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Risk factors for keratoconus in Israel: a case–control study

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Abstract

Purpose: Keratoconus (KC) is a progressive corneal thinning disorder with an uncertain aetiology. Environmental and genetic factors, including consanguinity, eye rubbing and possibly sun exposure, play a role in the aetiology of KC. Here we test for risk factors for KC in an Israeli population with particular emphasis on sun exposure.

Methods: This case–control study included KC patients who were diagnosed at Care Laser Medical Group, a refractive surgery clinic with branches throughout Israel. The control group included age, sex and ethnicity matched individuals who were randomly selected from patients presenting at the clinic for refractive surgery, but without KC. Study subjects were asked to fill out a self-administered questionnaire that included demographic and geographic details, questions on ocular and general health and sun exposure. Conditional logistic regression was used to analyse univariable and multivariable data to identify risk factors for KC.

Results: Seventy-three KC patients and 146 controls participated in the study. Univariable analyses demonstrated that eye rubbing [odds ratio (OR) = 3.76], positive family history of KC (OR = 6.10) and parents' education (<12 years, OR = 0.27, 0.23 for father's and mother's education respectively) were significant risk factors for KC. Univariable analyses of sun exposure behaviour during teenage years proved equivocal with some behaviours emerging as protective for KC (*wearing a hat outdoors*, OR = 3.13) or as risk factors (*spending time in the shade*, OR = 0.45), while others showed no association [*limiting time in the sun* (p = 0.51), and *wearing sunglasses* (p = 0.20)]. Most of the factors that were significant in the univariable analyses, also emerged as statistically significant in the multivariable model (OR = 3.37, 9.68, 0.35, 5.51 for *eye rubbing, family history, parental education*, *wearing a hat outdoors*, with the exception of *spending time in the shade* (p = 0.88).

Conclusions: Eye rubbing, parents' education (as a measure of socio-economic status) and having family members with KC emerged as significant risk factors for KC. The role of sun exposure in KC remains equivocal and warrants further research.

Introduction

Keratoconus (KC) is a corneal disorder of uncertain aetiology in which the para-central portion of the cornea becomes thinner and bulges forward in a cone-shaped fashion resulting in myopia, irregular astigmatism and eventually visual impairment.[1–3] The aetiology of the disease is multifactorial in which genetic and environmental influences play a role. The exact contribution of each to the aetiology of the disease is as of yet unknown.[4]

Evidence supporting a genetic contribution to the disease comes from several factors such as familial aggregation,[5–7]

high ectasia concordance in monozygotic compared to dizygotic twins,[8] genetic identification of several loci,[1,7,9] association with genetic systemic disorders[10] and parental consanguinity.[11,12] However, no causative gene/s has yet been found.[1,5,9,13] The development of the disease most likely requires an environmental influence such as atopy, corneal trauma (eye rubbing) or ultraviolet radiation combined with a genetic predisposition to elicit a cascade of biochemical events in the cornea which results in KC.[5,6,10,14] The effects of atopy and eye rubbing have been extensively investigated.[10,15]

The effect of ultraviolet radiations in the pathogenesis of the disease has not, to the best of our knowledge, been investigated thus far. Yet it would appear to be a compelling possibility because reports of prevalence rates of KC have revealed large differences based on geographical locations. Generally, countries with sunny and warm climates, such as India,[16] Israel,[17] Lebanon,[18] Iran,[19,20] and Saudi Arabia[21] have been found to have a higher KC prevalence than cooler and less sunny areas such as Northern USA,[23] Europe and Russia.[22–28] The difference could be accounted for by the disparate amounts of sun exposure prevailing in these areas, since it has been suggested that ultraviolet light as a source of oxidative stress may play a role in the aetiology of the disease.[29,30] Moreover, animal models also provide support for the role of ultraviolet exposure in KC aetiology such as increased apoptosis in rabbit corneas[31] and loss of keratocytes and subsequent corneal stromal thinning in mice.[32]

Although there have been many reports of the characteristics of KC[3,11,12,15,33–35] there is a paucity of case–control studies aimed at determining risk factors for KC. The first such report indicated eye rubbing as the most important risk factor using multivariate analysis,[36] later confirmed in a meta-analysis.[4] Another study conducted on a population of Palestinian patients also using multivariate analysis identified several risk factors, including a possible association with sun exposure.[11] Hitherto, a case–control study of risk factors has not been carried out on an Israeli population. The aim of this case–control study was to determine risk factors for KC in an Israeli population that is known to have a high prevalence of the disease[12,17] and to explore the effect of sun exposure on its aetiology. Elucidation of the aetiology is likely to lead to the discovery of new therapies and prevention of the disease.

Methods

The study was conducted at the Care Laser Medical Group, a refractive surgery clinic with branches throughout Israel. Most of the data were collected between September 2012 and April 2014. Patients came from all parts of the country. KC subjects were recruited from patients presenting for collagen cross-linking or from patients who were excluded from refractive surgery on the basis of KC. Controls were recruited from patients presenting to the clinic to investigate whether they were good candidates for refractive surgery. Controls were clinically and topographically evaluated and determined not to have any signs of KC by both the ophthalmologists and optometrists involved in the study. All patients were given a note inviting them to participate in this non-invasive screening test and to complete an anonymous questionnaire. Patients who volunteered to participate in the study were given an explanation of the research project and were asked to sign an informed consent form. The study followed the tenets of the Declaration of Helsinki and was approved by the Ethical Committee of Hadassah Academic College.

Patients with KC (thereafter called cases) were diagnosed by an ophthalmologist based on at least one of the following clinical signs; stromal thinning, Fleischer's, Vogt's striae, Munson, and corneal topography. In most cases imaging was done using a Sirius topographer (CSO, http://www.csoitalia.it/en/asp/home.asp?prod=1&dbpID=17) although a subset of patients were imaged using the Orbscan II (Orbtek).[37] The Sirius is a new topography device that has been validated in KC screening.[38]

At least three photos of each eye were usually taken, although only the best was saved. The corneal map of each participant was examined and a common KC pattern was characterized by asymmetric bow-tie with a skewed radial axis[3] and KC screening indices. The Sirius uses several validated KC screening indices to determine manifest KC and KC suspect status.[39,40] Both Orbscan and Sirius provide minimum, maximum and average keratometry values (K_{min}, K_{man}, K_{ave}, respectively). If a person had KC in only one eye, that person was defined as having the disease.

Controls consisted of patients who presented to the clinic during the study period. Previous research demonstrated that KC is more prevalent in men than women[17] and in certain ethnicities.[28,35,41] In addition, age is a factor as it is known to appear in the second and third decade of life.[3] Therefore, cases and controls were individually matched for age, sex and ethnicity. Patients with any systemic or ocular pathology (other than KC) were excluded.

The questionnaire

Both cases and controls were asked to complete the same self-administered questionnaire. This questionnaire has already been used in previous studies[11,12,17] and is based on one used by Owen and Gamble.[35] The questionnaire includes questions on demographics (age, gender, domicile, ethnicity, parents' education) and potential risk factors such as health status, family history of KC, contact lens wear, allergies, parental education, eye rubbing and con-

sanguinity. Consanguineous marriage refers to unions contracted between biologically-related individuals as second cousins or closer, including double first cousins, first cousins, and second cousins.

In addition, several questions were added related to sun exposure. These questions are based on validated questionnaires[42–44] and adapted for cultural considerations. They were found to be reliable and valid against conjunctival ultraviolet autofluorescence (UVAF) measurements.[45] Patients were asked to recollect sun exposure behaviour between the ages of 13 and 19 years, a period believed to either precede or to be the time of disease onset.[2] Each question was followed by estimating exposure levels regarding the number of hours or the frequency of the event (e.g. never, sometimes, always), as has been done previously.[42–44]

Data analysis

Analyses were done by using SPSS, version 22 (SPSS, Inc., www.ibm.com/software/analytics/spss/). Normality of continuous data was assessed with the Anderson-Darling Normality test Calculator.[46] The *t*-test was used for continuous variables if the normality assumption was satisfied and the Mann–Whitney test was used in cases when the data was not normally distributed. Univariable and multivariable conditional logistic regression analysis (utilising Cox proportional hazards model likelihood) were performed.[47]

Crude odds ratio (OR) and 95% confidence intervals were calculated to determine whether any exposure factor is significantly associated with KC. Using multivariable conditional logistic regression analysis, adjusted ORs were calculated for each predictor variable found to be significant in univariable analysis, to test for an association with KC while controlling for the effects of the other predictors. The predictor variables were binary and coded as 1 (KC present or yes) and 0 (KC absent or no). All tests were two-tailed, and values of $p < 0.05$ were consider statistically significant.

To avoid an underpowered study for the assessment of sun exposure based on a hat worn during teenage years we estimated the minimal sample size necessary to obtain a statistically significant power of 84% with 95% confidence. From a preliminary study it had been estimated that the proportion of controls who wore a hat during their teen years was 0.05 with an OR of 3.0 for the KC subjects who wore a hat. The minimal sample was found to be 71 cases and 142 controls using a formula given in Kirkwood and Sterne,[48] which takes into account the ratio of controls to cases.

Results

Of the people who met the eligibility criteria 219 volunteered to participate in this study. Seventy three patients with KC served as cases and 146 normal candidates for refractive surgery served as controls. *Table 1* presents demographic information for the two cohorts. Cases and controls were matched for age, gender and ethnicity. The mean age of the KC group was 27.4 ± 4. 9 years and the control group was 26.9 ± 5.1 years ($p = 0.5$). The majority of the participants in each group were male (64.4%; $p = 1.0$). In terms of ethnicity 61.4% were Jews, 35.6% were Arab Muslims and the remaining 2.7% were Druze (chi-square $p = 1.0$ for all ethnicities).

As shown in *Table 2*, keratometric parameters K_{min}, K_{max} and K_{ave} were significantly steeper in the KC group than in the control group. In addition, the corneal thickness at the thinnest point in the cornea was significantly thinner in the KC cohort. The majority of the cohort had bilateral KC ($N = 59$; 81%), while 10 had KC in the right eye only and four in the left eye only. Forty-four KC patients reported having undergone corneal surgery (14 in the right eye, four in the left eye and 26 in both eyes). The most common surgery was collagen cross-linking ($N = 40$; 91%), while the

Table 1. Demographic characteristics of cases (keratoconus, KC) and controls (patients without KC)

	Cases with KC	Controls	*p* value
N	73	146	
Age, year			
Mean ± SD	27.42 (4.89)	26.94 (5.11)	0.50†
Range	17–37	17–39	
Sex	*N* (%)	*N* (%)	
Female	26 (35.62)	52 (35.62)	1.00‡
Male	47 (64.38)	94 (64.38)	
Ethnicity			
Jew	45 (61.64)	90 (61.64)	1.00‡
Arab Muslim	26 (35.62)	52 (35.62)	1.00‡
Druze	2 (2.74)	4 (2.74)	1.00§

†*t*-test.
‡Chi square.
§Fisher test.

Table 2. Corneal data for controls and keratoconus (KC) (right eye used for control and worse eye for KC subjects) data from Sirius or Orbscan when Sirius was not available

	Control	KC	*p* value
K_{min} (D)	7.61 ± 0.29	6.85 ± 0.60	<0.001‡
K_{max} (D)	7.79 ± 0.31	7.44 ± 0.66	<0.001‡
K_{ave} (D)	7.70 ± 0.29	7.17 ± 0.58	<0.001‡
Thinnest thickness (μm)	518.53 ± 41.18	436.43 ± 45.66	<0.001†

†*t*-test.
‡Mann–Whitney test.

Table 3. Univariable analysis of risk factors for keratoconus

Exposure factor	Cases (n = 73) N (%)	Controls (n = 146) N (%)	OR 95% CI	Pearson chi-square; p value
Parental consanguinity[†,‡]				
No (ref)	66 (93.0)	129 (89.6)	0.65 (0.23–1.84)	0.42
Yes	5 (7.0)	15 (10.4)		
Father's education[§]				
0–12 (ref)	60 (83.3)	86 (58.9)	0.27 (0.13–0.57)	0.001*
>12	12 (16.7)	60 (41.1)		
Mother's education[§,¶]				
0–12 (ref)	63 (87.5)	90 (62.1)	0.23 (0.10–0.51)	<0.001*
>12	9 (12.5)	55 (37.9)		
Family history of KC				
No (ref)	54 (74.0)	139 (95.2)	6.10 (2.43–15.32)	<0.001*
Yes	19 (26.0)	7 (4.8)		
Asthma and eczema[¶]				
No (ref)	67 (91.8)	132 (91.0)	0.92 (0.33–2.54)	0.86
Yes	6 (8.2)	13 (9.0)		
Allergy				
No (ref)	59 (80.8)	124 (84.9)	1.34 (0.64–2.81)	0.44
Yes	14 (19.2)	22 (15.1)		
Eye rubbing				
No (ref)	27 (37.0)	105 (71.9)	3.76 (2.08–6.79)	<0.001*
Yes	46 (63.0)	41 (28.1)		
Smoking[¶]				
No (ref)	56 (76.7)	110 (75.9)	0.94 (0.48–1.84)	0.87
Yes	17 (23.3)	35 (241)		
Diabetes				
No (ref)	43 (58.9)	98 (67.1)	1.52 (0.80–2.86)	0.20
Yes	30 (41.1)	48 (32.9)		

*Significant risk factor.
[†]Are your parents related? Yes means that the parents are first degree relatives.
[‡]2 controls and 2 KC did not answer.
[§]1 KC did not answer.
[¶]1 control did not answer.

Table 4. Sun exposure risk factors for keratoconus

Exposure factor	Cases (n = 73) N (%)	Controls (n = 146) N (%)	OR 95% CI	Pearson chi-square; p value
Past exposures (recollections of age 13–19)				
Wearing a hat outdoors				
No (ref)	63 (86.3)	139 (95.2)	3.13 (1.125–8.656)	0.02*
Yes	10 (13.7)	7 (4.8)		
Time in the shade				
No (ref)	62 (84.9)	104 (71.2)	0.45 (0.21–0.94)	0.03*
Yes	11 (15.1)	42 (28.8)		
Limit time in the sun				
No (ref)	67 (89.3)	130 (89.0)	0.71 (0.25–1.97)	0.51
Yes	8 (10.7)	16 (11.0)		
Wearing sunglasses				
No (ref)	58 (79.5)	104 (71.2)	0.64 (0.33–1.26)	0.20
Yes	15 (20.5)	42 (28.8)		

*Significant risk factor.

Table 5. Multivariable analysis of association between predictors and keratoconus

Risk factor	Adjusted OR	95% CI	p
Family history of KC	9.68	2.83–33.08	0.000*
Eye rubbing	3.37	1.68–6.77	0.001*
Father's education[†]	0.35	0.15–0.83	0.018*
Wearing a hat	5.51	1.38–21.90	0.015*
Time in the shade	0.46	0.18–1.13	0.88

[†]1 KC did not answer, therefore analysis were done on 72 KC patients and 146 controls.
*Significant risk factor.

rest had penetrating keratoplasty or implantation of corneal ring segments.

Table 3 shows the univariable analysis of the various independent predictors for the KC and control groups. Parental education is often used as a test of socio-economic status (see[49] for a review). We found that KC patients had parents who were significantly less educated than controls (Crude OR, 0.27 $p < 0.001$ and 0.23, $p < 0.001$ for father's and mother's education, respectively). Previously recognised risk factors such as eye rubbing (Crude OR, 3.76; $p < 0.001$) and family history of KC (Crude OR 6.10; $p < 0.001$) were significantly associated with KC. In contrast, other recognised risk factors such as allergy (Crude OR, 1.34; $p = 0.44$) and parental consanguinity (Crude OR 0.65; $p = 0.42$) did not emerge as significant risk factors. Asthma/eczema, smoking and diabetes were not found to be significantly associated with KC in univariable analysis (Crude OR, 0.92 $p = 0.86$; 0.94, $p = 0.87$; 1.52, $p = 0.20$, respectively).

The results shown in *Table 4* relate to sun exposure. Wearing a hat outdoors was significantly associated with KC (Crude OR 3.13, $p < 0.02$), while spending more time in the shade was protective (Crude OR 0.45, $p < 0.03$. Limiting time in the sun and wearing sunglasses were not significantly associated with KC (Crude OR 0.71, $p = 0.51$, Crude OR 0.64, $p = 0.20$, respectively).

Multivariable analysis was performed using the five variables that emerged significant in the univariable analysis. One case did not answer a question so was excluded (together with the matched controls) from the multivariable analysis ($N = 216$). Since mother and father's education are typically highly correlated, only father's education was used. The model was also tested using the same parameters with mother's education instead of father's education and the results were similar (data not shown). The multivariable analysis confirmed the significance of four of the risk factors (*Table 5*). Parental education >12 years appeared to

Table 6. Percentage of family members with keratoconus from various studies of patients with keratoconus

Study	Year	Location	Percentage	Method
Hammerstein[57]	1974	Germany	19	Keratometry
Hallerman and Wilson[58]	1977	Germany	7	Self-reported
Ihalainen[23]	1986	Northern Finland	19	Self-reported
Ihalainen[23]	1986	Southern Finland	9	Self-reported
Kennedy *et al.*[24]	1986	USA	5	Self-reported
Zadnik *et al.*[59]	1998	USA	13.5	Self-reported
Wang *et al.*[53]	2000	USA	3.3	Videokeratography
Bawazeer *et al.*[36]	2000	Canada	8.2	Self-reported
Rabinowitz[6]	2003	USA	10	Self-reported
Owens and Gamble[35]	2003	New Zealand	23.5	Self-reported
Assiri *et al.*[21]	2005	Saudi Arabia	16	Self-reported
Reeves *et al.*[54]	2005	USA	10	Self-reported
Jordan *et al.*[52]	2011	New Zealand	12.4	Self-reported
Weed *et al.*[51]	2008	Scotland	5 white, 25 Asian	Self-reported
Karimian *et al.*[60]	2008	Turkey	14	Videokeratography
Kaya *et al.*[61]	2008	Turkey	11	Videokeratography
Khor *et al.*[33]	2011	Singapore	4.3	Self-reported
Jordan *et al.*[52]	2011	New Zealand	3.5 European, 17.7 Pacific, 21 Asian	Self-reported
Szczotka-Flynn *et al.*[62]	2008	USA	17.8	Self-reported
Millodot *et al.*[17]	2011	Jerusalem (mixed)	21.7	Self-reported
Shneor *et al.*[15]	2013	Tel Aviv (mostly Jewish)	27.9	Self-reported
Gordon-Shaag *et al.*[11]	2013	East Jerusalem (Arab)	22.9	Self-reported
Hashemi *et al.*[63]	2014	Iran	15	Self-reported
Shneor *et al.*[50]	2014	Haifa (Arab)	0	Self-reported
Current study	2015	Israel (mixed)	26	Self-reported

be protective of KC compared to controls (OR 0.35, $p < 0.02$). Conversely, low parental education 0–12 years is a risk factor (OR 1/0.35 = 2.86) for KC. Individual with a family history of KC and who habitually rubbed their eyes were 9.7 times and 3.4 times more at risk of KC than controls (OR 9.68, $p < 0.001$; OR 3.37, $p < 0.001$, respectively). Wearing a hat outdoors constituted a risk factor for KC (OR 5.51, $p < 0.02$), but limiting one's own time in the sun did not emerge as significant (OR 0.46; $p = 0.88$). The model containing these predictors was statistically significant ($n = 216$, df = 5, $\chi^2 = 49.66$, $p < 0.001$), indicating that it was able to distinguish between KC and controls.

Discussion

This case–controlled study aimed to evaluate risk factors for KC in age, gender and ethnicity matched cohorts in Israel. The results showed a significant association between KC and the following factors: family history of KC, eye rubbing and paternal education. This study represents the first methodical analysis of sun exposure in KC. Indeed, we report here that certain behaviours that are indicators of sun exposure are associated with KC, although the results are equivocal.

Both positive family history of KC and eye rubbing emerged as significant risk factors for KC, when all other predictors were controlled. A family history of the disease has been found in many studies (*Table 6*), although in two studies there was a lack of awareness of any family member with the disease.[16,50] The proportion of positive family history varies depending on whether the data are self-reported or as a result of assessment. There also appears to be a difference between countries, with Israel exhibiting a higher proportion, and also between ethnic groups: European vs Asian,[51] European vs Maori and Pacific populations[52] or in the very large families found in northern Finland compared to the south.[23] These discrepancies probably stem from a higher prevalence of KC in these relatively homogeneous populations.[17,23,35] Nevertheless it is generally accepted that there is an association between a person's KC and at least one other member of that person's family and this is further confirmed in several case–control studies[11,17,19,53] as well as in this study, but not in all.[36,54] A positive family history may only reflect environmental influences but could also indicate a genetic influence. It is not clear which is the most predominant factor in our study. Eye rubbing has been shown to be associated with KC[6,15,55,56] and this was confirmed in a multivariable analysis.[36] Furthermore, it was substantiated in a meta-analysis.[4]

The results of this study regarding an association between sun exposure and KC are equivocal. A possible association between KC and UV light has been alluded.[11,30]

However, this is the first systematic attempt to test for an association. Our questionnaire included four questions on sun exposure during teenage years. Two were found to be significantly associated with KC in the univariable analysis, but the results were contradictory. The KC cohort was more likely to spend time in the shade, while less likely to wear a hat in the sun. The other two questions yielded non-significant associations. In the multivariable model, only wearing a hat in the sun emerged as a risk factor. Therefore, the role of sun exposure in the pathogenesis of KC is still unclear and warrants further research.

Despite our equivocal results, there are two compelling reasons in favour of this hypothesis: first, a high prevalence of KC has been demonstrated in countries that have a great deal of sunshine, 2.3% in Israel,[17] 2.3% in India,[16] 3.3% in Lebanon,[18] 3.3% in Tehran,[20] 2.5% in Mashhad, Iran[63] and with an incidence of 20/10^5 in Saudi Arabia.[21] In contrast the prevalence of KC is much lower in countries with much less sun exposure, 0.05% in northern USA,[24] 0.03% in Finland,[23] 0.09% in Denmark,[25] 0.0002–0.0004% in the Urals, Russia,[27] 0.009% in Japan.[64] Secondly, the ultraviolet component of the sun is a well-known source of reactive oxygen species and excessive amounts of sunlight causes oxidative damage.[30] Additional evidence comes from animal studies in which mice exposed to UV light demonstrated degeneration of stromal collagen and stromal thinning with a marked loss of keratocytes.[32] This last study confirmed an earlier report of UV exposure of an anaesthetised rabbit cornea, which resulted in apoptosis of cells in all layers of the cornea as well as of keratocytes.[65]

However, it must be noted that UV radiations might provide a beneficial effect by inducing cross-linking of corneal collagen thus mitigating either the development or the progression of the disease,[66] which could partly explain our result. In addition, the different prevalence in geographic regions could be explained by ethnic differences rather than amount of sunshine. In fact, ethnic differences have been noted in people inhabiting the same geographic location: In the English Midlands, Asian (Indian, Pakistani and Bangladeshi) patients have been found to be 4.4 and 7.5 times more likely to have KC than Caucasians,[26,28] Maori in New Zealand have been reported to have a higher prevalence of KC than other people in the same country,[35] non-Persians (Arabs, Kurds, Turks) living in the same city in Iran have been found to have KC prevalence of 7.9% compared to 2.5% in a Persian ethnic group[20] and Indians have been found to have significantly steeper corneas than Chinese and Malays all living in Singapore.[67] It is worth noting that in each of the aforementioned studies the diagnostic criteria and age groups were controlled.

The discrepancy in KC prevalence between these various people could be explained by one aspect of the cultures of these communities, namely consanguinity. This was already suggested to account for the differences found in the English Midlands.[26,28] It was confirmed in one case–control study conducted among Palestinians[11] and in Israeli Arabs[12] with OR 4 ($p < 0.001$) and 5.1($p < 0.001$), respectively. Therefore it is possible that consanguinity and genetic influence may be more potent than the environmental influence of sun exposure. Consanguinity is a common factor in the Muslim world.[68–71] A number of population surveys have indicated that Israeli Arabs have a high rate of consanguinity ranging from 42% to 45%[72] with 28% being first cousin marriages.[73] For Israeli Jews, consanguinity is much lower, ranging from 1.5% to 7.1% depending on the community, with 0.4–1.2% being first cousins.[74] The fact that the majority of our cohort was Jewish (62%), may explain why consanguinity did not emerge as a risk factor in our study.

Our data showed an association between KC and parental education, the less educated the more likely to present the disease. The reason for this is not clear. Parental education has been linked to low socioeconomic status.[75] Such communities tend to be poor and their children more likely to live in environments with a disproportionate share of the air, water and waste contamination problems,[76] which are hazardous to their health.[77] As a consequence these children are either at risk or suffer from a host of health disorders, such as asthma, cancer, obesity and hyperactivity.[77] Although we have not observed obesity among KC patients, there are reports in the literature of such an association.[78–80] More research is needed to substantiate our finding.

Allergies have often been found more prevalent in KC patients than in controls.[15,35,55,56,81] Although we found an OR 1.34 in our study it was not statistically significant ($p = 0.44$). A similar result was also noted in Israel with an OR 1.3.[83] These results are similar to the findings of a multivariable analysis carried out by Bawazeer *et al.*[36] who concluded that atopy was not significantly associated with KC. Likewise our results for asthma and eczema were also not significant. This is in agreement with another study in Israel[15] and with other studies from hot sunny countries such as Australia,[82] Florida[83] and Saudi Arabia.[21]

Smoking and diabetes were not found to be significantly associated with KC in our study and this is in accord with other investigations, which have reported lower values than in the general population.[11,15,16,84] As opposed to the loss of tensile strength occurring in KC, diabetes stiffens the cornea.[85] In fact, diabetes is considered to be protective by inducing cross-linking of corneal collagen.[66]

There are several limitations to this study. Most data are based on the subject's verbal history and in particular the inherent weakness in sun exposure questionnaire, which is dependent on the patient's recollection of past experiences. However, since both KC and controls were asked the same questions the relative difference must still prevail. While we

did not validate the sun exposure questions against actual measurements of UVAF, the questions were very similar to those in a validated questionnaire.[45] Nevertheless, validation to UVAF in Israel would have made the results more convincing. Another limitation is that a selection bias may have occurred among patients. But as they were not aware of the nature of the study, there is little likelihood of systematic self-selection other than voluntary compliance or erroneous responses in one group more than in the other. Since both cases and controls presented at a private clinic for a self-funded procedure, socio-economic status is not likely to be a bias. In terms of minimum sample size, we estimated it based on only one variable. However, it must be noted that the results for other variables known to be associated with KC in the current study were found to be in good agreement with other studies.

In conclusion, using multivariable analysis in this case–control study, we found that family history of KC and eye rubbing were significantly associated with KC, but the results regarding sun exposure were equivocal. Interestingly, we found a significant association between parental education and KC. Further studies are required to ascertain whether sun exposure plays a role in the pathogenesis of KC.

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