

# A Cross-Sectional Analysis to Assess the Role of Atopy in Keratoconus Among Saudi Population

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**Background:** In cases of atopy, IgE antibodies are formed in reaction to certain environmental factors like house dust mites, pollen, or even food allergens. Some studies have shown an association between atopic diseases and keratoconus. This study aims to determine the prevalence of atopy and its associated factors among keratoconus patients.

**Materials and Methods:** A cross-sectional study was conducted among the Jazan population attending ophthalmology clinics regardless of their sex. Data collection started in August 2020 and finished in mid-June 2021. The sample was selected using the convenience sampling technique, and the total sample size was 83 participants. Data were collected via a questionnaire-based interview that contained 46 questions in the Arabic language. The data collected were analyzed using SPSS software.

**Results:** Family history is the leading predisposing factor for keratoconus ( $P < 0.001$ ). Also, eye rubbing was a significant ( $P < 0.015$ ) trigger for keratoconus. However, other factors, including demographic factors such as gender and atopic conditions, did not have any significant association.

**Conclusion:** A combination of genetic and environmental factors is the leading cause of the development of keratoconus; however, family history is the most influential factor, followed by eye rubbing.

**Keywords:** atopic disease, keratoconus, prevalence, risk factor, Jazan, Saudi Arabia

## Introduction

Atopy is described as a hereditary propensity to form immunoglobulin E antibodies (IgE) as a reaction to minute amounts of certain environmental factors, including house dust mites, pollen, or even food allergens.<sup>1</sup> Allergies are the clinical expression of atopic diseases; nevertheless, not all allergies are atopic diseases.<sup>2</sup> The most common characteristic of all atopic diseases is hypersensitivity of the skin and mucous membranes, and this hypersensitivity often runs in families.<sup>3</sup> Several risk factors have been identified for atopic diseases. Risk and triggering factors such as allergens, tobacco smoke, and occupational factors are the causative agents of allergic reactions or acute asthma in atopic patients. People with atopic dermatitis have a greater propensity to respond to specific antigens in the environment.<sup>4</sup> Epidemiological studies show that the incidence and prevalence of atopic diseases like asthma, hay fever, and atopic dermatitis are increasing in developing countries. However, the prevalence of atopic diseases has reached a plateau in developed western countries.<sup>1</sup> Atopic involvement in a person is linked with an increased incidence of development of one or more of the atopic conditions, such as asthma, atopic dermatitis (eczema), allergic rhinoconjunctivitis/hay fever, as well as food allergies.

However, atopy may manifest as asymptomatic sensitization, ie, it may be seen among patients who have proven allergic sensitization but may not display a clinical allergic reaction.<sup>1</sup>

Keratoconus is defined as an asymmetrical and worsening disease with severe effects on the acuity of vision as well as the life quality of the cases. It is also defined as a gradual thinning of the corneal stroma resulting in the modification of the tissue structure. Irregular astigmatism occurs due to a cone-shaped cornea. Corneal ectasia usually presents in young adults at puberty and may advance until the 3rd to 4th decade when physiological corneal cross-linking is established to be the disease's stabilizing agent.<sup>5</sup> The exact causes of keratoconus are still poorly understood. While most forms of keratoconus are known to be sporadic, several researchers have revealed a significant number of hereditary family keratoconus, whether via an autosomal recessive or dominant form. LOX is recognized as the collagen cross-linking enzyme lysyl oxidase, a gene important for cross-linking collagen, while elastin is viewed as a probable reliable indicator in keratoconus formation leading to a damaged corneal architecture. Environmental causes, including eye rubbing and the use of rigid contact lenses, have been linked to the condition. Those with allergic conditions have an increased chance of keratoconus formation.<sup>5</sup> The most frequently noted risk factors of excessive eye rubbing in keratoconus (KC) were allergies and atopic disorders. Nevertheless, irritation triggered by atopy, which contributes to rubbing of the eye, may be the most important contributing factor to KC.<sup>6</sup> The thinning of the cornea results in unequal astigmatism and myopia, which leads to mild-to-severe vision problems. Keratoconus is bilateral among 90% of cases but is typically asymmetrical in intensity as well as advancement. While no symptoms can accompany the initial stages of the disorder, as it advances, the common manifestation is mild to significant vision problems due to unequal astigmatism, myopia, and corneal scarring in some cases.<sup>6</sup>

Keratoconus disease is a bilateral, non-inflammatory corneal ectasia with an occurrence in the overall public of around one per 2000.<sup>7</sup> The frequency of keratoconus disease in the city of Asir in Saudi Arabia is twenty patients for every 100,000 people.<sup>8</sup> In total, 1638 people from one of the five cities in the Kingdom of Saudi Arabia (KSA) were referred to King Khaled's Eye Specialist Hospital for the treatment of keratoconus at an average annual reference rate of 136.5 cases per year. The overall distribution of people with keratoconus was almost similar among males and females, with a greater incidence of younger patients aged between 16 and 26. Keratoconus is an unexplained etiological condition, although much research has exhibited a connection with atopy.<sup>9</sup> From the start of the twentieth century, several descriptive surveys have documented the relationship between keratoconus and atopy.<sup>10</sup> In addition, keratoconus was identified in several different clinical studies. It may be an isolated sporadic disorder, or it may be combined with other uncommon hereditary diseases as well as with Down syndrome, connective tissue diseases, Leber's congenital amaurosis, hard contact lens wear, eye rubbing, and a strong family history of the condition.<sup>11</sup>

An association has been established between atopy and keratoconus for over 50 years, but several clinical studies have reported opposite findings. In studies carried out about 30 years ago, in 59% of keratoconus cases, an increased level of serum immunoglobulin E was observed. Nevertheless, as many people with allergic eye conditions rub their eyes vigorously, it has remained uncertain whether atopy itself or eye rubbing is the keratoconus-related cause. Harrison et al demonstrated that the condition occurs more often on the dominant hand side in atopic keratoconus cases. A case-control study published in 2000 by Bawazeer et al showed that there was an association between atopy and keratoconus, in addition to eye rubbing and keratoconus family history, in the univariate association, and demonstrated that only eye rubbing was still a strong indicator of keratoconus, in the multivariate study. They clarified that atopy may lead to keratoconus disease but most likely was a result of eye rubbing combined with atopy irritation.<sup>12</sup> Our study aims to estimate the prevalence of atopy and its associated factors among keratoconus patients in the Jazan region.

## Materials and Methods

The study's design is a cross-sectional study. The data were collected from people in the Jazan region who visited ophthalmology clinics in Prince Mohammad bin Nasser Hospital (PMNH) after obtaining their permission. Data collection started in August 2020 and ended in mid-June 2021. The prevalence of keratoconus varies worldwide, generally ranging from 0.0003% to 5%.<sup>1,2</sup> Many studies in the Kingdom of Saudi Arabia (KSA) have reported different prevalence rates in different geographical areas. A recent Saudi study reported a prevalence of 4.79% of keratoconus in Saudi patients aged 6 to 21 years.<sup>3</sup> Based on this estimate and using a cross-sectional study survey formula, the initial

sample size was set at 76 patients. The other parameters used for sample size calculation were a 95% confidence interval and an error margin not exceeding 5%. The inclusion criteria encompassed people who visited ophthalmology clinics, had files in PMNH in Jazan during the study period, and filled out a questionnaire with informed consent. Exclusion criteria included corneal pathologies other than keratoconus and prior corneal surgery.

Convenience sampling technique was employed from 2019 to 2021. Data were collected using a pre-designed questionnaire comprising three sections. The first section included an introduction. The second section included items on demographic data, smoking, presence of chronic diseases, questions on the presence of any allergic disease, methods of treatment and duration, as well as items on eye health, such as the presence of keratoconus and its duration, management, eye rubbing, and its triggers. The third section involved eye measurements and stages of severity. Questionnaire items were derived from previous studies that assessed the causes, risk factors of keratoconus, and its relation to allergies.<sup>1-5</sup> The questionnaire data were collected from patients after obtaining their permission. As no previous studies have used an Arabic-validated questionnaire, the questionnaire items were translated into Arabic by a healthcare physician and an expert translator fluent in both English and Arabic. The Arabic questionnaire was then back-translated into English by two other experts fluent in both languages, who were blinded to the original English version of the questionnaire. The back-translated version was compared with the original English version to ensure translation quality.

All collected data were analyzed using the Statistical Package for the Social Sciences (SPSS) software. The data were cleaned and entered into SPSS. Descriptive statistics were calculated for study variables (eg, percentages for qualitative variables, frequency, and mean and standard deviation for quantitative variables). The appropriate tests of significance (eg, chi-square) were applied, and P-values less than 0.05 were considered statistically significant. This study complies with the Declaration of Helsinki and was conducted according to ethics committee approval from The Institute Review Board (IRB) of Jazan Hospital (Approval number: No. 2052 dated 08/12/2020). Additionally, consent forms were obtained from all participants or parents/legal guardians of participants under 18 years, and they were informed that participation was entirely voluntary and that they could withdraw at any time.

## Results

Table 1 displays the demographic characteristics and ocular parameters of the keratoconus study participants. Among the genetic and environmental factors contributing to keratoconus, family history was a significant determinant, with a p-value of <0.001. Additionally, keratoconus patients reporting eye rubbing had a p-value of 0.015, indicating a high likelihood of suffering from Atopic syndrome (Tables 2 and 3). However, the risk of atopic syndrome among keratoconus patients based on gender was not statistically significant (p-value of 0.082), and its presence did not show statistical

**Table 1** Demographic Characteristic and Ocular Parameters of Keratoconus Subjects

Characteristic		Frequency	Percent
Gender	Male	49	50.0
	Female	49	50.0
Age Groups (years)	Less than 18	12	12.2
	18–24	27	27.6
	25–34	41	41.8
	35–49	18	18.4
Nationality	Saudi	92	93.9
	Non- Saudi	6	6.1

(Continued)

Table 1 (Continued).

Characteristic		Frequency	Percent
<b>Educational Level</b>	Primary	20	20.4
	Intermediate	10	10.2
	Secondary	20	20.4
	University and Postgraduate	48	49.0
<b>Occupational Status</b>	Students	27	27.6
	Governmental employees	18	18.4
	Private Sector employees	10	10.2
	Unemployed	35	35.7
	House wife	8	8.2
<b>Monthly Income (SR)</b>	Less than 5000	45	45.9
	5000 to less than 10,000	36	36.7
	10,000 to less than 150,000	11	11.2
	15,000 and more	6	6.1
<b>Marital Status</b>	Single	62	64.6
	Married	34	35.4
<b>Tobacco use</b>	Yes	9	9.2
	No	89	90.8
<b>Any chronic Conditions</b>	Yes	20	20.4
	No	78	79.6
<b>Descriptive ocular parameters</b>	Total # of Eyes examined	196	100
	Corneal thickness < 500 $\mu\text{m}$	84	85.7
	n (subjects)	98	100
		<b>Mean (SD)</b>	<b>Min-Max</b>
	Patient ages (years)	26.7(8.2)	8–48
	Duration of Keratoconus	5.5(6.0)	1–35
	CCT(Right)	457.6(67.4)	229–642
	CCT(left)	452.2(83.6)	32–655
	BDVA, decimal (Right)	044(0.33)	0.03–1
	BDVA, decimal (Left)	0.39(0.31)	0.05–1

**Abbreviations:** CCT, Central corneal thickness; BDVA, Best distance visual acuity; SD, Standard deviation; SR, Saudi Riyal; Min, Minimum; Max, Maximum.

significance on the severity of keratoconus (p-value of 0.743) either. Nonetheless, a significant number of patients diagnosed with atopic conditions are at risk of developing keratoconus. Figure 1 shows the distribution of atopic conditions in the keratoconus patients, while Figure 2 illustrates keratoconus among atopic and non-atopic groups according to the Amsler-Krumeich classification. Among the patients diagnosed with any atopic condition, 25.5%

**Table 2** Characteristics of Keratoconus Among the Study Population

		Keratoconus			p value
		Right Eye	Left Eye	Both	
Gender	Male	6(12.2)	7(14.3)	36(73.5)	0.705
	Female	8(16.3)	9(18.4)	32(65.3)	
Nationality	Saudi	12(13.0)	13(14.1)	67(72.8)	0.016
	Non-Saudi	2(33.3)	3(50.0)	1(16.7)	
Age Groups	Less than 18	2(16.7)	2(16.7)	8(66.7)	0.850
	18–24	3(11.1)	6(22.2)	18(66.7)	
	25–34	6(14.6)	4(9.8)	31(75.6)	
	35–49	3(16.7)	4(22.2)	11(61.1)	
Marital Status	Single	10(16.1)	11(17.7)	41(66.1)	0.607
	Married	4(11.8)	4(11.8)	26(76.5)	
Duration of Keratoconus (years)	One year or less	3(15.0)	5(25.0)	12(60.0)	0.317
	2–4	7(19.4)	4(11.1)	25(69.4)	
	5–9	2(8.0)	2(8.0)	21(84.0)	
	Ten or more	2(11.8)	5(29.4)	10(58.8)	
Blurred vision	Yes	2(8.7)	2(8.7)	19(82.6)	0.313
	No	12(16.0)	14(18.7)	49(65.3)	
Had a corneal transplant	Yes	0(0.0)	1(33.3)	2(66.7)	0.670
	No	14(14.7)	15(15.8)	66(69.5)	
Change the measurements of your glasses and/or lenses	Yes	8(17.8)	6(13.3)	31(68.9)	0.549
	No	6(11.3)	10(18.9)	37(69.8)	
Severity of Keratoconus	Stage I	3(8.6)	3(8.6)	29(82.9)	0.060
	Stage II	1(3.6)	8(28.6)	19(67.9)	
	Stage III	3(33.3)	2(22.2)	4(44.4)	
	Stage IV	2(15.4)	2(15.4)	9(69.2)	

**Note:** p-value based on Fisher exact test.

were diagnosed with keratoconus, with the highest prevalence observed among patients with dermatitis (7.1%), asthma (11.2%), and hay fever (13.3%). Lastly, [Figure 3](#) indicates an insignificant correlation between central corneal thickness (CCT) and the frequency of eye rubbing.

## Discussion

The results of the study support previous research and conclude that the etiology of keratoconus is multifactorial, involving both genetic and environmental factors. In this study, demographic attributes such as gender, age groups, and marital status showed no statistical significance in the development of keratoconus. However, consistent with findings from multiple previous studies, family history emerges as a significant risk factor for keratoconus. There is a strong association between keratoconus and parental consanguinity/endogamy, suggesting a substantial genetic component in its

**Table 3** Atopic Syndrome Among Keratoconus Patients

	Atopic Keratoconus patients			p-value
	Atopic Patients/ Keratoconus Patients	Proportion	95% CI	
Gender				0.082
Male	16/49	32.7	21.2–46.7	
Female	9/49	18.4	10.0–31.4	
Nationality				0.162
Saudi	25/92	27.2	19.1–37.1	
Non-Saudi	0/6	0.0	–	
Age Groups				0.026
Less than 18	3/12	25.0	9.1–53.8	
18–24	2/27	7.4	2.3–23.5	
25–34	16/41	39.0	25.6–54.4	
35–49	4/18	22.2	9.4–45.6	
Family History of Atopy				<0.001
Yes	16/29	55.2	37.4–71.6	
No	8/67	11.9	6.2–21.9	
Eye rubbing#				0.015
Yes	21/61	34.4	23.7–47.0	
No	4/36	11.1	4.5–25.4	
Severity of Keratoconus				0.743
Stage I	9/35	25.7	14.2–42.2	
Stage II	9/28	32.1	17.9–50.8	
Stage III	2/9	22.2	6.7–55.6	
Stage IV	2/13	15.4	4.7–42.8	
Overall	22/85	25.9	17.8–36.1	

**Note:** p-value based on Fisher exact test.

etiology.<sup>13</sup> The establishment of a family pedigree helps determine the most influential factor between genetics and the environment.<sup>14</sup>

Furthermore, this study confirms that environmental factors, including excessive eye rubbing and the presence of allergic disorders, may contribute to keratoconus. As shown in [Figures 1 and 2](#), over 75% of patients with keratoconus have an allergic disorder, particularly dermatitis, hay fever, or asthma. An estimated one-third of diagnosed keratoconus patients reported having an allergic disorder.<sup>12</sup> Although the allergic disorder is likely the cause of the increased frequency of eye rubbing, which exacerbates corneal injuries, [Figure 3](#) illustrates that the frequency of eye rubbing correlates with corneal thickness. While eye rubbing may not have direct statistical significance in the etiology of keratoconus, it could act as a trigger in a significant number of predisposed individuals.<sup>14</sup> Therefore, even though eye rubbing may not directly contribute to the development of keratoconus, it is likely to accelerate its progression.<sup>15</sup>

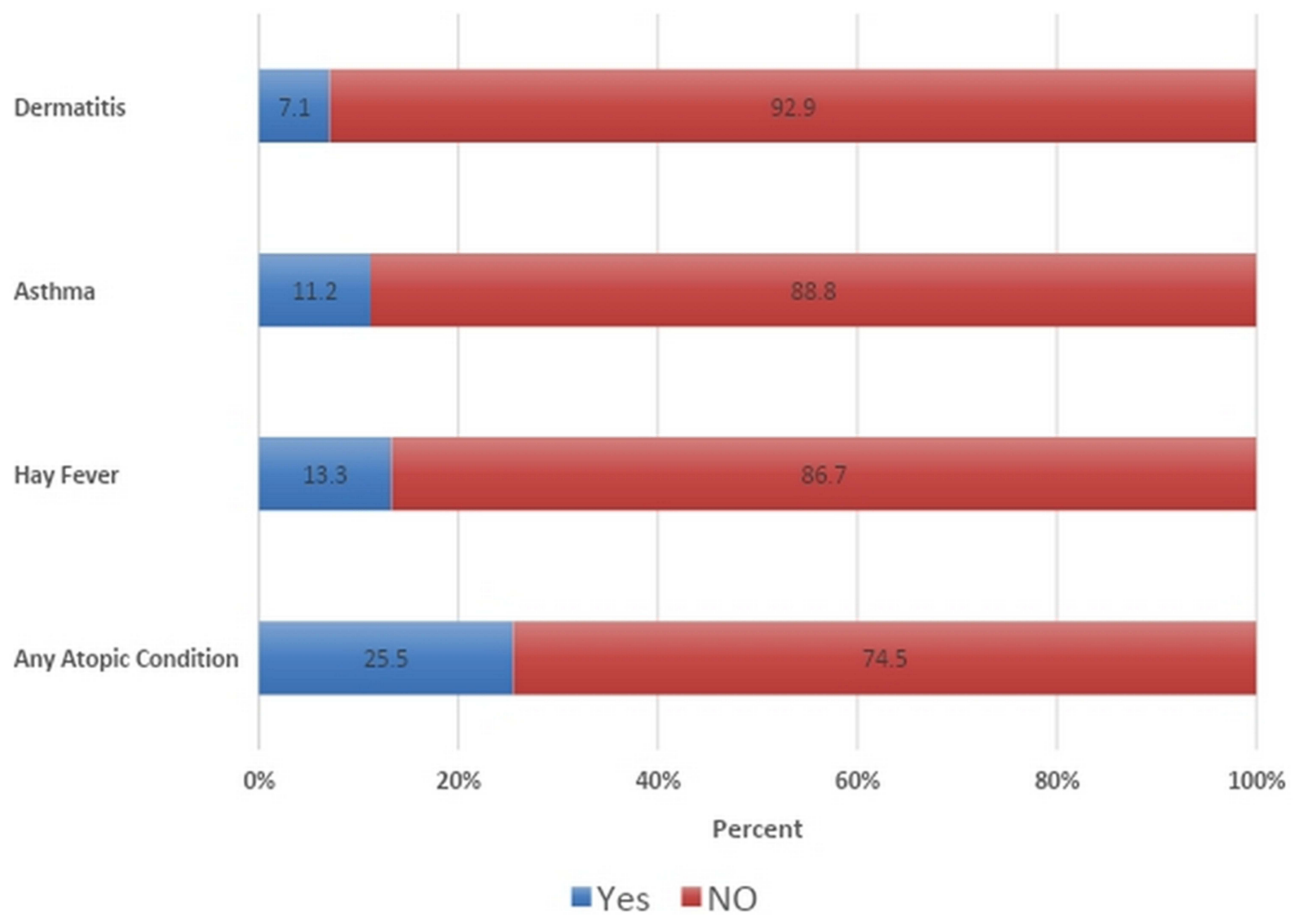


Figure 1 Distribution of atopic conditions in keratoconus patients.

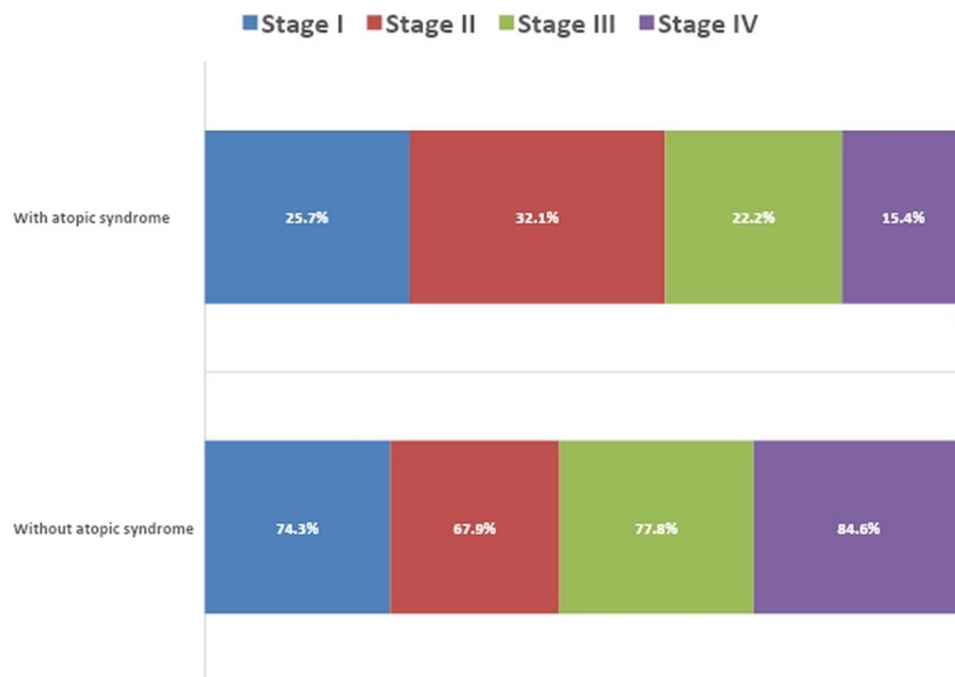
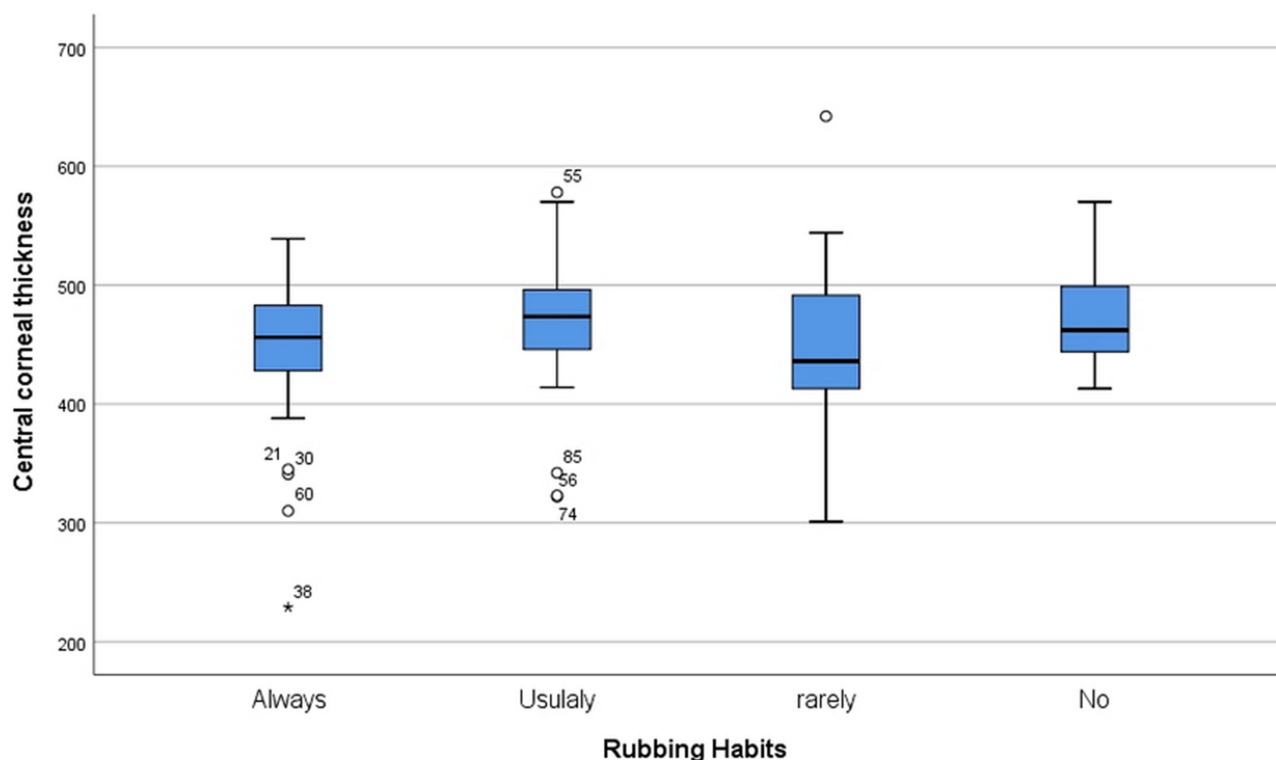


Figure 2 Keratoconus among atopic and non-atopic groups according to Amsler-Krumeich classification.



**Figure 3** Central corneal thickness (CCT) according to eye rubbing habits.

## Conclusion

The exact cause of keratoconus remains uncertain. A combination of genetic and environmental factors plays a crucial role in its occurrence among many individuals. Family history emerges as the most influential factor, with individuals having a relative diagnosed with keratoconus being at a higher risk of developing the condition than those without such a history.

## Significance of the Research

The research was considered as a database for this type of research so as to identify the risk factors to avoid them and improve treatment in the future.

## Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

## Ethics Approval and Consent to Participate

This study complies with the Declaration of Helsinki and was performed according to ethics committee approval from The Institute Review Board (IRB) of Jazan Hospital (Approval number: No. 2052 dated 08/12/2020). Additionally, consent forms were obtained from all participants or parents/legal guardians of participants under 18 years, and they were informed that the participation is totally voluntary and they can withdraw at any time.

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## Disclosure

The authors have declared that no competing interests exist.

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