HHS Public Access

Author manuscript

Ophthalmology. Author manuscript; available in PMC 2017 March 01.

Published in final edited form as:

Ophthalmology. 2016 March ; 123(3): 457–465.e2. doi:10.1016/j.ophtha.2015.10.035.

The Association Between Sociodemographic Factors, Common Systemic Diseases, and Keratoconus: An Analysis of a Nationwide Healthcare Claims Database

Maria A. Woodward, MD[1,2], **Taylor S. Blachley, MS**[1], and **Joshua D. Stein, MD, MS**[1,2,3]

[1]Department of Ophthalmology and Visual Sciences, University of Michigan Medical School

[2]Institute for Healthcare Policy & Innovation, University of Michigan

[3]Department of Health Management and Policy, University of Michigan School of Public Health

Abstract

Purpose—Several small-scale studies have reported associations between keratoconus (KCN) and an array of systemic diseases but no large-scale study has fully investigated this topic. The purpose of this study is to determine whether an association exists between common systemic diseases, sociodemographic factors, and KCN among a large, diverse group of insured individuals in the United States.

Design—Retrospective longitudinal cohort study

Participants—16,053 patients with KCN were matched 1:1 to 16,053 persons without KCN.

Methods—Persons with KCN were identified using International Classification of Diseases 9th Revision Clinical Modification (ICD-9-CM) billing codes and matched by age, sex, and overall health to a control group with no record of KCN. A multivariable logistic regression assessed whether sociodemographic factors and certain systemic diseases affected the odds of KCN.

Main Outcome Measures—Odd ratios (OR) with 95% confidence intervals (CI) of KCN

Results—After adjustment for confounders, blacks (adjusted OR=1.57, CI: 1.38–1.79, p<0.001) had 57% higher odds and Latinos (adjusted OR=1.43, CI: 1.26–1.62, p<0.001) had 43% higher odds of being diagnosed with KCN compared with whites. Asians had 39% reduced odds (OR=0.61, CI: 0.50–0.75, p<0.001) of being diagnosed with KCN compared to whites. Patients with uncomplicated diabetes mellitus (DM) had 20% lower odds of KCN (adjusted OR=0.80, CI: 0.71–0.90, p=0.002) while patients with DM complicated by end-organ damage had 52% lower odds of having KCN (adjusted OR=0.48, CI: 0.40–0.58, p<0.001) compared to those without DM.

Corresponding Author: Maria A. Woodward, MD, University of Michigan, Department of Ophthalmology and Visual Sciences, 1000 Wall Street, Ann Arbor, MI 48105, Phone: 734-763-5506, mariawoo@umich.edu.

Address for reprints:

1000 Wall Street, Ann Arbor, MI 48105

Conflict of Interest: No conflicting relationship exists for any author.

Persons with collagen vascular disease had 35% lower odds of KCN (adjusted OR=0.65, CI: 0.47–0.91, p=0.01). Other conditions found to have increased odds of KCN included sleep apnea (adjusted OR=1.13, CI: 1.00–1.27, p=0.05), asthma (adjusted OR=1.31, CI: 1.17–1.47, p<0.001), and Down syndrome (adjusted OR=6.22, CI: 2.08–18.66, p<0.001). There was no association between KCN and allergic rhinitis, mitral valve disorder, aortic aneurysm, or depression (p>0.1, for all comparisons).

Conclusions—Clinicians caring for persons with KCN should inquire about difficulties with breathing or sleeping and, when appropriate, refer patients to undergo evaluation for conditions such as sleep apnea or asthma. Lower risk of KCN in those with DM, potentially due to corneal glycosylation, opens an interesting area of research.

Keratoconus (KCN) is a chronic non-inflammatory ectatic condition with an insidious onset, often presenting with bilateral decreased vision due to increasing myopia and irregular astigmatism. Studies have reported that the prevalence of KCN ranges from 50 to 2,300 cases per 100,000, depending on the country studied.[1–3] This condition primarily affects working-age people between 18–40 years of age and, if left untreated, can have a profound impact on quality of well-being.

Understanding the association between systemic diseases and KCN may help elucidate the pathophysiology of the disease. In 2015, the Global Delphi Panel of Keratoconus and Ectatic Diseases, a group of 9 corneal subspecialists representing countries throughout the world, reported risk factors for developing KCN based on a post-meeting survey of the panelists which included ocular allergy, atopy, connective tissue disorders, and Down syndrome.[4] They also noted that persons of Asian and Arabian ethnicity may carry an increased risk of this disease.

Recent literature has focused on the potential connection between diabetes mellitus (DM) and KCN.[5–8] The biomechanical theory of KCN postulates that elevated glucose in patients with DM leads to glycosylation of corneal fibers, which causes collagen crosslinking and strengthens the cornea thus reducing the risk of developing ectasia and KCN.[9–12] While some clinical evidence supports this theory,[5,6] a recent case-control study of 1377 patients with KCN actually found that patients with DM were *more* likely to have KCN compared to controls.[7] Conflicting evidence in the clinical literature calls into question the nature of this association.[13]

A host of other systemic diseases have been reported to be associated with KCN including allergy, Down syndrome, collagen vascular disorders, aortic aneurysm, sleep apnea, atopy, asthma, and ocular allergy.[14–21] One theory suggests that KCN and atopy are associated because pruritis leads to eye rubbing, which causes mechanical ‘wear’ of the cornea and progressive ectasia.[16,22–26] Another theory is that the same human leukocyte antigens may be activated in KCN and allergic conditions.[16] Although a strong association has been reported between Down syndrome and KCN, the pathophysiologic connection is unclear.[27] Some have postulated that persons with Down syndrome are more likely to rub their eyes, leading to the same mechanical wear that may be involved in the association between allergy and KCN. Whether or not systemic diseases that affect collagen, such as mitral valve prolapse and collagen vascular disorders, are associated with KCN has also been debated in

the literature. Mitral valve prolapse and collagen vascular disease may be associated with KCN,[28–30] although other studies have found no such association.[31] Akcay and colleagues implicated abnormal or weak collagen structure in both mitral valve prolapse and collagen vascular disease.[32] Similarly, a single-center survey of patients with KCN by Gupta and coworkers found that sleep apnea was more prevalent in patients with KCN than in the general population.[33] These prior studies all had relatively small sample sizes ranging from 25 to 1,529 patients, so for many of these conditions, the researchers were limited in their ability to perform rigorous statistical analyses and adjust for potential confounding factors.

The purpose of this study is to use a health care claims database containing records for over 16,000 patients with KCN and controls matched by age, sex, and overall health to evaluate the association between various systemic diseases and KCN to help reconcile some of the conflicting reports in the literature.

Methods

Data Source

The Clinformatics DataMart database (OptumInsight, Eden Prairie, MN) contains detailed records of all beneficiaries in a large nationwide U.S. managed care network. The dataset contains all individuals with one or more International Classification of Diseases, Ninth Revision-Clinical Modification (ICD-9-CM) codes for eye-related diagnoses (360–379.9)[34], one or more Current Procedural Terminology (CPT) codes for any eye-related visits, diagnostic, or therapeutic procedures (65091–68899 or 92002–92499)[35], or any other claim submitted by an ophthalmologist or optometrist from January 1, 2001 through December 31, 2012. For each enrollee, the data included all medical claims for ocular and non-ocular conditions and sociodemographic information including age, sex, race, education level, personal income, and geographic setting of residence at plan enrollment (residence in an urban or rural setting). All data were de-identified prior to receipt by the researchers and the University of Michigan Institutional Review Board approved this as a non-regulated study.

Identification of Cases and Controls

Enrollees were included in the analysis if they met the following criteria: continuous enrollment in the medical plan, enrollment in the plan for at least one year, and ≥1 visits to an eye care provider (ophthalmologist or optometrist). The requirement of ≥1 visit to an eye care provider helped assure that all the enrollees had at least 1 opportunity to get diagnosed with KCN. Beneficiaries were identified with KCN (cases) if they had the following ICD-9-CM codes: 371.6, 371.60–.62. A confirmatory diagnosis of KCN at another visit on a separate date was required to classify an enrollee with KCN. A control group was randomly selected among patients with one or more visits to an eye care provider and no record of KCN who were enrolled in the medical plan between 2001 and 2012. Cases and controls were matched 1:1 on age at plan enrollment, sex, and overall health based on Clinical Risk Group (CRG) score. CRG is a measure of overall health status that is commonly used in health services research. It assigns persons to a risk group based on demographics and clinical diseases to predict future healthcare needs.[36]

Identification of Presence of Systemic Diseases

Systemic diseases chosen for this study were identified from a review of the literature of prior studies and case series that have reported associations between such conditions and KCN. ICD-9-CM diagnosis codes were used to identify individuals with the following systemic diseases of interest: DM, asthma, allergic rhinitis, mitral valve prolapse, collagen vascular disease, aortic aneurysm, Down syndrome, sleep apnea, and depression. Persons with DM were defined as having uncomplicated DM if they had no record of end-organ damage from this condition, while those with any record of end-organ damage, including nephropathy, retinopathy, neuropathy, or circulatory disorders, were characterized as having complicated DM. A listing of the specific ICD-9-CM codes for all conditions and procedures for this study can be found in Online Table 1 (available at www.aaojournal.org). Since the goal of this analysis was to identify associations between these systemic diseases and KCN and not to necessarily identify systemic conditions that cause KCN, we did not restrict diagnoses of these systemic conditions having occurred before the first record of KCN, thus cases and controls could have received the diagnosis of these conditions at any time while in the plan.

Analyses

Statistical analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, NC). Participant characteristics were summarized for the entire sample using means and standard deviations (SD) for continuous variables and frequencies and percentages for categorical variables.

Multivariable Regression Models—A multivariable logistic regression model was constructed to estimate the potential association of various systemic diseases with a diagnosis of KCN. The dependent variable in the model was a diagnosis of KCN. The independent variables included sociodemographic factors (race, income, education, urban/rural residential status) and all of the above-mentioned medical conditions of interest that have previously been reported to be associated with KCN, length of time in the medical plan, and number of visits to eye care providers. By including length of time in plan and number of eye visits in the model, we are accounting for these factors that can impact odds of getting diagnosed with KCN and other conditions.

In a second logistic regression model we assessed, among those persons with KCN, whether the same covariates listed above were associated with receipt of a diagnosis of severe KCN versus mild KCN. Persons were characterized with severe KCN if they had ≥1 record of keratoplasty surgery (CPT-4 codes 65710, 65730, 65750, 65755) during their time in the plan or if they were coded with ICD-9-CM code 371.62 (keratoconus with acute hydrops). Persons identified with KCN by codes 371.6 or 371.61 and with no record of keratoplasty or record of code 371.62 during their time in the plan were considered to have mild disease.

In a separate multivariable regression model adjusting for these same covariates as the previous model, we assessed the relationship between KCN and different manifestations of end-organ damage from DM (neuropathy, nephropathy, retinopathy, circulatory disease,

more than one of these manifestations). We also assessed KCN severity with different manifestations of end-organ damage from DM.

Checks of the models for multicolinearity were performed and none of the covariates were highly correlated with one another. For all analyses, p-values of <0.05 were considered statistically significant.

Results

A total of 16,053 beneficiaries with KCN met the study inclusion criteria along with 16,053 controls matched 1:1 by age, sex, and CRG score. (Figure 1) Among those diagnosed with KCN, 13,727 patients (85.5%) were characterized with mild KCN and 2,326 patients (14.5%) were characterized with severe KCN. The mean ± SD age at enrollment of patients with KCN (and matched controls) was 40.4 ± 13.0 years. The patients with KCN were enrolled in the plan for 4.7 ± 2.9 years, and controls were enrolled for 4.6 ± 2.9 years. The proportion of persons with KCN who graduated from college was higher than the controls (32.4% vs. 28.2%) as was the proportion with incomes ≥$100,000 (38.9% vs. 35.1%). (Table 1) As expected, patients with KCN had over double the number of visits to eye care providers (6.5 ± 7.1 visits) than the controls (2.6 ± 3.2 visits) (p<0.001). Online Table 2 (available at www.aaojournal.org) describes the characteristics of those with mild versus severe KCN.

Sociodemographic Factors

After accounting for confounding factors, blacks had a 57% higher odds of KCN than whites (adjusted OR=1.57, CI: 1.38–1.79, p<0.001), and Latinos had a 43% higher odds of KCN compared to whites (adjusted OR=1.43, CI: 1.26–1.62, p<0.001). Asian Americans had a 39% lower odds of KCN compared with whites (adjusted OR=0.61, CI: 0.50–0.75, p<0.001). Education level (p>0.05 for all comparisons) and personal income (p≥0.40 for all comparisons) were not associated with higher or lower odds of KCN. Compared to persons residing in urban communities, those living in large rural communities had a 20% lower odds of KCN (adjusted OR=0.80, CI=0.68–0.94, p=0.007). (Table 2)

Systemic Diseases

In the multivariable regression model, persons with uncomplicated DM had a 20% reduced odds of KCN (adjusted OR=0.80, CI: 0.71–0.90, p=0.002), and those with complicated DM had a 52% reduced odds of KCN (OR=0.48, CI=0.40–0.58, p<0.001) compared to those without DM. Persons with collagen vascular disease had 35% reduced odds (OR=0.65, CI=0.47–0.91, p=0.01) had reduced odds of KCN. By comparison, persons with sleep apnea had a 13% increased odds of KCN (OR=1.13, CI: 1.00–1.27, p=0.05), those with asthma had a 31% increased odds of KCN (OR=1.31, CI: 1.17–1.47, p<0.001), and persons with Down syndrome had over a 6 fold increased odds of KCN (OR=6.22, CI: 2.08–18.66, p<0.001). There was no significant association between allergic rhinitis (p=0.51), mitral valve prolapse (p=0.08), aortic aneurysm (p=0.39), or depression (p=0.96) and KCN (Table 2).

In the separate multivariable regression model, we assessed the relationship between KCN and different manifestations of end-organ damage from DM. In this model, patients who had multiple (>1) manifestations of end-organ damage from DM had 66% lower odds of KCN ($p<0.001$) compared to those without DM (data not shown).

Associations of Systemic Diseases with Mild versus Severe Keratoconus

Among enrollees with KCN, after adjustment for confounders, the following factors were associated with increased odds of receiving a diagnosis of severe KCN compared to mild KCN: black race (OR=1.31, CN 1.10–1.56, p=0.003), uncomplicated DM (OR=1.23, CI=1.02–1.48, p=0.03), sleep apnea (OR=1.29, CI=1.09–1.53, p=0.003), and asthma (OR=1.21, CI=1.03–1.42, p=0.02). Two factors were associated with reduced odds of severe KCN compared to mild KCN: allergic rhinitis (OR=0.82, CI=0.72–0.94, p=0.004) and female sex (OR=0.76, CI=0.68–0.85, p<0.001). There were no statistically significant difference among persons with complicated DM (p=0.40), Down syndrome (p=0.34), mitral valve prolapse (p=0.75), collagen vascular disease (p=0.58), aortic aneurysm (p=0.44) depression (p=0.25), and severity of KCN (Table 3).

Discussion

Using a large nationwide managed care network health care claims database enabled us to harness data on large numbers of patients with KCN to learn more about this relatively uncommon but serious ocular disease. These analyses identified several key findings. First, the odds of KCN vary by race. Blacks and Latinos had higher odds of KCN while Asian Americans had a reduced odds of this disease relative to whites. Second, we learned that patients with DM and those with collagen vascular disease were less likely to have KCN. By comparison, persons with asthma, sleep apnea, and Down syndrome had considerably higher odds of receiving a diagnosis of KCN.

We found that Black and Latino persons had approximately 50% higher odds of KCN compared with whites. To the best of our knowledge, this finding has not been noted in the literature, perhaps because prior studies lacked adequate numbers of racial minorities to assess for differences in risk of KCN by race. We also found that Asian Americans had reduced odds of KCN. This finding differs from the consensus of a Delphi panel, consisting of cornea subspecialists from United States, Brazil, Singapore, Japan, India, and France, who concluded that Asian persons had at higher risk of keratoconus.[4] The prior evidence substantiating a greater risk of KCN among Asian persons is somewhat limited. Two studies conducted in the United Kingdom with sample sizes of 338 and 75 patients with KCN reported a greater proportion of patients of Asian ethnicity compared with non-Asians.[37,38] Unlike our study, these investigations did not perform multivariable regression modeling to account for confounding factors. Nevertheless, additional work is needed to reconcile differences in the findings of these studies and ours with respect to whether Asian persons are at greater or lower risk of this disease.

Since we matched cases and controls by age and sex, we were unable to study whether these demographic factors impacted the risk of developing KCN. Several studies have reported that males are at higher risk for developing KCN.[1,15,19,20,38,39] Among the 16,053 persons

in this analysis identified with KCN, a greater proportion (58.9%) were male, which is in line with other studies. Moreover, we found that females had a 24% reduced odds of experiencing severe KCN compared with males.

After accounting for confounding variables, we did not find an association between education level or personal income and KCN. This is encouraging as one may suspect that patients with KCN would have limitations in education and employment because of limited vision from this disease but this appears to not be the case. Fortunately, advances in medical and surgical care, including use of rigid gas permeable contact lenses, have allowed many patients with KCN to achieve good visual acuity so they can be highly productive. It is important to note, though, that all of the patients with KCN in our study had health insurance and we suspect that these findings may not hold true for patients with KCN without health insurance.

Persons residing in large rural communities had lower odds of having KCN, and there was a similar trend in small rural populations. Possible explanations for this finding include persons residing in rural settings may be less likely to have access to corneal specialists for diagnosis and management of KCN and thus patients with mild or form fruste disease may go undetected in these settings. It is also possible that environmental pollutants in urban settings may exacerbate eye rubbing which could increase the odds of KCN.

Consistent with pathophysiologic mechanisms of crosslinking by glycosylation,[9–12] our study showed that persons with DM had considerably reduced odds of KCN. Those with DM complicated by end-organ damage had 52% lower odds of KCN and persons with uncomplicated DM had 20% lower odds of KCN compared to persons without DM. Additional analyses showed that persons with multiple manifestations of end organ damage from DM had 66% lower odds of KCN compared to persons without DM. These results align with the findings of a study by Seiler and coworkers who evaluated 571 patients with KCN.[5] Their group matched patients on age and sex with controls, and showed a 78% reduced odds of KCN ($p=0.03$) among persons with DM. In contrast, another case-control study by Kosker and colleagues, found that patients with DM were *more* likely to have KCN.[7] It is worth noting, the work by Kosker did not account for length of follow up by the physicians and may have also been affected by surveillance bias such that patients with DM in their study likely underwent more frequent ocular examinations and thus had a greater opportunity to get identified with KCN compared to the control group.[7] While the study by Seiler and ours may also be affected by surveillance bias, if DM increases the likelihood of seeking eye care and thus receiving a KCN diagnosis, one would expect more frequent interactions would bias the results to higher odds of KCN among persons with DM. Therefore our observation of a reduced odds of KCN among persons with DM suggests the true effect of a risk reduction may be larger than the levels we are capturing in our analysis once one considers differences in the frequency of eye care encounters between groups.

Kuo and colleagues reported that patients with more severe manifestations of DM were less likely to get diagnosed with severe KCN.[6] Although our analysis did not reveal that those with increased severity of DM had a reduced severity of KCN, we did find that those with multiple manifestations of end-organ damage from DM were less likely to get diagnosed

with KCN. If patients with DM as a group are indeed protected against KCN, therapies aimed at raising glucose levels in the cornea may be a viable therapeutic alternative to collagen crosslinking with riboflavin and ultraviolet light to prevent or treat KCN.

Consistent with published literature, we found that patients with Down syndrome had more than a 6 times higher odds of KCN.[15] Despite such a strong association in this and other studies, researchers have yet to identify specific genetic mutations linking these conditions.[27] Given some of the challenges that persons with Down syndrome have with communicating health concerns, a high index of suspicion for KCN is warranted in these patients since vision aids, corneal transplantation, and potentially collagen cross-linking treatment to halt disease progression may be able to improve the vision and quality of life of these patients. Furthermore, the findings of this analysis highlight the importance of regular eye care for patients with Down syndrome to monitor for KCN and other ocular diseases.

In our study, patients with asthma had 31% higher odds of having KCN. Moreover, those with asthma had a 21% increased odds of severe KCN. A recent cross-sectional study of adolescents evaluated by the Israeli Defense Force also showed an increased odds of KCN in persons with asthma ($p<0.001$).[20] In their study, asthma was diagnosed by pulmonary function tests or consultation with a pulmonologist. In light of the findings of our study and theirs, we feel it is appropriate to inquire about breathing difficulties in patients with KCN as one may identify patients with previously undiagnosed asthma who may benefit from treatment.

An association of sleep apnea, floppy eyelid syndrome, and KCN has been well established.[33,40–43] Gupta and colleagues conducted a survey of patients with KCN showing that 65% either had previously diagnosed sleep apnea or were at high risk for sleep apnea by the Berlin questionnaire.[33] In our study, a greater proportion of persons with KCN had sleep apnea (10.6% vs. 8.7%), and patients with sleep apnea had 13% higher odds of KCN. Sleep apnea was also associated with more severe KCN. Given the increased morbidity and mortality associated with sleep apnea, it may be reasonable to administer the Berlin questionnaire to patients with KCN to screen for sleep apnea and consider requesting a formal sleep study for those found to be at high risk.

In our study, there was no statistical significant difference between controls and persons with KCN in receiving a diagnosis of allergic rhinitis. In a study of Israeli adolescents, there was an increased odds of KCN among these patients ($p<0.001$),[20] but allergic rhinitis was diagnosed by self-report, and not with quantitative diagnostic tests as was the case with asthma. We believe the diagnosis of allergic rhinitis likely represents a heterogeneous group of conditions of varying severity which makes it challenging to adequately analyze using claims data as we have attempted to do. Genetic studies have identified candidate genes for KCN linked to atopic disease including filaggrin mutations in atopic dermatitis and interleukin 1 pathway changes that occur with mechanical injury in keratoconic eyes.[27] Additional research is needed to better understand whether allergic rhinitis is associated with KCN.

Our study has several strengths. This study is, to the best of our knowledge, the largest to date focused on persons with KCN with over 16,000 cases identified in the database. We had a diverse group of patients of different sociodemographic profiles with relatively large numbers of racial minorities. These analyses identified patients with KCN residing in communities throughout the country who were receiving care by an array of different eye care providers including optometrists, comprehensive ophthalmologists, and corneal specialists. As such, the findings may have more generalizability relative to single center studies or those from academic centers that may be a biased sample of those with more severe disease.[44] In addition, claims data does not rely on patient self-report of medical conditions such as KCN. Others have demonstrated patient self-report is less reliable compared with diagnoses made by medical professionals.[45]

Our study also has several limitations. First, without access to clinical records, we cannot confirm the presence of KCN among those identified as cases or absence of disease in controls.[44] That said, a study by Center for Medicare and Medicaid Services found the specialty of ophthalmology has one of the lowest rates of improper coding of ocular diagnoses.[46] Moreover, to help ensure that those who had been coded with KCN did indeed have the disease we required a confirmatory diagnosis on a separate visit. Second, it is difficult with claims data alone to determine causality between specific systemic diseases and KCN. This limitation is acknowledged. The purpose of the study was to identify whether these conditions are associated with one another or not. Additional studies using other data sources are needed to establish whether a causal relationship is present among the conditions we found to be associated with KCN. Third, we adjusted our regression model for important confounding factors but the data source lacks clinical detail on other factors such as eye rubbing, family history of KCN, and ocular and systemic diseases identified prior to plan enrollment. Lastly, all patients included had health insurance. Additional research using other data sources is needed to determine whether the findings can be generalized to the uninsured or those with other forms of insurance.

In conclusion, this study identified several factors that were associated with an increased or decreased risk of KCN. Clinicians should be aware that patients with KCN might have breathing issues and sleep disorders that carry risk of morbidity and mortality and should refer patients with KCN who are suspected to have sleep apnea or asthma to medical specialists for further evaluation. Caregivers of Down syndrome should be aware of KCN as a cause of vision impairment and make sure that persons with this condition are regularly seen by eye care professionals to monitor for KCN and other ocular diseases. The reduced odds of KCN among persons with DM supports the notion that corneal crosslinking may help stabilize the cornea from developing ectasia and KCN in persons with DM and this finding may help researchers identify novel treatment options to try to prevent or treat KCN.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial Support:

MAW: National Eye Institute, Bethesda, MD; K23 Mentored Clinical Scientist Award K23EY023596-01.

JDS: Research to Prevent Blindness “Physician Scientist Award”

The funding organizations had no role in the design or conduct of this research.

Abbreviations

KCN	Keratoconus
DM	Diabetes Mellitus

References

1. Kennedy RH, Bourne WM, Dyer JA. A 48-year clinical and epidemiologic study of keratoconus. Am J Ophthalmol. 1986; 101:267–73. [PubMed: 3513592]
2. Jonas JB, Nangia V, Matin A, et al. Prevalence and associations of keratoconus in rural maharashtra in central India: the central India eye and medical study. Am J Ophthalmol. 2009; 148:760–5. [PubMed: 19674732]
3. Krachmer, JH.; Mannis, MJ.; Holland, EJ. Cornea. Mosby: Elsevier; 2011.
4. Gomes JA, Tan D, Rapuano CJ, et al. Global consensus on keratoconus and ectatic diseases. Cornea. 2015; 34:359–69. [PubMed: 25738235]
5. Seiler T, Huhle S, Spoerl E, Kunath H. Manifest diabetes and keratoconus: a retrospective case-control study. Graefes Arch Clin Exp Ophthalmol. 2000; 238:822–5. [PubMed: 11127568]
6. Kuo IC, Broman A, Pirouzmanesh A, Melia M. Is there an association between diabetes and keratoconus? Ophthalmology. 2006; 113:184–90. [PubMed: 16368147]
7. Kosker M, Suri K, Hammersmith KM, et al. Another look at the association between diabetes and keratoconus. Cornea. 2014; 33:774–9. [PubMed: 24915014]
8. Naderan M, Naderan M, Rezagholizadeh F, et al. Association between diabetes and keratoconus: a case-control study. Cornea. 2014; 33:1271–3. [PubMed: 25343697]
9. Wollensak G, Spoerl E, Seiler T. Stress-strain measurements of human and porcine corneas after riboflavin-ultraviolet-A-induced cross-linking. J Cataract Refract Surg. 2003; 29:1780–5. [PubMed: 14522301]
10. Goldich Y, Barkana Y, Gerber Y, et al. Effect of diabetes mellitus on biomechanical parameters of the cornea. J Cataract Refract Surg. 2009; 35:715–9. [PubMed: 19304094]
11. Spoerl E, Huhle M, Seiler T. Induction of cross-links in corneal tissue. Exp Eye Res. 1998; 66:97–103. [PubMed: 9533835]
12. Dyer DG, Dunn JA, Thorpe SR, et al. Accumulation of Maillard reaction products in skin collagen in diabetes and aging. J Clin Invest. 1993; 91:2463–9. [PubMed: 8514858]
13. Prakash G, Sharma N, Titiyal JS. Association between diabetes and keratoconus? Ophthalmology. 2007; 114:1034. author reply 1034–5. [PubMed: 17467545]
14. Gasset AR, Hinson WA, Frias JL. Keratoconus and atopic diseases. Ann Ophthalmol. 1978; 10:991–4. [PubMed: 697285]
15. Krachmer JH, Feder RS, Belin MW. Keratoconus and related noninflammatory corneal thinning disorders. Surv Ophthalmol. 1984; 28:293–322. [PubMed: 6230745]
16. Harrison RJ, Klouda PT, Easty DL, et al. Association between keratoconus and atopy. Br J Ophthalmol. 1989; 73:816–22. [PubMed: 2818991]
17. Nemet AY, Vinker S, Bahar I, Kaiserman I. The association of keratoconus with immune disorders. Cornea. 2010; 29:1261–4. [PubMed: 20802320]
18. Agrawal VB. Characteristics of keratoconus patients at a tertiary eye center in India. J Ophthalmic Vis Res. 2011; 6:87–91. [PubMed: 22454716]
19. Weed KH, MacEwen CJ, Giles T, et al. The Dundee University Scottish Keratoconus study: demographics, corneal signs, associated diseases, and eye rubbing. Eye. 2008; 22:534–41. [PubMed: 17237755]

20. Merdler I, Hassidim A, Sorkin N, et al. Keratoconus and allergic diseases among Israeli adolescents between 2005 and 2013. Cornea. 2015; 34:525–9. [PubMed: 25782404]
21. Cingu AK, Cinar Y, Turkcu FM, et al. Effects of vernal and allergic conjunctivitis on severity of keratoconus. Int J Ophthalmol. 2013; 6:370–4. [PubMed: 23826535]
22. Bawazeer AM, Hodge WG, Lorimer B. Atopy and keratoconus: a multivariate analysis. Br J Ophthalmol. 2000; 84:834–6. [PubMed: 10906086]
23. Zadnik K, Steger-May K, Fink BA, et al. Between-eye asymmetry in keratoconus. Cornea. 2002; 21:671–9. [PubMed: 12352084]
24. Jafri B, Lichter H, Stulting RD. Asymmetric keratoconus attributed to eye rubbing. Cornea. 2004; 23:560–4. [PubMed: 15256993]
25. Carlson AN. Expanding our understanding of eye rubbing and keratoconus. Cornea. 2010; 29:245. [PubMed: 20098158]
26. Yeniad B, Alparslan N, Akarcay K. Eye rubbing as an apparent cause of recurrent keratoconus. Cornea. 2009; 28:477–9. [PubMed: 19411974]
27. Abu-Amero KK, Al-Muammar AM, Kondkar AA. Genetics of keratoconus: where do we stand? J Ophthalmol. 2014:641708. [PubMed: 25254113]
28. Beardsley TL, Foulks GN. An association of keratoconus and mitral valve prolapse. Ophthalmology. 1982; 89:35–7. [PubMed: 7070771]
29. Sharif KW, Casey TA, Coltart J. Prevalence of mitral valve prolapse in keratoconus patients. J R Soc Med. 1992; 85:446–8. [PubMed: 1404188]
30. Lichter H, Loya N, Sagie A, et al. Keratoconus and mitral valve prolapse. Am J Ophthalmol. 2000; 129:667–8. [PubMed: 10844063]
31. Street DA, Vinokur ET, Waring GO 3rd, et al. Lack of association between keratoconus, mitral valve prolapse, and joint hypermobility. Ophthalmology. 1991; 98:170–6. [PubMed: 2008274]
32. Kalkan Akcay E, Akcay M, Uysal BS, et al. Impaired corneal biomechanical properties and the prevalence of keratoconus in mitral valve prolapse. J Ophthalmol. 2014; 2014:402193. [PubMed: 24864193]
33. Gupta PK, Stinnett SS, Carlson AN. Prevalence of sleep apnea in patients with keratoconus. Cornea. 2012; 31:595–9. [PubMed: 22333661]
34. CPT. 2006: Current Procedural Terminology Professional Edition. Chicago, IL: American Medical Association; 2006.
35. ICD-9-CM for Physicians. Vol. 1 and 2. Salt Lake City, UT: Contexo Media; 2006. International Classification of Diseases 9th Revision Clinical Modification.
36. Hughes JS, Averill RF, Eisenhandler J, et al. Clinical Risk Groups (CRGs): a classification system for risk-adjusted capitation-based payment and health care management. Med Care. 2004; 42:81–90. [PubMed: 14713742]
37. Pearson AR, Soneji B, Sarvananthan N, Sandford-Smith JH. Does ethnic origin influence the incidence or severity of keratoconus? Eye. 2000; 14:625–8. [PubMed: 11040911]
38. Georgiou T, Funnell CL, Cassels-Brown A, O'Conor R. Influence of ethnic origin on the incidence of keratoconus and associated atopic disease in Asians and white patients. Eye. 2004; 18:379–83. [PubMed: 15069434]
39. Wagner H, Barr JT, Zadnik K. Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study: methods and findings to date. Con Lens Anterior Eye. 2007; 30:223–32.
40. Mojon DS, Goldblum D, Fleischhauer J, et al. Eyelid, conjunctival, and corneal findings in sleep apnea syndrome. Ophthalmology. 1999; 106:1182–5. [PubMed: 10366090]
41. Saidel MA, Paik JY, Garcia C, et al. Prevalence of sleep apnea syndrome and high-risk characteristics among keratoconus patients. Cornea. 2012; 31:600–3. [PubMed: 22495032]
42. Pihlblad MS, Schaefer DP. Eyelid laxity, obesity, and obstructive sleep apnea in keratoconus. Cornea. 2013; 32:1232–6. [PubMed: 23471083]
43. Gencer B, Ozgurhan EB, Kara S, et al. Obesity and obstructive sleep apnea in patients with keratoconus in a Turkish population. Cornea. 2014; 33:137–40. [PubMed: 24322802]
44. Stein JD, Lum F, Lee PP, et al. Use of health care claims data to study patients with ophthalmologic conditions. Ophthalmology. 2014; 121:1134–41. [PubMed: 24433971]

45. Patty L, Wu C, Torres M, et al. Validity of self-reported eye disease and treatment in a population-based study: the Los Angeles Latino Eye Study. Ophthalmology. 2012; 119:1725–30. [PubMed: 22537615]

46. Muir KW, Gupta C, Gill P, Stein JD. Accuracy of international classification of diseases, ninth revision, clinical modification billing codes for common ophthalmic conditions. JAMA Ophthalmol. 2013; 131:119–20. [PubMed: 23307227]

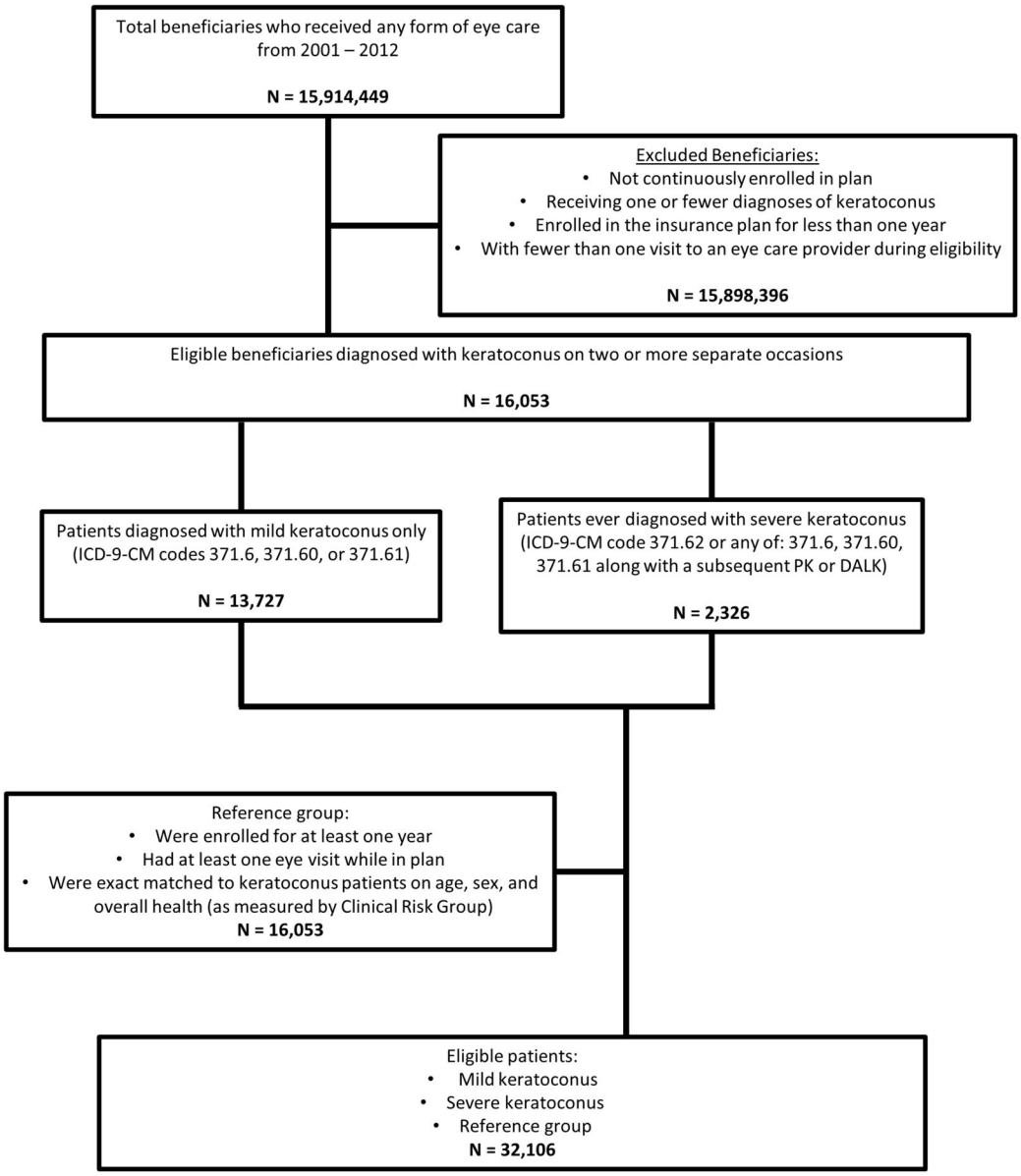

Figure 1.

Selection of beneficiaries for analysis. Abbreviations: ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; PK, penetrating keratoplasty; DALK, deep anterior lamellar keratoplasty.

Ophthalmology. Author manuscript; available in PMC 2017 March 01.

Table 1

Socio-demographic characteristics by case status, N (column %) or Mean (SD)

Variable	Value	Controls	Keratoconus Cases	Total	p-value
Total, N (row %)		16,053 (50.0)	16,053 (50.0)	32,106	
Age at Enrollment *		40.4 (13.0)	40.4 (13.0)	40.4 (13.0)	0.98
Time in Plan (years)		4.6 (2.9)	4.7 (2.9)	4.7 (2.9)	0.0002
Number of Eye Visits		2.6 (3.2)	6.5 (7.1)	4.6 (5.8)	< 0.0001
Sex *	Male	9,456 (58.9)	9,456 (58.9)	18,912 (58.9)	1.00
	Female	6,597 (41.1)	6,597 (41.1)	13,194 (41.1)	
Race (N_{miss}=3,391)	White	11,367 (79.0)	10,708 (74.8)	22,075 (76.9)	< 0.0001
	Black	1,055 (7.3)	1,467 (10.2)	2,522 (8.8)	
	Latino	1,209 (8.4)	1,535 (10.7)	2,744 (9.6)	
	Asian	612 (4.3)	414 (2.9)	1,026 (3.6)	
	Other	152 (1.1)	196 (1.4)	348 (1.2)	
Education (N_{miss}=2,076)	Less than High School	178 (1.2)	206 (1.4)	384 (1.3)	< 0.0001
	High School Diploma	4,089 (27.2)	3,331 (22.2)	7,420 (24.7)	
	Some College	6,446 (42.9)	6,507 (43.4)	12,953 (43.1)	
	College Diploma	4,236 (28.2)	4,866 (32.4)	9,102 (30.3)	
	Advanced Degree	71 (0.5)	100 (0.7)	171 (0.6)	
Income (N_{miss}=5,327)	< $30K	550 (4.1)	540 (4.0)	1,090 (4.1)	< 0.0001
	$30K – < $60K	4,560 (34.0)	4,054 (30.3)	8,614 (32.2)	
	$60K – < $100K	3,591 (26.8)	3,577 (26.8)	7,168 (26.8)	
	$100K – < $125K	1,829 (13.6)	1,939 (14.5)	3,768 (14.1)	
	≥ $125K	2,879 (21.5)	3,260 (24.4)	6,139 (22.9)	
Urban/Rural Status (N_{miss}=240)	Urban	14,213 (89.1)	14,660 (92.1)	28,873 (90.6)	< 0.0001
	Large Rural	915 (5.7)	684 (4.3)	1,599 (5.0)	
	Small Rural	815 (5.1)	579 (3.6)	1,394 (4.4)	
Diabetes	None	13,450 (83.8)	13,991 (87.2)	27,441 (85.5)	< 0.0001
	Uncomplicated	1,731 (10.8)	1,517 (9.4)	3,248 (10.1)	

Variable	Value	Controls	Keratoconus Cases	Total	p-value
	Complicated	872 (5.4)	545 (3.4)	1,417 (4.4)	
Asthma		1,721 (10.7)	2,292 (14.3)	4,013 (12.5)	< 0.0001
Allergic Rhinitis		4,115 (25.6)	4,549 (28.3)	8,664 (27.0)	< 0.0001
Mitral Valve Prolapse		873 (5.4)	853 (5.3)	1,726 (5.4)	0.62
Collagen Vascular Disease		209 (1.3)	170 (1.1)	379 (1.2)	0.04
Aortic Aneurysm		96 (0.6)	90 (0.6)	186 (0.6)	0.66
Down Syndrome		8 (0.0)	62 (0.4)	70 (0.2)	< 0.0001
Sleep Apnea		1,402 (8.7)	1,697 (10.6)	3,099 (9.7)	< 0.0001
Depression		1,200 (7.5)	1,210 (7.5)	2,410 (7.5)	0.83
Clinical Risk Group *	1 (Healthiest)	5,178 (32.3)	5,178 (32.3)	10,356 (32.3)	1.00
	2	4,486 (27.9)	4,486 (27.9)	8,972 (27.9)	
	3	6,186 (38.5)	6,186 (38.5)	12,372 (38.5)	
	4 (Least healthy)	203 (1.3)	203 (1.3)	406 (1.3)	

* Matching variable

Continuous variables compared using two-sample t-tests, and categorical variables compared using Chi-square tests.

Uncomplicated Diabetes defined as lack of end-organ damage.

Complicated Diabetes defined as having accompanying end-organ damage.

Table 2

Conditional logistic regression model estimating associations of various covariates with keratoconus

Variable	Value	Odds Ratio (95% CI)	p-value
Time in Plan (years)		0.91 (0.90, 0.92)	< 0.0001
Number of Eye Visits		1.34 (1.32, 1.36)	< 0.0001
Race	White	REF	
	Black	1.57 (1.38, 1.79)	< 0.0001
	Latino	1.43 (1.26, 1.62)	< 0.0001
	Asian	0.61 (0.50, 0.75)	< 0.0001
	Other	1.17 (0.84, 1.64)	0.36
Education	Less than High School	REF	
	High School Diploma	0.85 (0.60, 1.21)	0.37
	Some College	1.12 (0.79, 1.59)	0.53
	College Diploma	1.24 (0.87, 1.78)	0.24
	Advanced Degree	1.75 (0.98, 3.13)	0.06
Income	< $30K	REF	
	$30K – < $60K	0.97 (0.79, 1.18)	0.74
	$60K – < $100K	0.98 (0.80, 1.21)	0.88
	$100K – < $125K	0.90 (0.72, 1.13)	0.37
	≥ $125K	1.00 (0.80, 1.24)	0.97
Urban/Rural Status	Urban	REF	
	Large Rural	0.80 (0.68, 0.94)	0.007
	Small Rural	0.87 (0.73, 1.04)	0.12
Diabetes	None	REF	
	Uncomplicated*	0.80 (0.71, 0.90)	0.0002
	Complicated**	0.48 (0.40, 0.58)	< 0.0001
Asthma		1.31 (1.17, 1.47)	< 0.0001
Allergic Rhinitis		1.03 (0.95, 1.12)	0.51
Mitral Valve Prolapse		0.87 (0.74, 1.02)	0.08
Collagen Vascular Disease		0.65 (0.47, 0.91)	0.01
Aortic Aneurysm		0.82 (0.52, 1.29)	0.39
Down Syndrome		6.22 (2.08, 18.66)	0.001
Sleep Apnea		1.13 (1.00, 1.27)	0.048
Depression		1.00 (0.88, 1.15)	0.96

* Uncomplicated Diabetes defined as lack of end-organ damage.

** Complicated Diabetes defined as having accompanying end-organ damage.

Table 3

Multivariable logistic regression model estimating associations of various covariates with severe keratoconus, compared with mild keratoconus

Variable	Value	Odds Ratio (95% CI)	p-value
Sex	Male	REF	
	Female	0.76 (0.68, 0.85)	< 0.0001
Race	White	REF	
	Black	1.31 (1.10, 1.56)	0.003
	Latino	1.16 (0.97, 1.38)	0.10
	Asian	0.76 (0.53, 1.10)	0.15
	Other	0.83 (0.50, 1.39)	0.48
Clinical Risk Group	1 (Healthiest)	REF	
	2	0.96 (0.83, 1.11)	0.60
	3	0.84 (0.72, 0.98)	0.03
	4 (Least Healthy)	0.58 (0.33, 1.00)	0.051
Age at Enrollment		0.98 (0.98, 0.99)	< 0.0001
Time in Plan (years)		0.89 (0.87, 0.91)	< 0.0001
Number of Eye Visits		1.13 (1.12, 1.14)	< 0.0001
Education	Less than High School	REF	
	High School Diploma	1.16 (0.71, 1.91)	0.55
	Some College	0.92 (0.56, 1.51)	0.73
	College Diploma	0.79 (0.47, 1.31)	0.36
	Advanced Degree	0.33 (0.11, 1.01)	0.051
Income	< $30K	REF	
	$30K – < $60K	1.18 (0.87, 1.60)	0.28
	$60K – < $100K	1.15 (0.83, 1.58)	0.40
	$100K – < $125K	1.05 (0.74, 1.48)	0.80
	≥ $125K	0.94 (0.67, 1.33)	0.73
Urban/Rural Status	Urban	REF	
	Large Rural	1.08 (0.83, 1.40)	0.58
	Small Rural	1.06 (0.80, 1.41)	0.70
Diabetes	None	REF	
	Uncomplicated	1.23 (1.02, 1.48)	0.03
	Complicated	0.87 (0.64, 1.20)	0.40
Asthma		1.21 (1.03, 1.42)	0.02
Allergic Rhinitis		0.82 (0.72, 0.94)	0.004
Mitral Valve Prolapse		0.96 (0.74, 1.24)	0.75
Collagen Vascular Disease		0.85 (0.48, 1.50)	0.58
Aortic Aneurysm		0.73 (0.33, 1.62)	0.44
Down Syndrome		1.43 (0.69, 2.95)	0.34

Variable	Value	Odds Ratio (95% CI)	p-value
Sleep Apnea		1.29 (1.09, 1.53)	0.003
Depression		1.13 (0.92, 1.39)	0.25