are no well-established animal models available. To date, the only animal model proven useful for studying keratoconus has been in mice.[3] Furthermore, there is a strong genetic component involved with the likelihood of developing keratoconus, which mouse models cannot assist with in our understanding of its relationship to the disease.[7] In addition to genetics, development of the condition may also be related to mechanical eye rubbing, eczema, asthma, and atopy/allergy. A meta-analysis completed in 2020 studying keratoconus prevalence and risk factors reported odds ratios for eye rubbing, eczema, asthma, allergy, and family history of keratoconus to be 3.1, 3.0, 1.9, 1.4, and 6.4, respectively.[8] As a multifactorial condition, it is apparent that multiple etiologies may

contribute to the development and progression of keratoconus, with genetics arguably playing the largest role.

The global prevalence and incidence of keratoconus has been historically difficult to determine and is speculated to be underrepresented with current estimates. This is due to a lack of detection in subclinical cases that are not yet visually significant. Early methods of diagnosing keratoconus such as observing a scissor reflex on retinoscopy, abnormal keratometry mires, and subjective ocular changes observed with a slit-lamp are not sensitive or specific enough to identify cases of keratoconus until the condition becomes more advanced.[3] Today, with the availability of corneal topography and tomography testing and improved built-in software analysis for these devices, the detection of keratoconus has improved. Now, even incipient cases can be diagnosed and managed prior to significant visual changes occurring. These advancements to technology have led to increased reporting rates for all stages of the condition. As of 2020, the most recent global prevalence report for keratoconus is 138 per 100,000 persons, but this is still believed to be an underestimate of the true disease prevalence.[8] More recently, a study looking at keratoconus prevalence within a pediatric population reported a prevalence rate of 1 in 334.[9] This finding helps corroborate the narrative that our current prevalence reporting of patients with keratoconus is underestimated across all age groups.

In the beginning stages, keratoconus can often be misinterpreted as simple refractive error changes. It is not until clinical signs become apparent and visual acuity declines that practitioners can confidently diagnose the condition without use of more specific objective testing. By the time a patient reaches this stage, impairments to their

visual potential and quality of life have already occurred and unfortunately cannot be restored. As previously noted, these changes occur in the second to third decade of life, which is a period of personal, professional, and physical growth for most individuals. During this time, onset of keratoconus and its accompanying symptoms can significantly impact an individual's educational opportunities, job prospects, and overall quality of life.[10]

Previous studies have found that a diagnosis of keratoconus can have a negative impact on the emotional well-being of the individual affected. Patients with keratoconus report a direct effect on their functional vision which impairs their ability to drive, read, recognize faces, and engage in other leisure and daily tasks. The inability to participate in these activities leads to a decreased quality of life related to all the following domains: psychological, social, professional, financial, daily, and student life.[11] Even patients with a best corrected visual acuity of 20/20 in at least one eye perceive a reduced ability to perform social duties. This disproportionate perception of functional vision highlights the anxieties related to disease progression and the unknown future impacts on vision that many patients with keratoconus experience.[12] Keratoconus also impacts society and the health care system at an economic level. A study completed in 2010 showed that patients with keratoconus had a predicted lifetime cost of $28,767, and specifically in the U.S., the total lifetime economic burden of keratoconus treatment was $3.8 billion.[13] A more recent 2023 report showed that on average, a patient with keratoconus spends $2,341 annually for out-of-pocket expenses related to glasses, contact lenses, and medical treatment.[14] Patients with

keratoconus also have higher rates of depending on government assistance than the general population indicating a higher financial burden on health care spending.

To help limit the financial burden and rate of disease progression, early detection of the condition is imperative. Detection of keratoconus in the earliest stage of disease development can help identify individuals sooner who would benefit from medical disease progression intervention. In the United States and other developed nations, keratoconus is treated with corneal crosslinking to help stop progression and halt deterioration of vision.[15] Corneal cross-linking is a photochemical procedure that helps prevent progression of keratoconus which was first tested in humans beginning in the early 2000s.[16] The procedure was officially approved by the FDA in 2016 and has since become a part of the standard treatment plan for patients with mild-moderate keratoconus.[16] The Dresden protocol is the standard cross-linking procedure and involves an epithelium-off technique with the use of riboflavin and ultraviolet light (UVA). This protocol requires a minimum corneal thickness of 400 µm to ensure protection of the corneal endothelium, lens, and retina from the UVA used during the procedure.[17] Therefore, early detection of disease progression is essential to ensure individuals are receiving treatment prior to experiencing corneal thinning that would disqualify them from the procedure. The goal of this process is to strengthen the corneal stroma through cross-linking formation between the collagen molecules and extracellular components. This therapy has been proven to be successful at halting the progression of keratoconus, but factors such as the length of procedure time, exclusion of patients with corneal thickness less than 400 µm, and discomfort/risk of infection secondary to removal of the corneal epithelium all contribute to the limitations of the

therapy. Therefore, current research efforts related to a trans-epithelial or "epi-on" procedure are being conducted to hopefully improve patient comfort and minimize post-procedure complications without jeopardizing treatment effect. Conversely, in developing countries, advanced keratoconus remains the number one reason for corneal transplants.[3] In order to reduce the number of patients with advanced disease requiring corneal transplantation, early detection is critical.

Keratoconus can be reliably detected with corneal topography and clinical observation for common signs indicating keratoconus such as Vogt striae, Fleischer ring, corneal scarring, or scissoring reflex with retinoscopy. Some measurable primary changes that precede symptoms include mild, localized corneal steepening, increased differences in superior and inferior corneal curvatures, increased higher order aberrations (HOAs), and changes to corneal thickness.[18,19] The use of automated topography and tomography scans can help detect these initial changes prior to significant visual reduction. Currently, corneal topography is the primary objective diagnostic tool used for detecting keratoconus.[19] However, in subclinical cases, topography alone is not enough to differentiate abnormal corneas from normal.

Strong efforts have been made among the scientific community to reduce the challenges surrounding subclinical detection of keratoconus. Although detection of subclinical keratoconus in its earliest stages has been extensively explored, definitive diagnostic criteria remain elusive. Emphasis has been placed on determining what objective data has the greatest sensitivity and specificity for diagnosing preclinical and early keratoconus. The introduction of corneal tomography capturing on devices like the

Pentacam has been useful in discriminating ectatic from normal corneas. However, tomography devices are expensive and cost anywhere between $10,000 to $50,000, so many clinicians will not have access to these devices in common practice.[20] Additionally, tomographical data alone may still miss subtle cases of keratoconus. In order to prevent this oversight, studies have recommended also using corneal thickness distribution/pachymetry and corneal aberration data to aid in pre-symptomatic diagnosis.[19,21,22] Of note, many Scheimpflug imaging and tomographic devices have created various machine learning algorithms to assist in early objective detections.[23]

A study in 2016 reported the top four indices provided by tomography devices proved useful in subclinical keratoconus detection include the Pentacam Belin Ambrosio Deviation Display (BAD-D), the Index of Vertical Asymmetry (IVA) metric comparing inferior and superior corneal curvature, 5^{th} order aberrations on the front surface of the cornea (most notably vertical coma), and the Index of Surface Variance (ISV).[24] Additionally, another report from 2012 discussed the use of wavefront-guided aberrometry for better characterization of the early optical changes in subclinical keratoconus. This study concluded that a root-mean-square (RMS) error for horizontal and vertical coma greater than 0.275 µm was indicative of keratoconus with a sensitivity and specificity of 98% and 99%, respectively.[25] When used in conjunction with other HOA metrics, it was significant for discriminating between normal eyes and eyes with subclinical keratoconus. Lastly, the Sirius tomographer system developed an algorithm that considers front and back corneal symmetry, RMS of corneal HOAs, corneal thickness, and the best fit radius of the front corneal surface to classify subclinical versus clinical keratoconus; reports using this

machine index have confirmed proper classification with a 92% accuracy.[22] All these studies report improved accuracy in detecting early keratoconus when scoring indices combine several different corneal metrics. Nevertheless, there is still no single parameter that can unequivocally diagnose cases of incipient keratoconus, so this remains a pertinent area of research.

In addition to tomography derived indices, corneal topography metrics are also valuable when detecting cases of subclinical keratoconus. Three common topographic indices that are repeatedly discussed in the literature include central keratometry (K), skewed radial axis (SRAX) index, and the inferior-superior dioptric asymmetry (I-S) index. The central keratometry value is the average corneal power for Placido rings with diameters of 2, 3, and 4 mm. Previous studies report values below 47.2 D are considered normal and values greater than 48.7 D are indicative of keratoconus.[26] However, Maeda et al. reported observing families of emmetropes with central corneal readings between 48 -50 D with no signs of corneal ectasia present.[27] Additionally, a study by Randleman et al. reported that only 4 of 171 cases of corneal ectasia had a central keratometry reading greater than 47.2 D, indicating this metric is not particularly useful in differentiating normal from abnormal when used in isolation.[28] The SRAX index is used to express the angle between the steepest radial axis in the superior and inferior meridians. In cases of irregular astigmatism, this value will be larger and indicate a skewed orientation for the location of the steep superior and inferior axis meridians. Previous studies have determined that a SRAX value > 20° is indicative of keratoconus, however this value is more valuable for eyes with corneal astigmatism >1.5 D.[29-31] There are currently no known studies that have reported a possible

SRAX value that could be used to differentiate keratoconus suspects from clinical keratoconus or normal eyes.

The I-S index defines the power difference between the average inferior and superior cornea with a higher value indicating greater asymmetry. In 1989 Rabinowitz et al. developed this I-S index and reported a value between 1.4 – 1.9 D to be indicative of subclinical keratoconus and values greater than 1.9 D to be consistent with a diagnosis of keratoconus.[32] However, in subsequent works by these authors, the cut-off value used for differentiating a keratoconus suspect from normal was 0.80 D with a 95.7% correct classification rate.[33,34] Additionally, another study reported the probability of having a normal, suspicious, or keratoconic cornea given an I-S index of 1.0 or greater was approximately 20%, 58%, and 90%, respectively.[26] This index was not originally designed to differentiate subclinical from clinical keratoconus, however, it is speculated a value between 1.0 – 1.4 D could be used to help determine whether an individual should be considered a keratoconus suspect. The I-S index has also been previously compared to the index of height decentration (IHD) which is automatically calculated by the Pentacam software. This value determines the amount of vertical decentration for elevation data; a value >0.014 is considered abnormal and >0.016 is considered pathological for corneal ectasia.[35] In a study by Wahba et al., they found the IHD and I-S indices are highly correlated ($r^2 = 0.874$) with a validated regression formula which relates the two indices.[36] The published corresponding I-S values for the abnormal (0.014) and pathological (0.017) IHD values are 1.0 and 1.4, respectively.[36] These findings help justify the use of 1.0 D as

a potential cut-off I-S value for classifying keratoconus suspects and 1.4 D for classifying clinical keratoconus.

One corneal metric that is often underutilized when analyzing indices for keratoconus detection is corneal eccentricity. Despite the substantial research conducted over the last decade that has contributed to the understanding of keratoconus, corneal eccentricity has often been overlooked. Corneal eccentricity is a dimensionless constant defined by the flattening of the cornea towards the periphery and designates how much the corneal shape differs from a perfect sphere.[37-39] A positive eccentricity value relates to a prolate shaped cornea while a negative eccentricity relates to an oblate cornea.[40] In the average human cornea, the front surface curvature flattens from apex to the periphery. In cases of keratoconus, this gradual flattening appears more extreme due to the abnormal steepening at the corneal apex. Studies report the average corneal eccentricity is between 0.4 and 0.6 with no statistical difference between men and women.[41] Subsequently, some research shows a slight decrease in corneal eccentricity with age, but other studies report stable eccentricity throughout life so this data is inconclusive.[42] In keratoconic eyes, the eccentricity value is larger and values greater than 0.8 are statistically significant for this condition.[38] According to a previous study, an increase in eccentricity may occur prior to slit-lamp findings making it a potential diagnostic factor for keratoconus in its primary stages.

As previously mentioned, the currently reported prevalence rates for keratoconus are suspected to be an underestimate of the true disease prevalence. This is despite the majority of studies being published after 2000 and with the availability of corneal

tomography devices. Additionally, it is difficult to compare the findings across current studies due to the variety of study design, sample sizes included, measurement techniques, geographic location, and age of study participants. In order to improve current estimates of the disease prevalence, more research is needed to add to current literature findings. More importantly, it is highly valuable to study subject populations with a large sample size, diverse demographic make-up, and a population age that would capture individuals with a higher likelihood of having the condition of interest. Therefore, it is proposed a study completed at a large university setting would be of value for studying the prevalence of a condition that mostly presents and affects individuals between the ages of 18-35. To date, there are no known studies in the United States (USA) that have observed prevalence rates of keratoconus within this specific age group despite this condition often presenting in the second or third decade and progressing until the fourth decade of life.

To aid in expanding the current keratoconus prevalence literature, a retrospective study utilizing data collected over seven years at a large college campus setting was proposed. The primary objective of this study is to determine the prevalence of keratoconus within the target population, as well as investigate a possible prevalence rate for keratoconus suspects. This will aid in further solidifying accurate prevalence reports of clinical and subclinical cases of keratoconus. A secondary objective of this study is to explore if topographic indices other than those typically used to identify keratoconus show significant differences when comparing normal, suspicious, and keratoconic eyes. Additional information regarding corneal biometric data will help provide insight as to

which metrics may be beneficial in determining subjects at risk for keratoconus development.

Chapter 2. Methods

A retrospective study design was completed to analyze previously collected data from a Marco OPD Scan-III device (software version 1.16.04, Nidek Co., Ltd, Gamagori, Japan) in order to evaluate the eyes of a population of undergraduate and graduate students attending college in a large university setting. This study was reviewed and approved by the Institutional Review Board at The Ohio State University. All students at The Ohio State University who presented for eye care at The Ohio State University College of Optometry Wilce Student Health Center completed pre-examination data collection using the OPD Scan-III device. The OPD Scan-III device functions as an autorefractor, keratometer, pupillometer, corneal topographer, and wavefront aberrometer. Data collected from this device can be used to evaluate the curvature of the cornea and the optical quality of images a patient perceives. A total of 7,876 patient files were collected on the OPD machine from July 2017 – April 2024. Due to the retrospective study design, access to exam records and patient demographic information besides gender (male or female) and date of birth were not available. Patient age was calculated utilizing the patient's date of birth and date of image capture/exam.

All 7,876 patient files collected were eligible for initial review to determine if quality data had been previously captured. A pre-determined quality scan inclusion criteria of at least 15 Placido rings present was used as a cut-off value. In the event an individual

subject had data from multiple exam dates, the most recent scans were reviewed. If the most recent exam data did not meet the quality inclusion criteria but earlier exam data meeting quality standards was present then this data was used instead. Both right and left eye exam data was reviewed for all subjects, however only right eye exam data is reported for the final population comparison analysis. When presenting prevalence data, both right and left eye final totals are reported. Final subject counts used for comparison analysis and prevalence determination are represented in the flow charts in Figures 3 and 4, respectively.

Data meeting quality standards were further evaluated to classify subjects into normal, subclinical, or clinical keratoconus groups via both subjective and objective methods.

Subjective Classification: Topographical Map Examination

Once a scan was determined to meet the 15 Placido ring quality standard, the axial and elevation maps for each subject were reviewed by single clinical examiner. During the initial review of each individual topography map, the examiner determined if the subject had a topographical appearance that aligned with one of three categories: normal, keratoconus suspect/abnormal, or myopic refractive surgery/ortho-k appearance. Normal maps included round, oval, or symmetric bow-tie patterns. Keratoconus suspect maps contained asymmetric bowtie, skewed, inferior steepening, superior steepening, or atypical map patterns. The myopic refractive surgery/ortho-K group contained maps with a flat central area adjacent to a ring of greater corneal power typical of topography for patients who wear orthokeratology lenses or have had myopic refractive surgery. There were 149

subjects who were in the myopic refractive surgery/ortho-K group and were not further evaluated for the purpose of this study. Once the initial classification for each subject was determined, the investigator further reviewed the abnormal topographies and subjectively diagnosed each individual with keratoconus or as a keratoconus suspect. This subjective classification was based on clinical expertise and assessment of the axial topography map. Axial topography maps were utilized for the initial subjective classification as this was the default map output by the OPD software.

Objective Classification: Calculated Corneal Indices Application

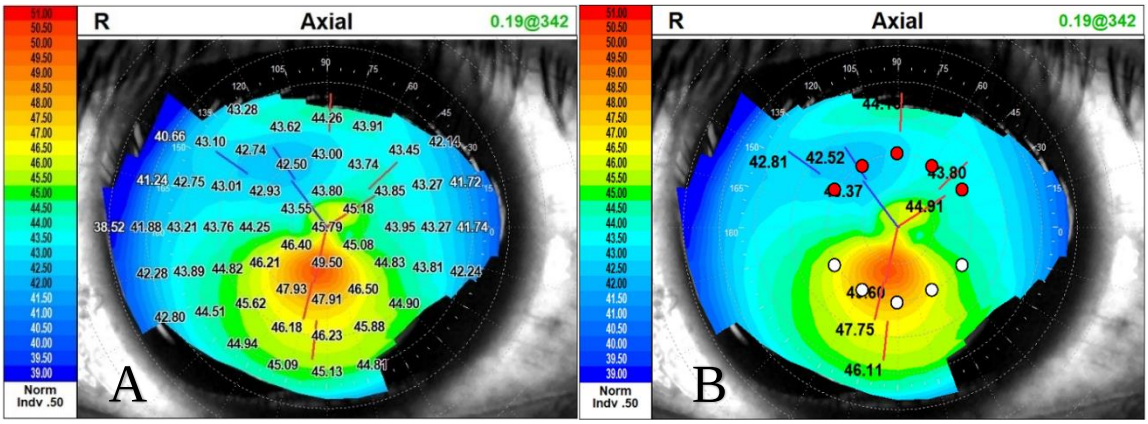
To objectively diagnose each suspicious subject, three calculated criteria were applied to differentiate between normal, suspect, and keratoconus classifications. The indices used for this process included maximum keratometry values (K_{max}), inferior-superior dioptric asymmetry (I-S) index, and the skewed radial axis (SRAX) index. The methods for calculating the I-S and SRAX indices are described below and have been adapted from previously described methods by Rabinowitz and Rasheed.[43] For each of the three objective criteria, classification indices were determined based on previously reported values.[26,27,31,43-45] These criteria are presented in Table 1.

- K_{max} represents the maximal keratometric value and was directly recorded from the axial map of each cornea.

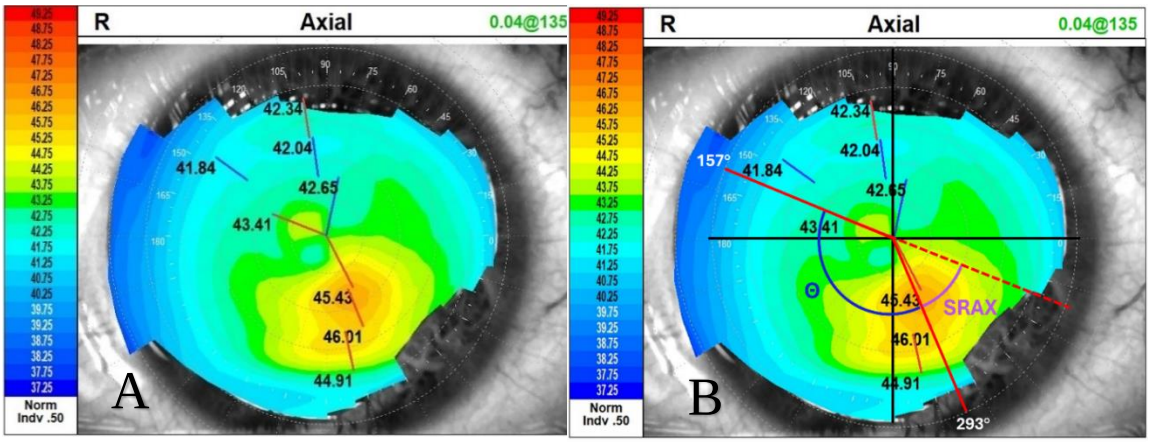
- I-S value: the amount of asymmetry between the inferior and superior steepening of the cornea. This value is calculated by subtracting the superior average keratometry value

from the inferior average keratometry value. The average values were determined using 5 keratometry points along the superior and inferior cornea 2.0 mm from the center at 30-degree intervals (i.e. superior points at 30, 60, 90, 120, and 150 degrees; inferior points at 210, 240, 270, 300, and 330 degrees). Figure 1 shows an example for calculating this index.

- SRAX value: the angle between the steepest meridians located above and below the horizontal meridian. The smallest angle between the semi-meridians is subtracted from 180°, resulting in the SRAX index. Figure 2 shows an example for calculating this index.



(A) Axial map with keratometry values. (B) Axial map indicating the areas along a 2 mm radius from the center used to determine the inferior (white) and superior (red) average keratometry values.
Figure 1. Corneal topography of the right eye used to calculate the I-S index



(A) Axial map showing the software generated steep (red) and flat (blue) meridians. (B) Axial map indicating the axis for the steep meridians used in the SRAX calculation. The steepest meridian above the horizontal meridian is at 157°. The steepest meridian below the horizontal meridian is at 293°. The smaller angle between the two steep meridians (Θ) is subtracted from 180 to determine the SRAX value. In this example, the SRAX is 180 – (293 – 157) = 44°.

Figure 2. Corneal topography of the right eye used to calculate the SRAX index

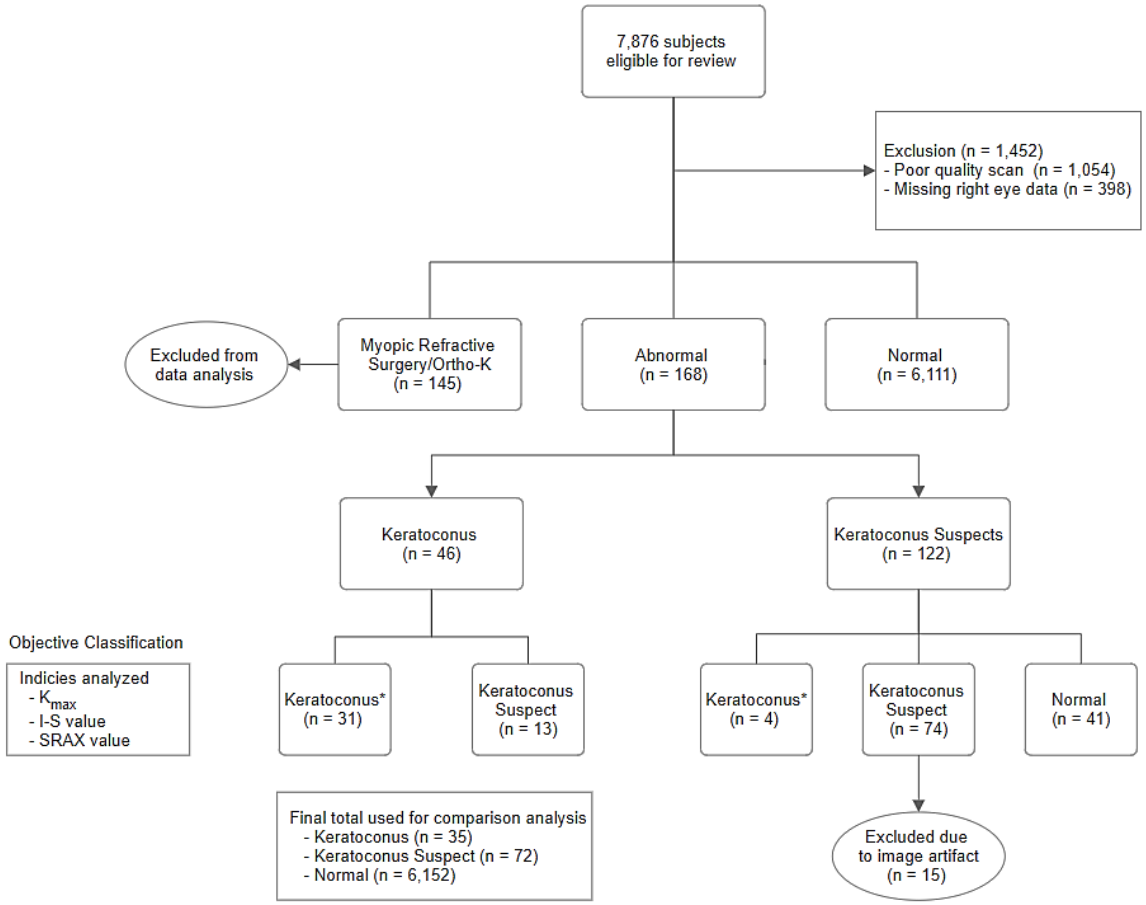
OBJECTIVE INDICES USED FOR CLASSIFICATION OF CONDITION			
Index	Normal	Keratoconus Suspect	Keratoconus
K_{max}	< 45 D	45 D – 47 D	≥ 47.2 D
I-S	< 1.0 D	1.0 D – 1.4 D	> 1.4 D
SRAX	< 10°	10° – 20°	> 21°

Table 1. Objective indices used for determining diagnosis classification based on corneal topography data

A subject was classified as having keratoconus if the data met all three objective criteria. In the event that only two of the three criteria were met, additional review was

completed. If the subject did not meet SRAX or K_{max} criteria but the I-S index was ≥ 1.9 D then the subject was classified as having clinical keratoconus (n = 6). If the subject did not meet I-S criteria but the K_{max} was ≥ 50 D then the subject was classified as having clinical keratoconus (n = 2). A diagnosis of keratoconus suspect was given if the subject had at least two qualifying suspect criteria, one qualifying keratoconus criteria, or if clinical keratoconus was present in the adjacent eye. Subjects were classified as being normal if they had only one suspicious classification index.

This process for subjective and objective classification was completed for all eligible right and left eye data. The final objective classification groups were used for further group comparison analysis and prevalence determination. Only right eye data was utilized for group comparison analysis. Figure 3 represents a flow outline for this classification process. Prevalence determination was considered per person and used both right and left eye data. A subject was counted as having the condition if a final classification of keratoconus was present in at least one eye. Figure 4 represents a flow outline for the population disposition regarding prevalence determination.



* 5 subjects were determined to have pellucid marginal degeneration and not included in final group count

Figure 3. Flow diagram demonstrating population disposition of only right eye data during the categorization process and final counts used for study comparison analysis

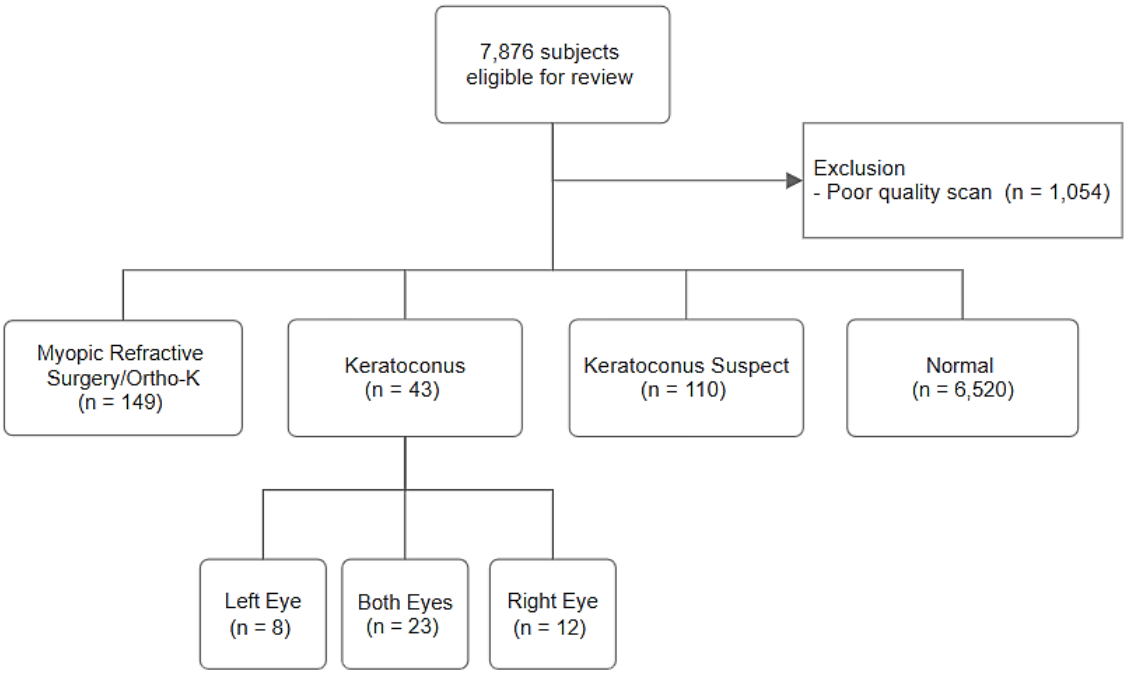


Figure 4. Flow diagram demonstrating population disposition for final group counts utilized for prevalence determination

Analysis of Additional OPD Derived Data

In addition to age and gender, the data collected by the OPD Scan-III for each patient included various indices deemed important for investigation by the investigator. The included indices were directly obtained from the OPD Scan-III device using the following pre-set machine parameters. These variables were used for a secondary analysis after eyes were objectively classified as normal, keratoconic, or as a keratoconic suspect. The machine derived variables were not used to aid in corneal group classification.

- Simulated keratometry values for the flat ($SimK_1$) and steep ($SimK_2$) meridians measured at 3.0 mm in the corneal center in diopters (D)
- Astigmatism index (AST) which quantifies the degree of corneal astigmatism ($SimK_2 – SimK_1$)

- Automated refractive power (D) including central sphere, cylinder, and axis values
- Mesopic and photopic pupil size (mm)
- Corneal eccentricity (e) measured along a 6.0 mm zone
- Total root-mean-square (RMS) measured in diopters (D) analyzed at the subjects mesopic pupil size
- Total higher order aberration (HOA), total corneal HOA, total corneal sphere HOA, total corneal coma HOA, and total corneal trefoil HOA values reported in microns (μm) and analyzed at the subjects mesopic pupil size

Statistical Analysis

Statistical analysis was performed using the software for Windows SPSS (version 29.0, SPSS, Chicago, Illinois, USA). Statistical significance was set at $p < 0.05$. The Kolmogorov Smirnoff test was run to test for sample normality, all variables were normally distributed except for age. For sample descriptive statistics, only the right eyes of subjects with qualifying data were included. When determining population disease prevalence, both right and left eye data were analyzed. An individual was counted in the total disease prevalence if the subject had corneal ectasia in at least one eye. This value was divided by the total population count of those eligible for assessment (including all subjects who met scan quality standards (n = 6,822)) and multiplied by 100,000. Clopper–Pearson exact confidence intervals (CIs) were evaluated to calculate 95% CIs for the prevalence of keratoconus. This process was also completed to determine the prevalence of keratoconus suspects in this sample population. Descriptive statistics were run to describe the

population distribution regarding subject age, gender, and average (mean ± SD) values for a variety of variables. A one-way analysis of variance (ANOVA) with Bonferroni post-hoc for multiple comparisons was run to compare sample means for all variables among the three classification groups.

Chapter 3. Results

Population Prevalence

A total of 6,822 subjects met scan inclusion criteria and were used in the total population count when determining keratoconus prevalence. When evaluating the prevalence of keratoconus using both right and left eye data, there were 12 subjects with clinical keratoconus in just the right eye, 8 with keratoconus in just the left eye, and 23 subjects with keratoconus in both eyes. For subjects with a keratoconus diagnosis in one eye, the adjacent eye was classified as a keratoconus suspect. There were no cases of unilateral keratoconus based on combined subjective and objective classification in this study. Considering both right and left eye keratoconus classification, there was a total of 43 subjects who had at least one eye with keratoconus in this study population. The prevalence of keratoconus for this sample is 0.63% or 630 per 100,000 persons (95% CI: 0.46% - 0.85%). There was a total of 110 subjects who were classified as a keratoconus suspect in both eyes or had one suspicious eye and one normal eye. The prevalence for keratoconus suspects in this population was 1.612% or 1,612 per 100,000 persons (95% CI: 1.3% - 1.9%).

Subject Classification by Right Eye Data

A total of 7,876 subject files were collected on the OPD machine from July 2017 – April 2024 and were eligible for initial review. Of these, 1,452 files were excluded due to poor quality scans (n = 1,054) and missing right eye data (n = 398).

Based upon topography examination, of the remaining 6,424 individuals, 145 were initially classified as having a myopic refractive surgery/ortho-k appearance with topography, 168 were classified as abnormal, and the remaining 6,111 were considered normal. The 168 abnormal subjects were further classified subjectively into keratoconus (n = 46) and keratoconus suspect (n = 122) groups. Of the 46 subjective keratoconic eyes, 31 were confirmed to have keratoconus, 13 were keratoconus suspects, and 2 were determined to have pellucid marginal degeneration after applying objective metric classification. After objective classification, the initial 122 keratoconus suspects were recategorized with the following findings: 4 keratoconic eyes, 74 keratoconus suspects, 41 normal corneas, and 3 eyes with pellucid marginal degeneration. Additionally, there were 15 subjects with data that looked suspicious but was later determined to be a result of image capture artifact. These 15 subjects were excluded from the final sample total used for secondary analysis. The final total count for each category was 35 keratoconus, 5 pellucid marginal degeneration, 72 keratoconus suspects, and 6,152 normal when considering only right eye data. This final grouping was used for further secondary outcome data analysis, and eyes with pellucid marginal degeneration were omitted during the comparison of the group data (n total = 6,259).

Secondary Outcomes

All results reported in this section were determined using the final total sample and objective classification groups discussed in the final right eye subject classification section. The median (IQR) age for the total sample population is 26.02 (22.68 – 28.66) years with a minimum age of 15.72 and maximum age of 71.07 reported. There were 3,986 (63.7%) female subjects and 2,273 (36.3%) male subjects used for the final population comparison analysis. The average (mean ± SD) values for the total sample as well as for each group (normal, keratoconus suspect, keratoconus) are presented in Table 2. Also presented in Table 2 are the p-values for each variable that showed a significant difference in mean between the three groups with ANOVA analysis. Further post-hoc multiple comparison analysis with Bonferroni correction determined there was a significant difference between all possible group combinations for the variables $SimK_2$, eccentricity, corneal RMS, total corneal coma HOA, refractive cylinder power, and AST. Regarding gender, total corneal HOA, and total corneal trefoil HOA, there was a significant difference between keratoconic eyes and both normal and suspect eyes; however, there was no difference for these variables between normal and suspect eyes. There was only a significant difference between normal and keratoconic eyes for age and corneal sphere HOA. $SimK_1$ had a significant difference between all groups except for suspect and keratoconic eyes.

Population Demographics					
Variable (mean ± SD)	**Total (n = 6,259)**	**Normal (n = 6,152)**	**Keratoconus Suspect (n = 72)**	**Keratoconus (n = 35)**	**ANOVA p-value***
Age (y)	26.30 ± 4.98	26.27 ± 4.96	27.73 ± 5.66	29.66 ± 5.14	<0.001§
Gender (n (%))					0.012‡
Female	3,986 (63.7)	3,924 (63.8)	48 (66.7)	14 (40.0)	
Male	2,273 (36.3)	2,228 (36.2)	24 (33.3)	21 (60.0)	
$SimK_1$ (D)	42.77 ± 1.53	42.75 ± 1.51	44.15 ± 1.42	44.36 ± 1.88	<0.001⁂
$SimK_2$ (D)	43.92 ± 1.63	43.88 ± 1.60	45.61 ± 1.38	47.07 ± 2.60	<0.001†
AST (D)	1.15 ± 0.73	1.14 ± 0.71	1.45 ± 0.85	1.80 ± 3.23	<0.001†
Sphere (D)	-2.82 ± 2.76	-2.82 ± 2.76	-3.05 ± 2.80	-1.75 ± 2.56	
Cylinder (D)	-0.67 ± 0.73	-0.66 ± 0.70	-0.90 ± 0.95	-2.41 ± 1.98	<0.001†
Axis (°)	76 ± 69	76 ± 69	86 ± 72	70 ± 56	
Mesopic Pupil Size (mm)	6.26 ± 0.88	6.26 ± 0.88	6.20 ± 0.90	6.07 ± 0.88	
Photopic Pupil Size (mm)	4.43 ± 0.82	4.43 ± 0.82	4.33 ± 0.78	4.26 ± 0.96	
Corneal Eccentricity (e)	0.38 ± 0.26	0.38 ± 0.25	0.23 ± 0.36	-0.13 ± 0.85	<0.001†
Corneal RMS (D)	0.61 ± 0.61	0.60 ± 0.58	1.00 ± 1.26	2.15 ± 1.59	<0.001†
Total HOA (µm)	1.13 ± 9.35	1.12 ± 9.42	1.16 ± 3.48	1.70 ± 1.42	
Total Corneal HOA (µm)	0.57 ± 2.15	0.56 ± 2.16	0.73 ± 0.54	2.48 ± 1.73	<0.001‡
Corneal Sphere HOA (µm)	0.30 ± 0.38	0.30 ± 0.38	0.35 ± 0.22	0.58 ± 0.80	<0.001§
Corneal Coma HOA (µm)	0.30 ± 0.51	0.29 ± 0.48	0.50 ± 0.45	2.09 ±1.45	<0.001†
Corneal Trefoil HOA (µm)	0.23 ± 1.03	0.22 ± 1.03	0.27 ± 0.26	0.87 ± 0.69	0.001‡

† significant difference between all group combinations
‡ significant difference between keratoconus and normal, and keratoconus and suspects
§ significant difference between only keratoconus and normal
⁂ significant difference between keratoconus and normal, and normal and suspect

Table 2. Population mean ± SD values for total, normal, suspect, and keratoconus groups for various study indices

Chapter 4. Discussion

Prevalence Considerations

With the data collected for this population over the course of seven years, the prevalence of keratoconus was 630 per 100,000 persons. This prevalence value is greater than the most recently reported 2020 global prevalence of 138 per 100,000 and falls approximately in the middle of the prevalence range for other previously reported studies.[8] Additionally, this rate is about twice as much as the recently published pediatric study completed in Chicago that had a reported rate of 300 per 100,000.[9] It is not surprising that this population had a prevalence twice as large given the age of the two study samples and the typical age of onset for the keratoconus.

The prevalence rate determined in this study is most similar to a 1959 study completed in the United States in Indiana. This study was carried out by the University of Indiana and assessed 13,395 eyes with a keratoscope over the course of 10 days at the Indiana state fair; the reported prevalence rate based on this keratoscopic survey was reported as 0.6% or 600 per 100,000 persons.[46] This study included all ages but the majority of subjects were in the 10-19 (n = 2,848), 30-39 (n = 1,971), and 20-29 (n = 1,757) age cohorts, which is a similar, if not slightly younger, sample than the one reviewed in this current study.[46] Despite the Indiana study being completed in the late 50s prior to the advent of corneal tomography, keratoconus was still detected in a similar percentage of the

population as the current study. This connection helps support the used of keratometric observation as a useful screening method for keratoconus.

The prevalence rate for keratoconus has been difficult to compare across previous studies due to the various sample sizes, population geographic location, disease determination method, and the age of the subjects studied. Some studies utilize large database data and medical record codes (ICD/DTC codes) to determine whether a subject has keratoconus. In these reports, the sample sizes used are on the magnitude of hundreds of thousands to millions of subject records evaluated. However, the studies with medical record review methods typically have the lowest prevalence rates with the lowest at 4 per 100,000 from a 2009 study done in the US to the highest rate of 265 per 100,000 from a 2017 study completed in the Netherlands.[47,48] These lower prevalence rates despite large sample sizes begs the question if diagnostic code examination is actually helpful when reporting keratoconus prevalence or if future study designs should focus efforts on more clinical observation detection methods.

The geographic location of a study and the demographic make-up of the subjects analyzed greatly impacts the reported prevalence rates. Historically, the studies published from countries in the Middle East such as Iran, Iraq, Saudi Arabia, Egypt, Turkey, and Oman have had the highest reported prevalence rates ranging from 760 – 4800 per 100,000 persons.[49-54] This differs significantly from European studies that have reported lower prevalence rates ranging between 6.8 – 549 per 100,000 persons.[55-60] Furthermore, two studies from Japan and China that utilized topography metrics for disease determination reported prevalence rates of 850 and 900 per 100,000 persons, respectively.[61,62] Lastly, a

study completed by Chelliah et. al specifically studied 15 medical students aged 18-24 in southern India and determined the prevalence of keratoconus for this population was 3.9%.[63]

For the current study, racial demographic data was not available to use for analysis. However, the racial make-up of the Ohio State University student body is published and can arguably be used as a racial demographic proxy. In 2022, The Ohio State University-Main Campus had a total enrollment of 60,540 students. The racial composition of total enrolled students at this time was 61.1% White, 8.6% Asian, 7.51% Black or African American, 5.59% Hispanic or Latino, 4.21% Two or More Races, 0.0562% American Indian or Alaska Native, and 0.0413% Native Hawaiian or Other Pacific Islanders.[64] Interestingly, despite the majority of Ohio State students being White, the prevalence of keratoconus for this population was greater than previously reported European studies and more similar to rates reported from Middle Eastern and Asian based study sites. Additional comparison studies will have to be completed to answer what role racial demographics plays in contributing to keratoconus prevalence, but for now this is a potential contributing factor.

Previous studies observing the prevalence of keratoconus have also reported the proportion of male and female subjects who have the condition to determine if keratoconus affects men and women equally. The majority of the studies have found non-significant differences between male and female keratoconus prevalence with some reporting a higher proportion of men being affected and some reporting women being more affected. The findings from this study are interesting regarding the percentage differences of men and

women with keratoconus. These results found a significant difference regarding gender between the keratoconus group and the other two groups. However, there was not a significant difference between the normal and suspect groups when it came to gender.

The total sample used for this study had 63.7% female and 36.3% male. This approximately 2:1 female to male ratio remained fairly consistent for the normal and suspect groups. However, when evaluating the keratoconus group, the gender break down changes and the majority of participants in this group are male (60%). This finding is interesting and suggests that even though the majority of the total sample population was composed of primarily females, participants in the keratoconus group are disproportionately male subjects.

One caveat to this observation is the possible input error when recording participant gender. Since this is a retrospective study, it is possible the information recorded on the OPD device is partially inaccurate. When creating a patient file, the examiner is required to manually input a subject's name, date of birth, and gender. If a gender is not selected during this process, the default setting is to categorize the subject as a female. Therefore, it is possible that the disproportionate male to female ratio for the total population could be due in part to this data collection error and the inability to verify each subject's true gender categorization. Despite this limitation, it would be expected the percentage of incorrectly classified subjects would be similar regardless of ocular condition. Unless examiners were more cognizant of reporting the gender for subjects who had corneal ectasia or abnormal findings during the comprehensive exam, it is unlikely the gender ratio differences between the keratoconus group and all other groups would be due to this possible data collection

error alone. Continued prospective research will be needed to validate the gender discrepancies observed with this study sample to confirm if men are truly more effected by keratoconus compared to women.

Classification Agreeability

When comparing classification aggregability between clinical subjective and index driven objective classification methods, there is fairly good agreeability when it comes to diagnosing subjects with keratoconus. Of the original 46 subjects who were subjectively considered to have keratoconus based upon the appearance of the topographies, only 13 subjects were switched to the suspect group after objective indices were considered. This indicates that subjective classification alone falsely diagnosed 28% of the subjects in this group. Additionally, when considering the subjectively classified keratoconus suspect group, 4 of the 122 (3.3%) subjects were incorrectly classified by topographical appearance and actually had keratoconus based on objective measures. These findings suggests that when subjective clinical determination for group classification is used alone, it is fairly sensitive for accurately detecting those with clinical keratoconus. However, there was ~ 1/3 of subjects who had false positive outcomes, and subjective methods alone did lead to an over-diagnosis for this condition.

For a condition like keratoconus where loss of functional vision cannot be restored after changes have occurred, it is arguably better to over-diagnose than to allow someone to progress undetected. The possible negative impact of over-diagnosing based upon corneal topography would be sending individuals for additional testing that may not be

warranted. Most of the time this additional testing does not result in added risk to the subject and testing is minimally invasive. Therefore, it is reasonable to conclude that expert clinical determination with axial topography alone is a fairly good screening tool. However, due to the availability of more objective measures, using additional metrics if accessible when differentiating normal from abnormal corneas is preferable. In situations where advanced special testing is not available, corneal topography with clinical assessment can serve as a good screening tool for keratoconus.

Method and Variable Considerations

A potential limitation with the study method design is the location of the keratometry values used when calculating the I-S index. When this index was first formulated by Rabinowitz et al., a ring radius of 3 mm was used to calculate the amount of vertical corneal asymmetry.[32] For this study, a 2 mm radius was used instead of 3 mm. This was decided because, the axial map output for the Nidek OPD Scan-III had exact keratometry values available for the axis locations used in the I-S calculation at a 2 mm radius location but not at a 3 mm radius. In order to reduce error during manual calculation it was determined using a Placido ring closer to the center would be more beneficial than attempting to use values that are less repeatable. Additionally, there were some subjects who did not have data captured at all points needed for the I-S calculation along the 3 mm ring radius. Having missing data would alter the outcomes of the calculation, so it was decided to use a method that could be consistent across all subjects.

A possible concern when using a different radius for determining the I-S index is the potential for calculating artificially higher or lower I-S values, which could possibly lead to improper categorization of subjects. For subjects with inferior steepening closer to the center, a 2 mm radius location could lead to a greater I-S value and possibly be enough to improperly classify someone who is a suspect as having keratoconus. Additionally, a subject with a more peripheral area of corneal steepening could have a lower I-S index when calculated with a 2 mm radius. This could lead to inappropriately classifying a subject as normal when they are actually a keratoconus suspect.

Another study by Bühren et al. used the Orbscan device to calculate the I-S index, and a 2 mm radius was also used to determine this value.[65] Results from this study align well with findings from the current study regarding the I-S index and therefore support the use of the 2 mm ring radius. Additionally, previous studies using a variety of topography and tomography devices have published average I-S and K_{max} values for normal, suspect, and keratoconic eyes for the respective study populations (Table 3.). When comparing these previous average values to the group average indices values from this study, it is reasonable to conclude that the average values align well with trends reported by previous authors. Therefore, despite using a slightly different calculation method for the I-S index, it is still a reliable value to use during objective classification.

Previously reported demographic topographic index values (mean ± SD)				
Parameter	**Normal**	**Keratoconus Suspect**	**Keratoconus**	**Device Used**
K_{max} (D)	44.57 ± 1.50	-	54 ± 6.12	Pentacam[66]
	44.13 ± 1.24	44.89 ± 2.03	53.19 ± 6.01	Pentacam[67]
	44.65 ± 1.54	-	53.94 ± 5.26	Pentacam[68]
	45.54 ± 20.7	46.15 ±2.12	-	Pentacam[69]
	44.2 ± 1.30	45.4 ± 1.70	54.7 ± 5.20	GALILEI[70]
	44.26 ± 1.34	44.61 ± 2.56	47.97 ±4.78	OPD Scan-III[71]
	45.49 ± 1.92	45.91 ± 1.97	55.14 ± 7.66	Pentacam[72]
	44.45 ± 4.69	-	51.71 ± 5.21	Pentacam[73]
	45.11 ± 1.56	44.03 ± 1.50	-	Pentacam[74]
	45.06 ± 1.75	45.83 ± 2.08	53.80 +4.64	Pentacam[75]
	45.43 ± 2.10	46.62 ± 2.21	54.12 ± 4.47	Sirius[75]
	45.09 ± 1.29	**46.48± 1.38**	**51.81 ± 4.77**	**OPD Scan-III***
I-S (D)	0.04 ± 0.44	-	4.88 ± 3.03	Pentacam[68]
	0.58 ± 0.40	0.96 ± 0.50	8.44 ± 4.30	GALILEI[70]
	0.57 ± 0.52	1.20 ± 0.92	4.44 ± 2.76	TMS-1[26]
	0.02 ± 0.41	0.73 ± 0.47	4.4 ± 3.01	OPD Scan-III[71]
	0.20 ± 0.60	0.64 ± 0.47	-	Pentacam[74]
	0.12 ± 0.53	1.28 ± 0.96	5.56 ± 3.28	Pentacam[75]
	0.18 ± 1.21	1.68 ± 3.01	6.67 ± 5.06	L80 Wave+[76]
	0.49 ± 0.25	**0.79 ± 0.49**	**4.68 ± 3.14**	**OPD Scan-III***

* Values from current study population

Table 3. Mean ± SD K_{max} and I-S indices for normal, suspect, and keratoconus groups based on previously reported literature

In this study there were only 2 individuals who were subjectively classified as having keratoconus who did not meet the I-S criteria of > 1.4 D. In these two cases the final diagnosis was determined because the K_{max} was > 50 D and SRAX value was > 20°. After

reviewing the axial maps in more detail, the two subjects who did not meet I-S criteria had more centralized and temporal steepening. This observation highlights how the I-S index alone may miss cases of central/nipple keratoconus or less common horizontal steepening. As with other topography indices, the I-S value should not be used in isolation to determine a clinical or subclinical keratoconus diagnosis, but it is a helpful objective index to utilized when topography findings are borderline.

When the data for each subject was extracted from the OPD machine, the RMS and HOA data was calculated using the mesopic pupil size of the analyzed eye. Previously published studies have traditionally used a constant pupil size when comparting HOA data. This is in part because as pupil size increases, the amount of HOA present typically increases. Therefore, individuals with larger pupil sizes are going to have inherently higher levels of HOA, regardless of corneal condition, compared to individuals with smaller pupils. It is possible that RMS and HOA data from this study could have more variability that other studies in which a single stable pupil size was used when calculating these values. It should be noted that there was not a statistically significant difference between mesopic pupil size across all three classification groups, but there was a significant difference for all RMS and corneal HOA data. These findings indicate that despite the variety in pupil size between subjects, this variation did not significantly impact the differences present regarding HOA metrics across the three groups. Additionally, use of mesopic pupil size data could better represent a subject's habitual level of HOAs, lending to a more realistic metric proxy for experienced visual capability.

Secondary Outcome Considerations

The invention of corneal tomography capturing devices has greatly improved the ability to detect cases of subclinical and early keratoconus. However, these devices are expensive and not always readily available for practitioner access outside of academic or hospital-based settings. The financial barrier to owning a device with Scheimpflug imaging capability can limit the ability to assess past the anterior corneal surface and result in delayed diagnosis and management for patients with early keratoconus. Therefore, it is important to continue validating topographic indices that are useful in detecting and differentiating keratoconus suspects from normal corneas. Previously reported indices that have been utilized in the objective classification of keratoconus are therefore important areas of study and future exploration.

Based upon the findings of this study, potential objective biometrics that may be useful in differentiating between normal, subclinical, and true keratoconus subjects are: $SimK_2$, corneal eccentricity, corneal RMS, total corneal coma HOA, refractive cylinder power, and AST. All of these variables had a significant difference in mean values between all group combinations and may serve as helpful differentiating factors when classifying corneal maps as normal or abnormal. Additionally, another metric that may be useful in identifying keratoconus suspects from normal eyes is the $SimK_1$ value. This variable was significantly different for suspects and keratoconic eyes when compared to normal corneas. The possibility of using simulated keratometry values, refractive cylinder, and AST as objective indices is significant due to the increased availability of collecting this data in clinical practice. Further determination and validation of useful cut-off-points for these

indices can aid clinicians in their decision making when evaluating a patient with abnormal refractive findings but no clinical signs of corneal ectasia. Better definitions of these indices will ultimately lead to an improvement in subclinical keratoconus detection without having to rely on more advanced detection indices and algorithms on topographic and tomographic devices that may not be equally accessible on a global level.

As previously mentioned, the index of corneal eccentricity has not been extensively explored as a possible metric for early keratoconus detection. This is possibly due to the narrow range of normal eccentricity values typical for the average population. Despite this narrow range, findings from this study did find a significant difference in mean eccentricity values between all group combinations. However, the mean values obtained from the OPD for each group were unexpected and different than what is observed in previous publications.[77,78] As previously mentioned, corneal eccentricity is a unitless value that represents the rate of corneal curvature change with a more positive value being indicative of a more prolate shaped cornea.[40] With this expectation, it is predicted that subjects with keratoconus would have an increase in this metric as their eyes become more inherently prolate in shape.

The average mean eccentricity values for the keratoconus group in this study sample contradicts this prediction as the mean eccentricity value was actually negative, indicating a more oblate corneal structure. This trend is also true for the keratoconus suspects as the mean eccentricity values was lower (less positive) when compared to normal eyes but greater (more positive) than the keratoconus group. Further review of the data for this metric revealed a minimum and maximum eccentricity value for the

keratoconus subjects to be -1.46 and 2.01, and the majority of subjects for this group had an eccentricity value that was negative in nature. These considerations help determine there was not a large negative outlier present within the data set that could arbitrarily alter the mean value for this index.

A possible explanation for this observation is the limited ability of the OPD Scan-III device to detect eccentricity values that are outside of the normal expected range. It is possible for cases of advanced prolate shaped corneas, the device is unable to compute and extrapolate an accurate eccentricity value that is representative of the true corneal shape. Therefore, even despite there being significant differences between the three group averages, caution is advised when considering eccentricity as a potential diagnostic index. Future studies utilizing the same capturing device will be needed to help validate these findings or determine if the current study population had an abnormal distribution for corneal eccentricity.

Study Limitations

A major limitation for this study was the retrospective study design and inability to confirm condition diagnosis with clinical exam findings such as visual acuity, retinoscopy, or slit-lamp biomicroscopy. Despite this limitation, the use of both subjective and objective classification methods were supported through previous literature and classification methods. Additionally, the use of a device that relies on Placido-based topography could result in misleading topography maps that appear abnormal but are actually irregular due to poor image capture. Some potential causes for this data acquisition error when

completing measurements include poor tear film stability, small lid apertures and eyelash artifacts, contact lens induced warpage, or ocular misalignment during data capture.[79] Efforts were made to exclude subjects that appeared to have poor quality images during the initial review of all patient files, however, it is possible some subjects with at least 15 Placido rings present still had some irregularities present on the topography maps.

Future considerations to help minimize this potential error would be to utilize elevation and instantaneous maps in addition to axial topography maps. In this study, the axial map was used during initial scan quality assessment because it was the default map available for review on the OPD device. Given the number of patient files and time it took to review each individual subject, additional assessment of multiple topography maps per subject would have increased the time needed to complete this project by weeks to months. Therefore, with additional time and possibly a secondary clinical investigator, multiple topography map examination would be more feasible and could possibly help detect more subtle cases of keratoconus.

Another limitation to this study is not having demographic information regarding a subject's race or ethnicity. Due to this lack of information, it is difficult to determine the racial make-up of the study sample and whether this aligns with the reported racial demographic present on The Ohio State University's campus. Additionally, without this information it is impossible to confidently generalize the prevalence rates to other previously reported studies and determine if this is an overestimate, underestimate, or well aligned estimate with the true prevalence rate for this condition. Future studies are required

involving similar sample sizes and with reported racial demographics in order to help correlate the findings of this study to future findings.

Chapter 5. Conclusion

The primary objective for this retrospective review was to determine the prevalence of keratoconus in the sample population. The prevalence of keratoconus for this study sample was 0.63% or 630 per 100,000 which is greater than the most recently reported global prevalence. These findings relate well to some previous studies completed in the US. However, not having racial demographic information for the study subjects limits the ability to generalize these findings to other study populations. Despite this limitation, the findings from this study provide valuable information regarding the disease prevalence of keratoconus present for college-aged students who attend a large university setting. With the knowledge that keratoconus prevalence may be higher than previously reported data, it can lead to heightened awareness for the possible signs and symptoms associated with the condition. Ultimately, this will result in earlier detection, treatment interventions, and better long-term prognosis for patients.

Additionally, the secondary outcomes from this study revealed there may be corneal metrics such as simulated keratometry values, corneal astigmatism, and higher order aberration data that can serve as indices to detect subclinical and early keratoconus. This knowledge may lead to future study ideas that will ultimately lead to earlier detection of keratoconus and improvement in disease management and treatment initiation. Early classification of concerning anterior corneal surface metrics combined with clinical

assessment has the potential to detect individuals at risk for this condition prior to clinical signs and symptoms presenting. A combined clinical assessment with objective classification is ultimately what will be best at detecting a keratoconus suspect and ensuring the proper measures are taken to monitor the condition and prevent disease progression. Ultimately, resulting in less reduction in a person's visual potential, improved quality of life, and reduced economic impact throughout the individual's life.

The results from this study emphasize the need for continued research, specifically more longitudinal large scale, objective data evaluation studies, which can help compare findings from previous works and develop new methods for early keratoconus detection and more accurate disease prevalence reporting.

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