The Epidemiology and Etiology of Keratoconus

Ariela Gordon-Shaag, Michel Millodot, Einat Shneor

ABSTRACT
Keratoconus is a noninflammatory disorder characterized by ectasia of the central or inferior portion of the cornea. This review presents the scant epidemiological information known to date and the factors believed to cause the development of the disease. They are the genetic factors for which evidence come from family studies, twin studies and genetic loci. There appears to be multiple genes causing a keratoconus phenotype with variable penetration. However, the genetic predisposition might not be enough; environmental factors, such as eye rubbing, atopy and UV exposure, may have a role in generating the disease.

Keywords: Keratoconus, Epidemiology, Cornea, Prevalence.

How to cite this article: Gordon-Shaag A, Millodot M, Shneor E. The Epidemiology and Etiology of Keratoconus. Int J Keratocon Ectatic Corneal Dis 2012;1(1):7-15.

Source of support: Nil
Conflict of interest: None declared

INTRODUCTION
Keratoconus (KC) is a heterogeneous disorder that can be divided into three categories as follows:
1. Isolated KC associated with rare genetic disorders.
2. KC in the setting of a commonly reported association, such as Down syndrome and Leber’s congenital amaurosis.
3. Isolated KC with no known associations. The focus of this review is the epidemiology and etiology of the third category, which is by far the most common and has the greatest impact on public health.

The term keratoconus (KC) comes from the Greek words keras (horn) and konos (cone) and the condition has been known since the middle of the 19th century. KC is a developmental anomaly in which the inferior or central portion of the cornea becomes thinner and bulges forward in a cone-shaped fashion as a result of noninflammatory thinning of the corneal stroma. Thinning of the superior portion of the cornea has been reported but is very rare. The corneal thinning induces irregular astigmatism and myopia leading to mild to marked visual impairment.

In the vast majority of cases (in excess of 90%), keratoconus is bilateral, although usually asymmetric in severity and progression. In many cases, the disorder may start unilaterally, but eventually, the other eye becomes involved. Li et al reported that approximately 50% of clinically normal fellow eyes progressed to KC within 16 years.

The disease has its usual onset at puberty and, in many cases, progresses until the third to fourth decade of life, when it usually arrests. Although a large proportion of keratoconic patients can be managed with contact lenses, an average of about 20% of all keratoconic corneas require keratoplasty; some authors report markedly different surgical indication rates of 6.5 and 12 to 45%. Diagnosis of Keratoconus
Early stages of the disease may not be accompanied by any symptoms, but as it progresses, the main symptom is mild to severe visual impairment due to irregular astigmatism, myopia and frequently, corneal scarring. As the disease progresses irregular astigmatism resulting in ‘scissoring’, reflex is noted when performing retinoscopy. Later, partial or complete accumulation of iron deposits may be seen around the base of the KC cone called Fleischer’s ring and Vogt’s striae, which are vertical lines produced by compression of Descemet’s membrane may be seen near the apex of the cone. Corneal scarring is also common. In advanced cases of KC, the ectatic cornea becomes visible to an observer and on looking downward the protrusion will push the lower lid out in a v-shaped dent called Munson’s sign. In extremely advanced and severe cases, breaks in Descemet’s membrane referred to as hydrops have been observed. These breaks cause stromal edema, vision loss and associated pain.

However, the most sensitive method of detecting early KC is corneal topography. Typical patterns of irregular astigmatism are described by Rabinowitz. Corneal topography has become more commonplace and routine in ophthalmic practice and is now seen as the gold standard test in diagnosing and monitoring KC.

The topographic patterns of KC corneas differ qualitatively and quantitatively from normal corneas. Qualitatively, the most common KC pattern is an asymmetric bow-tie with a skewed radial axis. The quantitative topographic characteristics of keratoconus are an increased area of corneal power and inferior-superior (IS) power asymmetry. Several quantitative videokeratography-derived indices have been developed to assess the topographic pattern of KC, such as KPI (keratoconus prediction index), KSI (keratoconus similarity index) and KISA an index based on K (K-value), IS (inferior-superior steepening), AST (degree of regular corneal astigmatism) and SARX (skewed radial axis) values.
Age Differences

The proportion of keratoconic patients is relatively common in youth. However, it is much less common in middle-aged and elderly individuals. Lass et al. found that 70% of their 417 patients were between 21 and 40 years of age and only 10% were beyond 50 years. In the collaborative longitudinal evaluation of keratoconus (CLEK) conducted in the United States of America in the 1990s, very few patients beyond the age of 60 years were noted (Table 1). A recent review of a large keratoconus sample by Ertan and Muftuoglu included the finding of a smaller number of keratoconic eyes and less severe disease in older patients. It has been inferred that keratoconic patients may have a higher mortality rate than unaffected population, possibly due to some complications or associated diseases, such as obesity, although the mortality rate of keratoconus was found to be similar in the normal population. However, improved diagnostic methods and associated increased detection of subtle forms of keratoconus may give rise to an apparently increasing incidence, if some less severe cases remain undetected in older age groups. Increased rates of diagnosing keratoconus may also be associated with increased interest in assessing corneas for refractive surgery.

Epidemiology

There is paucity of reports on the prevalence on KC around the world and few estimates are based on population-based studies. Several studies have estimated the prevalence of KC in different parts of the world, though only one in the Middle East. These studies are summarized in Table 2. Prevalence figures vary widely from 0.0003% in Russia to 2.3% in Maharashtra, India. The first population-based prevalence study was carried out using a Placido disk. However, the most commonly cited prevalence is 0.054% found in Minnesota, USA, in which, the diagnosis was based on a mixture of scissors movement in retinoscopy and keratometry. This figure was not dissimilar to the results found in Finland or Denmark. KC prevalence from French army recruits was higher (1.2%). While this was the first study using videokeratography, the indices used were more compatible with suspect than definite cases.

Recently, a population-based study in Israel found the prevalence of KC to be 2.34% (2,340 per 100,000). This result represents a far higher estimate of prevalence (2.34%) than the commonly cited figures of 0.05 to 0.23% for Western countries and is at least 10 times higher. In one population-based study in India with a similarly high prevalence of KC (2.3%), the diagnosis was made using keratometry. Most other studies were based on hospital records, which are likely to underestimate the true prevalence of the disease as patients presenting in hospitals are usually symptomatic and early forms of the disease are missed. Moreover, these studies also ignore the number of patients treated by independent optometrists and ophthalmologists.

To our knowledge, only one study has been carried out on an Arab population. Assiri et al. assessed the incidence in a province of Saudi Arabia using a clinic-based protocol and found it to be 20/100,000 (0.02%).

Table 1: Age distribution of keratoconus patients in the CLEK survey (Zadnik et al. with permission of Wolters Kluwer Health)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Percentage of sample (n = 1,579 patients)</th>
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</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>4</td>
</tr>
<tr>
<td>20-29</td>
<td>26</td>
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<tr>
<td>30-39</td>
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<td>60-69</td>
<td>3</td>
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<tr>
<td>&gt;70</td>
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</table>

Etiology and Pathogenesis

KC appears to be a multifactorial disease caused by a combination of genetic and environmental factors. The exact contribution of each to the etiology is as yet unknown.

Socioeconomic and Demographic Factors

Keratoconus affects both genders, although it is unclear whether significant differences between males and females exist. The preponderance of men over women has been noted in the most recent studies. Georgiou et al. reported a difference of 2.6 times higher in men than women. Some, mainly older studies, have not found differences in the prevalence between genders. Others have found a greater prevalence in females. Millodot et al. found five times more men than women, although that was a very small sample of KC subjects.

Ethnic Differences

Ethnic differences may also account for the discrepancy in prevalence between the various studies. Tanabe et al. reported a prevalence of KC in Japan of less than one-third of that seen in white Caucasians. Most importantly, the reports of two surveys in the UK indicated a prevalence of 4.4 and 7.5 times greater for Asian (Indian, Pakistani and Bangladeshi) subjects compared to white Caucasians. These results concur with the higher values of prevalence found in India. The results of Millodot et al. with Israeli Arabs and Jews support the anecdotal observation of a high prevalence of KC in the Middle East. Assiri et al. also found a high incidence in Saudi Arabia. Jordan et al. found that Maori and Pacific ethnicity were overrepresented in a large KC cohort.
In both UK studies, it was noted that most of the Asian subjects were Muslim with a high prevalence of consanguinity, a factor often associated with a high rate of genetic disease. Although Jaber and Halpern\(^40\) have reported that Israeli Arabs have a much higher percentage of consanguineous marriages than Israeli Jews, there was no statistically significant difference between the prevalence of KC in the two groups in the study in Jerusalem.\(^30\) However, a possible difference may have been concealed by the fact that the sample of Arab subjects was small (n = 200) compared to Jews (n = 766).

**Genetic Factors**

There is accumulating evidence supporting a genetic basis for this disease. The bilaterality, though usually of incomplete penetrance, of the disease noted above strongly supports a genetic basis. The evidence of a genetic contribution to keratoconus has been provided by three types of studies: Family studies, twin studies and genetic analyses.

**Family Studies**

Ihalainen\(^9\) documented a family history in KC patients of 9% in Southern Finland compared to 19% in the north of the country. She attributed this results to the more pronounced effect of gene pooling in the larger families of these communities, in whom the prevalence of KC was about fourfold higher than in the south. Rabinowitz\(^41\) reported the result of a case-control study in which a designed self-administered questionnaire was used to determine possible causative factors in 218 keratoconus patients and 183 normal age-matched controls. The only two factors for which there was a statistical difference were positive family history and eye rubbing. The latter was present in 83% of KC subjects compared to 58% in normal controls. A reported positive family history was noted in 10% of KC patients compared to 0.05% of age-matched controls (a difference of 200×). In a survey carried out by Owens and Gamble in New Zealand,\(^33\) 23.5% of patients reported having one or more relatives with the condition, which the authors attributed in part to the larger families of Maori/Polynesian population.

The authors also mentioned that though there is no recorded prevalence of KC in Maori/Polynesian groups, the clinical impression is that this disease is particularly common place in these ethnic groups. Millodot et al\(^30\) found that the percentage of KC patients who reported at least one first degree relative with the disease was 21.74% for the whole cohort, but it was higher, though not significantly higher, for the Israeli Arabs than for the Israeli Jews, possibly reflecting the propensity of Israeli Arabs to have large families compared to Israeli Jews. Interestingly, the percentage of controls who reported a family history of KC in first degree relatives was 1.7%. This figure is much higher than in other countries (0.05-0.23%)\(^1\) and concurred with the high prevalence of KC found in this Israeli population.

In Bawazeer et al\(^31\) study in Canada, the control group of subjects without KC had a family history of 0%. Most other reports of KC patients indicate lower figures of family history: It was 13.5% in the CLEK study\(^36\) and 6 to 10% in other studies.\(^1\) However, it is important to note that the above descriptions of positive family history are based on questionnaires and KC patient’s verbal responses. On the other hand, in an investigation using videokeratography on 95 keratoconic families, Wang et al\(^35\) found a prevalence of KC in 3.34% in first-degree relatives, which is 15 to 67 times higher than the general population prevalence of 0.05 to 0.23%.\(^35\) Family pedigrees of keratoconic patients in two or three generations have also added weight to a

<table>
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<tr>
<th>Author</th>
<th>Location</th>
<th>Age (years)</th>
<th>Sample size</th>
<th>Incidence</th>
<th>Prevalence</th>
<th>Source</th>
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<tbody>
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<td>Hofstetter(^26)</td>
<td>Indianapolis, USA</td>
<td>1-79</td>
<td>13395</td>
<td>600/100,000</td>
<td>Population</td>
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<tr>
<td>Tanabe(^38)</td>
<td>Muroran, Japan</td>
<td>10-60</td>
<td>2601-P</td>
<td>9/100,000</td>
<td>Hospital</td>
<td></td>
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<tr>
<td>Kennedy(^27)</td>
<td>Minnesota, USA</td>
<td>12-77</td>
<td>64-P</td>
<td>2.0/100,000</td>
<td>Hospital</td>
<td></td>
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<tr>
<td>Ihalainen(^9)</td>
<td>Finland</td>
<td>15-70</td>
<td>294-P</td>
<td>1.5/100,000</td>
<td>Hospital</td>
<td></td>
</tr>
<tr>
<td>Santiago(^29)</td>
<td>France</td>
<td>18-22</td>
<td>670</td>
<td>1190/100,000</td>
<td>Hospital</td>
<td>Army recruits</td>
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<tr>
<td>Goskova(^24)</td>
<td>Urals, Russia</td>
<td>10-44</td>
<td>382-P</td>
<td>4.5/100,000-W</td>
<td>Hospital</td>
<td></td>
</tr>
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<td>Pearson(^34)</td>
<td>Midlands, UK</td>
<td>10-44</td>
<td>382-P</td>
<td>19/100,000</td>
<td>Hospital</td>
<td>57/100,000</td>
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<td>Ota(^7)</td>
<td>Tokyo, Japan</td>
<td>325-P</td>
<td>325-P</td>
<td>9/100,000</td>
<td>Hospital</td>
<td>229/100,000</td>
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<td>Georgiou(^37)</td>
<td>Yorkshire, UK</td>
<td>74-P</td>
<td>74-P</td>
<td>3.3/100,000-W</td>
<td>Hospital</td>
<td>25/100,000-A</td>
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<td>Assiri(^23)</td>
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<td>8-28</td>
<td>125-P</td>
<td>20/100,000</td>
<td>Hospital</td>
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<td>Nielsen(^28)</td>
<td>Denmark</td>
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<td>1.3/100,000</td>
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<td>Ljubic(^32)</td>
<td>Skope, Macedonia</td>
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<td></td>
<td>86/100,000</td>
<td>Hospital</td>
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<td>Jonas(^25)</td>
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<td>≥30</td>
<td>4667</td>
<td>6.8/100,000</td>
<td>Population</td>
<td>College student</td>
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<td>18-54</td>
<td>981</td>
<td>2300/100,000</td>
<td>College student</td>
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</table>

A: Asian; W: White; P: Patient
genetic contribution\textsuperscript{19,42} but, to our knowledge, none of these studies have evaluated KC in all generations with corneal topography. It would be valuable to assess whether cone morphology between family members is similar since it would reinforce the notion of a genetic etiology of the disease.

**Twin Studies**

Twin studies constitute a strong research model to evaluate genetic and environmental factors in the disease pathogenesis. The higher rate of concordance between monozygotic twins, the greater is the evidence of a primary genetic causation. If concordance is greater between monozygotic compared with dizygotic twins, genetic factors are likely play a key role in the disease phenotype.

There is scarcity in the literature of studies of KC in twins. To date, 21 pairs have been reported. In general, KC studies have reported monozygotic twins concordant rather than discordant for KC, especially when twins were examined with modern computerized videokeratoscopy.\textsuperscript{43-45} Twin studies showed a 54% concordance rate among monozygotic twins.\textsuperscript{43,44} This concordance supports the evidence of heredity as a genetic factor in the etiology of KC.\textsuperscript{43} In such cases, both autosomal dominant and recessive patterns of inheritance have been described.\textsuperscript{31,35}

Conversely, reports of monozygotic twins who were discordant for keratoconus have been published.\textsuperscript{33,46,47} This can be explained by epigenetic, stochastic and environmental factors. In cases in which there was KC discordance in identical twins, eye rubbing and hormonal influences were suggested as possible environmental factors involved in the etiology of KC.\textsuperscript{46}

Parker et al\textsuperscript{47} and Owens and Watters\textsuperscript{33} using videokeratography on a set of identical twins with KC found differences in severity and discordant cone types, but the Owens and Watters study may have been confounded by the fact that subjects were able to wear their contact lenses up to 3 days prior to corneal topography. Nevertheless, these results do not preclude the possibility that a significant genetic component for the disease may still exist.\textsuperscript{44}

To date, none of the published twin studies have assessed the zygosity of the twins using genetic markers which may have significantly altered their results. If twins were erroneously classified as monozygotic or dizygotic, it would greatly alter the findings.

**Genetic Loci**

Wang et al\textsuperscript{35} applied segregation analysis to a large cohort of keratoconic patients and their relatives, and their conclusion was that genes play a major role in the development of keratoconus. Genome-wide linkage analysis of affected pedigrees has shown evidence of disease susceptibility genes mapping to several putative chromosomal loci.\textsuperscript{48-51} Mutations in the VSX1 gene have been reported to be associated with KC by direct sequencing in familial panels.\textsuperscript{52,53} However, in a large panel of KC patients, mutations in this gene were not observed.\textsuperscript{50} Li et al\textsuperscript{54} have recently carried out fine mapping of a large cohort of KC subjects and ethnic match controls with single nucleotide polymorphisms. Their findings suggest SNP rs4954218 located near the RAB3GAP1 gene, previously reported to be associated with corneal malformation, is a potential susceptibility locus for keratoconus. Burdon et al\textsuperscript{55} recently published the results of two parallel genome-wide mapping studies using SNPs with large KC cohorts. Their results implicate genetic variation at the HGF locus with keratoconus susceptibility.

Despite this wide body of evidence, a direct genetic etiology has still not been established.

**Association Studies**

Although a majority of KC patients do not have other ocular or systemic diseases, there are instances of associations with a large number of ophthalmic and systemic diseases (see Rabinowitz)\textsuperscript{41}, but of particular interest, are the associations with conditions of genetic origin. They include Down syndrome,\textsuperscript{56,57} Leber’s congenital amaurosis\textsuperscript{41,58,59} and some connective tissue and collagen disorders, such as Ehlers-Danlos syndrome,\textsuperscript{60} Marfan syndrome\textsuperscript{61,62} and osteogenesis imperfecta.\textsuperscript{63} These associations add further support for a genetic contribution to the disease and could potentially provide information on chromosomal loci.\textsuperscript{64,65}

**Environmental Factors**

Despite the evidence of a genetic etiology, most reported KC cases are sporadic without a family history of the disease.\textsuperscript{1} Although the etiology of the KC remains unclear, researchers have identified several environmental factors in the progression of the disease. Environmental factors include atopy and mechanical trauma which could occur as a result of chronic eye rubbing and contact lens wear\textsuperscript{66,67} and those related to increased oxidative damage, such as ultraviolet radiation.

**Eye Rubbing**

One of the most important factors is the chronic habit of abnormal eye rubbing (CHAR) which is strongly associated with the progression of KC. This association has been demonstrated by numerous case series and large case-controlled studies.\textsuperscript{1,2,31,36,66,68} Moreover, asymmetric
Keratoconus has been found to be associated with abnormal eye rubbing of the more severely affected eye.\textsuperscript{69-71} Multiple reports link vigorous eye rubbing to the development of acute hydrops.\textsuperscript{72-74} Mashor et al\textsuperscript{75} suggested an association between Tourette syndrome and keratoconus with chronic eye rubbing being the suggested mechanism. In fact, a recent case report described bilateral self-induced keratoconus in a patient with Tourette syndrome associated with compulsive eye rubbing.\textsuperscript{76} Coyle\textsuperscript{77} reported the case of an 11-year-old boy who, at age 5, discovered he could stop his paroxysmal atrial tachycardia by vigorously massaging his left eye (up to 20 times per day). At age 7, his ocular examination was normal. By age 11, the patient developed unilateral KC in his left eye. Similarly, Gritz\textsuperscript{78} reported a patient with a history of vigorous daily ritual massage of the left eye leading to unilateral KC. He suggested that the microtrauma of eye rubbing by susceptible individuals injures the epithelium, leading to cytokine release, myofibroblast differentiation, a change in biomechanical forces and thinning of corneal tissue. This cascade of events might produce the ectatic process recognized as keratoconus. In fact, trauma may be the common underlying factor in eye rubbing, vernal and atopic disease, contact lens wear and Down syndrome that via a common biochemical cascade, leads to development of KC.\textsuperscript{69} McMonnies also hypothesizes that a reduction in shear strength and cone-forming deformation may be responses to rubbing trauma.\textsuperscript{56}

Allergy and atopy have been the most commonly addressed risk factors for CHAR in KC.\textsuperscript{79} However, a review of reports of CHAR indicated a range of other provocative factors for, or associated with, abnormal eye rubbing included dryness induced ocular irritation, psychogenesis, mental stress or emotional tension and compulsive behavior.\textsuperscript{70}

The question arises as to whether KC patients are more susceptible to adopting a CHAR that has a psychogenic basis, especially in light of reports of KC patients having unusual personality characteristics.\textsuperscript{80-83}

In contrast, a significant association between KC and eye rubbing was not found in either the studies of Owens and Gamble\textsuperscript{33} or Millodot et al.\textsuperscript{30} The discrepancy may be accounted for by the level of eye rubbing, which is related to the association.\textsuperscript{70} Alternatively the amount of dust in dry climates may induce frequent eye rubbing (KC patients and controls) concealing a possible association with keratoconus. Nevertheless, in a meta-analysis of five studies, which included a control group comparing the effect of eye rubbing in KC patients, three of the studies showed a statistically significant difference and two did not (Table 3 and Fig. 1). Notwithstanding the variations in the criteria used by the different authors to classify eye rubbing, the overall result showed that eye rubbing is a significant environmental factor (OR: 2.23, 95% CI 1.87 to 2.65; \( p < 0.001 \)).

**Atopy**

A large body of literature presents an association between atopy, which includes asthma, eczema, hayfever and keratoconus.\textsuperscript{3,12,18,79,84,85} However, the effect of atopy is controversial.\textsuperscript{86,87} Several authors did not find a statistically significant difference between a group of control and keratoconic patients.\textsuperscript{31,88} Yet, Kaya et al\textsuperscript{85} showed that individuals with keratoconus and atopy had a steeper and thinner ectatic area than individuals with keratoconus but without atopy. However, it is possible that the itching induced by atopy, which leads to eye rubbing is the most significant contributor to KC. This hypothesis was confirmed in a case-control study by Bawazeer et al\textsuperscript{31} who found a significant association of atopy in a univariate analysis.\textsuperscript{80-83}

![Fig. 1: Forest plot of meta-analysis of odds ratio with 95% confidence interval of eye rubbing in KC patients compared to controls from several studies detailed in Table 3](image)

### Table 3: Meta-analysis of odds ratio (OR) with 95% confidence interval (CI) of eye rubbing in KC patients and controls from several studies

<table>
<thead>
<tr>
<th></th>
<th>KC (n/total)</th>
<th>Control (n/total)</th>
<th>p-value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bawazeer et al\textsuperscript{31}</td>
<td>22/49</td>
<td>8/71</td>
<td>0.001</td>
<td>3.98 (1.64-9.66)</td>
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<tr>
<td>Rabinowitz\textsuperscript{41}</td>
<td>183/218</td>
<td>95/183</td>
<td>0.003</td>
<td>1.62 (1.18-2.22)</td>
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<tr>
<td>McMonnies and Boneham\textsuperscript{70}</td>
<td>44/53</td>
<td>18/53</td>
<td>0.008</td>
<td>2.26 (1.07-4.74)</td>
</tr>
<tr>
<td>Weed et al\textsuperscript{36}</td>
<td>96/200</td>
<td>39/100</td>
<td>0.36</td>
<td>1.23 (0.98-1.91)</td>
</tr>
<tr>
<td>Millodot et al\textsuperscript{30}</td>
<td>8/22</td>
<td>224/938</td>
<td>0.31</td>
<td>1.52 (0.67-3.45)</td>
</tr>
<tr>
<td>All trials</td>
<td>353/542</td>
<td>384/1313</td>
<td>&lt;0.001</td>
<td>2.23 (1.87-2.65)</td>
</tr>
</tbody>
</table>

\*Estimated numbers based on the text
analysis, but it was not confirmed in a multivariate analysis when taking into account all other factors (the only significant association was with eye rubbing).

A recent case, control study of a large cohort of KC patients (n = 426) with age and gender matched controls (n = 1704) yielded evidence that the allergy and the immune system have a role in KC. The study showed a significant association between KC and the following immune disorders: Rheumatoid arthritis, ulcerative colitis, autoimmune chronic active hepatitis, Hashimoto thyroiditis, arthropathy, asthma, environmental allergy and irritable bowel syndrome. This may point to the role of the immune system in the pathogenesis of KC.99

UV Exposure
It is possible that environmental factors may have contributed to the high prevalence found in Jerusalem,30 where the climate is characterized by dry conditions during most months of the year, hot summers and excessive UV radiations. The city is situated in an area 750 meters above sea level with a mean of 3,397 hours of sunshine a year according to the ‘Climatological Information for Jerusalem, Israel’ (www.gb.weather.gov.hk). Such weather conditions are not unlike those prevailing in the Nagpur district of Maharashtra in India,25 as well as in the Asir province of Saudi Arabia,23 where a large incidence of the disease was observed. On the other hand, in countries with much lower average, annual temperatures and sun exposure, such as Finland,9 Denmark,28 Minnesota,27 Japan,38 Macedonia32 and the Urals in Russia,37 the prevalence of KC is remarkably lower in comparison (see Table 2).

Although to our knowledge, there is no study of the effects of sun exposure on KC in humans, ultraviolet light which is a source of oxidative stress appears to be a compelling risk factor in the development of the disease. Support for this comes from studies showing that keratoconic corneas have an inability to process reactive oxygen species thereby leading to oxidative damage90,91 due to reduced levels of antioxidants, such as superoxide dismutase.92 This is thought to trigger what is referred to as a cascade of events leading to KC, such as an alteration of various corneal proteins, increased enzyme activities and apoptotic cell death.91 Moreover, animal models of apoptosis as a result of exposure to ultraviolet radiation in rabbit cornea93 and loss of keratocytes and subsequent corneal stromal thinning in mice94 support the possibility of sun exposure as a risk factor for KC in genetically susceptible individuals. The human cornea has a high incidence of acquired chromosome abnormalities in the keratocyte tissue. These cytogenetic abnormalities are absent in childhood and accumulate throughout life.95 The reason for this has not been elucidated, but it is possible that it is caused by environmental factors, such as sun exposure.

It may be worth noting, though, that UV radiation might provide a beneficial effect by inducing cross-linking of corneal collagen thus mitigating the progression of the disease.96 Further research is needed to support these hypotheses.

Miscellaneous Factors
Exposures to environmental toxins have also been shown to be associated with KC. In the Urals, KC was found to be more prevalent in urban setting than in rural ones. In addition, the highest prevalence was found in the Chelyabinsk district, an area that has many toxic industries.24 Paradoxically, one study found a negative correlation between cigarette smoking and KC in patients being treated with corneal collagen cross-linking.97

The asymmetrical nature of the disease is another piece of evidence pointing to the role of environmental factors. Although it is usually a bilateral disease, the clinical asymmetry originally manifests as a unilateral disease and progresses to a bilateral disease with large between eye differences in clinical severity.5,98 In contrast, eye diseases with a primarily genetic etiology and high penetrance (e.g. retinoblastoma), manifest bilaterally.99 This suggests that the microenvironment of each eye also contributes to the severity of the disease.

CONCLUSION
Keratoconus is a slowly, progressive noninflammatory disease that has been first described since the 19th century and has been the subject of numerous investigations. Reviews of the disease have appeared periodically.1,2,67 Yet, its epidemiology has received scant attention and too often assumed to be equal to a prevalence of 54 per 100,000, a figure determined by keratometry and scissors reflex in retinoscopy in the 1980s.27 Most of the other prevalence studies have inferred a prevalence for the general population based on hospital or clinic records and not population-based studies. There is still a need to obtain thorough epidemiological studies in different parts of the world with diverse climates and ethnic groups. Despite intense research into its etiology over the last decades, it is still poorly understood. Keratoconus is certainly multifactorial with a genetic component based on several gene abnormalities and this perhaps represents the basic factor that renders individuals susceptible to the disease. Yet, this may not be sufficient and environmental factors, such as eye rubbing in particular, atopy and/or UV radiation, may be essential...
to interact with the abnormal genes and to produce keratoconus. Further research in the molecular genetics of keratoconus will help to elucidate the etiology of this serious disorder.

ACKNOWLEDGMENTS
We would like to thank Dr Liat Gantz for critical reading of the manuscript. Dr Einat Shneor was supported by a grant from the Israel Society for Psychobiology.

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