Review Article

Prevalence and Risk Factors of Keratoconus in Iran: A Narrative Review

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Abstract

Purpose: Keratoconus (KCN) is a progressive ectatic disorder of the cornea with variable prevalence across populations. This narrative review synthesizes evidence on the prevalence and risk factors of KCN in Iran, highlighting regional and genetic heterogeneity.
Materials and Methods: A comprehensive literature search was conducted across PubMed, Scopus, Web of Science, SID, and MagIran for studies published between 1990 and 2025. Eligible studies included population-based surveys and case-control analyses reporting on KCN prevalence and risk factors in Iranian populations.
Results: Prevalence estimates in Iran range from 0.76 % in Shahroud to 4.0 % in rural regions, with localized values reaching 3.3 % in Tehran. Significant geographic and ethnic variation was observed, including higher prevalence among non-Persian ethnic groups. Major risk factors include family history, consanguinity, eye rubbing, vernal keratoconjunctivitis, and low socioeconomic status. Genetic studies identified associations with polymorphisms in COL4A4, TIMP-1, KIF26B, and LOX, while VSX1 and MIR184 showed no pathogenic involvement. Environmental factors such as ultraviolet radiation, arid climate, and low humidity also contribute. Behavioral and inflammatory mechanisms, particularly eye rubbing and allergic symptoms were consistently linked to disease onset and progression.
Conclusion: KCN in Iran exhibits substantial regional, ethnic, and genetic diversity. Gene–environment interactions appear central to disease risk. National-level surveillance, standardized diagnostics, and multicenter genetic studies are needed to improve early detection and guide tailored interventions. The scarcity of available studies underscores the urgent need for expanded epidemiological and genetic research to address regional disparities and refine preventive strategies.

Keywords: Keratoconus; Prevalence; Risk Factors; Genetic Predisposition to Disease; Consanguinity; Ultraviolet Rays; Eye Rubbing; Corneal Topography.

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Introduction

Keratoconus (KCN) is a progressive, noninflammatory corneal ectasia characterized by stromal thinning and anterior corneal protrusion, leading to irregular astigmatism and visual impairment [1]. It typically presents during adolescence or early adulthood and may progress to severe visual disability if undiagnosed or untreated [1].

The global prevalence of KCN varies widely, reflecting differences in ethnicity, environment, diagnostic techniques, and study design [2]. Omer [2] reported international rates ranging from 0.3 % to over 3 % depending on the region and population studied, with particularly high prevalence among Israeli Arabs (3.18 %) and in parts of India (2.3 %). These variations underscore the influence of geographic and genetic diversity on KCN distribution [2].

In the Middle East, KCN is considered significantly more common than in other regions, with some studies reporting rates as high as 5 % [3,4]. Environmental contributors such as high ultraviolet radiation, arid climate, and dusty atmospheric conditions are frequently cited [2]. Shabani et al.,[5] also identified low humidity as a significant ecological risk factor that may contribute to disease pathogenesis in dry regions.

Iran presents a particularly important setting for KCN research due to its broad ethnic heterogeneity, variable rates of consanguinity, and diverse climatic conditions [6,7]. Local studies have reported substantial variation in KCN prevalence, from 0.76 % in Shahroud to 4.0 % in rural populations and up to 3.3 % in Tehran [8-11].

Clinical findings in Iranian patients also suggest a later mean age of diagnosis compared to other Asian populations, which may reflect delayed detection or differences in risk profile [12]. These patterns highlight the necessity of population-specific research that accounts for Iran's genetic structure, regional environment, and socioeconomic gradients [1].

Despite the clinical importance of KCN, there remains a notable lack of large-scale epidemiological studies on its prevalence in Iran. This review synthesizes the available Iranian evidence to clarify the prevalence and risk factors of KCN within the national context. A narrative review format was chosen due to methodological heterogeneity across studies, including differences in diagnostic criteria and outcome measures.

Materials and Methods

Search Strategy

This narrative review was conducted to identify and report studies addressing the prevalence and risk factors of KCN in the Iranian population. A search was performed across five databases: PubMed, Scopus, Web of Science, SID (Scientific Information Database), and MagIran. The search included studies published from 1990 to 2025.

Keywords were combined using Boolean operators as follows: ("keratoconus" OR "corneal ectasia") AND ("prevalence" OR "epidemiology" OR "risk factors") AND ("Iran" OR "Iranian population") AND ("genetic" OR "environmental" OR "behavioral"). Reference lists of included articles were also screened to identify additional relevant publications.

Eligible studies included population-based surveys, clinical series, and case-control studies that reported on KCN prevalence or associated risk factors in Iranian populations. Studies focused exclusively on diagnosis, treatment outcomes, or non-Iranian cohorts were excluded.

The objective of this review was to describe the distribution of KCN prevalence and to outline reported genetic, environmental, and behavioral risk factors based on the existing Iranian literature. Selected international studies were cited only to provide comparative context where relevant.

Study Selection

Titles and abstracts of retrieved articles were independently screened by two reviewers to assess eligibility. Full-text versions of potentially relevant studies were then reviewed in detail. Disagreements between reviewers were resolved through discussion and consensus.

Inclusion and Exclusion Criteria

Studies were included if they reported on the prevalence or risk factors of keratoconus in Iranian populations and employed population-based, clinical, or case-control designs. Exclusion criteria included case reports, editorials, reviews, conference abstracts, studies focused solely on treatment or diagnosis, and research conducted outside of Iran. Only articles published in English or Persian with accessible full texts were considered.

Data Extraction

From each eligible study, data were extracted on study design, geographic location, sample size, participant demographics, diagnostic criteria or tools used for keratoconus detection, prevalence estimates, and odds ratios for associated risk factors. Data extraction was performed by one reviewer and cross-verified by a second reviewer to ensure consistency.

Assessment of Study Quality and Heterogeneity

Although no formal risk-of-bias assessment was applied, variability in study design, methodology, and diagnostic criteria was noted and considered in the interpretation of results.

Final Study Yield

A total of 20 studies met the inclusion criteria and were included in the final synthesis. This relatively small yield reflects broader gaps in region-specific ophthalmic research, with only 20 studies identified over a 35-year period despite a comprehensive search across local and international databases.

Prevalence of KCN in Iran

Prevalence estimates of keratoconus (KCN) in Iran vary substantially across regions and study populations. In a population-based study of 2,667 individuals from rural areas in northern and southwestern Iran, the prevalence of KCN was 4.0 % (95 % CI: 3-4) [9]. Hashemi et al., [11] conducted a cross-sectional population-based study in Tehran using Orbscan topography on 442 participants with a mean age of 40.8 years. The age- and sex-standardized prevalence of KCN was 3.3 % (95 % CI: 0.1-5.5), with bilateral KCN at 1.8 % (95 % CI: 0.2-3.5). Prevalence was higher in men (3.9 %) than in women (2.6 %), though not statistically significant (P = 0.341). The prevalence increased with age (OR = 1.05 per year, 95 % CI: 1.01-1.08), and was 2.5 % in Persians versus 7.9 % in non-Persians (OR = 3.33) [11].

In a cross-sectional study of 2,546 university employees in Shiraz, the prevalence of KCN was 0.98 % (95 % CI: 0.6-1.4 %), with no significant differences by sex (male: 1.0 %, female: 0.94 %, P = 0.58) or age (KCN mean = 39.3 years, non-KCN = 40.4 years, P = 0.43) [10].

In a population-based study conducted in Shahroud on individuals aged 40 to 64 years, the prevalence of KCN was found to be 0.76 % [8]. Among 4,592 participants, 35 were

Table 1: Comparative prevalence of KCN by regions

Country/Region	Prevalence (%)	Author (Year)
Iran (urban/rural)	0.76 - 4.0	Mohammad-Rabei et al.,[1] Hashemi et al., [8] Hashemi et al.,[9] Hashemi et al.,[11]
Saudi Arabia (pediatric screening)	Up to 4.79	Gomes et al.,[3]
Middle East (general)	2.3 - 4.79	Santodomingo-Rubido et al.,[13]
Asia (general)	0.9 - 3.3	Santodomingo-Rubido et al.,[13]
Western countries	< 1	Santodomingo-Rubido et al.,[13]

diagnosed with KCN in at least one eye [8].
A summary of prevalence of KCN by regions is presented in table 1.

Risk Factors and Disease Patterns in Iran

Genetic Predispositions

The prevalence of keratoconus (KCN) in Iran demonstrates considerable regional variation, reflecting the country's diverse environmental, ethnic, and demographic landscape.
Mehrjoo et al.,[6] highlighted the substantial genetic heterogeneity within the Iranian population, noting distinct ancestry profiles and inbreeding levels among various ethnic groups. For example, Baluchis, Sistanis, and Iranian Arabs exhibited high inbreeding coefficients (FI = 0.012-0.013), whereas Gilaks and Kurds had near-zero levels (FI = 0.0001-0.0010). These differences have direct implications for genetic disease studies, including KCN, and demonstrate that Iran should not be treated as a genetically uniform population [6].
Yari et al.,[14] identified genetic polymorphisms in COL4A4 and TIMP-1 that were significantly associated with KCN risk, with protective effects observed particularly among male carriers of the TIMP-1 variant.
Sargazi et al.,[15] reported significant associations between KCN and two genetic polymorphisms, COL4A4 and KIF26B, in southeastern Iranian patients, suggesting genetic susceptibility involving extracellular matrix and cellular transport pathways.
Saravani et al.,[16] identified a significant association between the COL4A4 gene polymorphism and KCN risk in a southeastern Iranian population. The AA genotype had an odds ratio of 2.1 (P = 0.036), and the A allele showed a significant risk association (OR = 1.5, 95 % CI: 1.1-2.2, P = 0.018), supporting the involvement of collagen IV-related extracellular matrix defects in disease pathogenesis [16]. Niazi et al.,[17] examined the association of two lysyl oxidase (LOX) gene intronic polymorphisms, rs2956540 and rs10519694, with KCN in 178 Iranian patients and 180 healthy controls. They found a significant association for rs10519694, where T allele carriers were more common in KCN patients (P = 0.001), and this SNP was identified as a potential predictor for KCN risk (OR = 2.01, P = 0.001). Although rs2956540 also showed a higher frequency of C allele

carriers among patients (P = 0.017), logistic regression did not support it as a significant predictor (P = 0.323) [17].

The relation between family history and the KCN supports these genetic predispositions [18]. Dehkordi et al.,[19] screened exons 2, 3, and 4 of the VSX1 gene in 50 KCN patients and 50 controls from Chaharmahal va Bakhtiari province using PCR-SSCP, heteroduplex analysis, and sequencing [19]. No pathogenic mutations were identified; detected polymorphisms were benign, suggesting VSX1 is unlikely to play a major role in this population [19].

Farzadfard et al.,[20] sequenced the entire pri-miR-184 region in 47 Iranian KCN patients, 25 of whom had a positive family history [20]. The study concluded that MIR184 mutations are not a major cause of KCN in the Iranian population [20].

Together, these findings underscore the need for standardized diagnostic approaches and regionally stratified epidemiologic studies to more accurately characterize the national burden of KCN in Iran.

Familial History

Family history and consanguinity have emerged as strong and consistent risk factors for keratoconus (KCN) in Iranian populations, reflecting the role of both genetic inheritance and population structure in disease susceptibility.

Rabei et al.,[1] identified parental consanguinity as a significant risk factor (OR = 1.76, P = 0.029). Family history in first-degree relatives had an odds ratio of 12.53 (P < 0.001), and in second-degree relatives,7.52 (P < 0.001).

Mohaghegh et al.,[10] identified a strong association between family history and KCN, with an odds ratio of 21.0 (95 % CI: 9.0-48.0, P < 0.001). Naderan et al.,[18] also found a significant association between family history and KCN in a Tehran-based case–control study of 461 KCN patients and 461 controls, with an odds ratio of 7.09 (95 % CI: 3.69-13.64, P < 0.001). The presence of additional KCN cases within a family was also associated with increased disease severity (P = 0.032 and P = 0.028).

Jamali et al.,[7] conducted a case-control study in Fars province comparing 415 KCN surgery patients to 415 controls. The proportion of parental first-cousin marriage was significantly higher in patients (35.4 %) than in controls (18.3 %). The mean inbreeding coefficient was 0.0291 in patients compared to 0.0135 in controls, a statistically significant difference (T = 8, df = 828, P < 0.001) [7]. These findings support consanguinity as a significant genetic risk factor for KCN in the Iranian population.

Hashemi et al.,[9] investigated familial aggregation in a rural Iranian population. The odds ratio was 1.63 (95 % CI: 1.12-3.41) for sibling pairs and 1.24 (95 % CI: 0.81-4.27) for parent-offspring relationships, with no elevated risk found among spouses [9].

These findings collectively support the hypothesis that familial aggregation and consanguinity contribute significantly to KCN risk in Iran, underscoring the importance of genetic counseling and population-specific genetic studies.

Environmental and Behavioral Factors

A range of environmental exposures, behavioral patterns, and demographic factors have been implicated in the etiology of keratoconus (KCN), often interacting with individual susceptibility to influence disease onset and progression in Iranian populations.

Rabei et al.,[1] also identified several independent risk factors, including severe eye rubbing (OR = 10.63, P < 0.001), vernal

keratoconjunctivitis (OR = 7.51, P = 0.003), and systemic conditions such as migraine, hypertension, or thyroid disease (OR = 6.83, P = 0.021). Socioeconomic status and education level were inversely associated with risk: the odds of KCN were significantly lower in individuals with higher income (OR = 0.31, P < 0.001) and education (OR = 0.18, P = 0.024). Residence in western Iran was associated with increased risk (OR = 2.07, P = 0.013), while individuals of Fars ethnicity showed lower odds (OR = 0.58, P = 0.042).

Naderan et al.,[18] also reported that eye rubbing (OR = 3.35, 95 % CI: 2.35-4.77, P < 0.001), itchy eyes (OR = 12.58, 95 % CI: 5.14-30.79, P < 0.001), and low educational level (OR = 1.34, 95 % CI: 1.13-1.59, P = 0.001) were significantly associated with KCN. Smoking and sun exposure were not statistically significant.

Mohaghegh et al.,[10] also found that elevated LDL cholesterol (≥110 mg/dL) was significantly associated with KCN, with an odds ratio of 3.00 (95 % CI: 1.20-6.40, P = 0.01).

Jamali et al.,[7] reported a strong association between KCN and eye rubbing, with an odds ratio of 6.8 (95 % CI: 3.92-11.82, P < 0.001). Use of sunglasses was also associated with increased odds of KCN (OR = 2.16, 95 % CI: 1.43-3.27, P < 0.001), while other factors such as allergies; asthma, eczema, and smoking were not statistically significant.

In the Shahroud Eye Cohort, no significant sex difference was observed in KCN prevalence: women had a prevalence of 0.79 % compared to 0.72 % in men [8]. However, patients with KCN had a significantly younger mean age (47.6 years) compared to non-keratoconic individuals (50.9 years) [8].

In contrast, a population-based study of 2667 rural residents in northern and southwestern Iran found a significantly higher prevalence in men (5 %) compared to women (3 %), with an odds ratio for male sex of 2.1 (95 % CI: 1.08-4.08, P = 0.031) [9]. The highest prevalence was observed in the 31-40 year age group (5 %) [9]. Collectively, these findings highlight the multifactorial nature of KCN risk in Iran, where environmental stressors, lifestyle behaviors, and socioeconomic determinants contribute alongside biological factors to regional and individual variability in disease burden.

A summary of KCN risk factors identified in Iranian populations, along with supporting evidence from key studies, is presented in table 2.

Discussion

Keratoconus (KCN) epidemiology in Iran reflects a complex interplay of genetic, environmental, and socioeconomic factors, with clear regional variability. Ziaei et al., [21] reported an annual incidence of 22.3 per 100,000 in Yazd province, substantially higher than rates reported in European populations, underscoring the importance of region-specific research into genetic and environmental determinants.

Multiple studies highlight the genetic architecture of KCN in Iran. Yari et al., [14] demonstrated associations with extracellular matrix-related genes, including COL4A4 and TIMP-1, and noted possible sex-specific protective mechanisms. They also suggested that oxidative stress susceptibility, influenced by variation in antioxidant defense genes, may contribute to disease pathogenesis. Supporting this, Sargazi et al.,[15] identified significant associations with KIF26B and COL4A4 polymorphisms, and Saravani et al.,[16] emphasized extracellular matrix disruption as

Table 2: Risk factors for KCN in Iranian populations

Risk Factor	Evidence from Iranian Studies	Key References
Genetic predispositions	Polymorphisms in COL4A4, TIMP-1, KIF26B, and LOX significantly associated with KC risk. VSX1 and MIR184 not major contributors.	Yari et al.,[14]; Sargazi et al.,[15]; Saravani et al.,[16]; Niazi et al.,[17]; Dehkordi et al.,[19]; Farzadfard et al.,[20]
Consanguinity	Common in specific ethnic groups (e.g., Baluchis, Sistanis, Iranian Arabs) with high inbreeding coefficients. Strongly associated with KCN risk.	Rabei et al.,[1]; Mehrjoo et al.,[6]; Jamali et al.,[7]
Family history	Very strong association in first- and second-degree relatives. Also linked to disease severity.	Rabei et al.,[1]; Hashemi et al.,[9]; Mohaghegh et al.,[10]; Naderan et al.,[18]
Eye rubbing	Strong independent risk factor. Frequently reported and often associated with itchy eyes and vernal keratoconjunctivitis.	Rabei et al.,[1]; Jamali et al.,[7]; Naderan et al.,[18]
Atopy (eczema, asthma)	Inconsistent statistical significance. Often linked indirectly through increased eye rubbing behavior.	Jamali et al.,[7]
Environmental (UV, humidity)	Higher KC prevalence in rural/southern/western regions, likely related to sun exposure and dryness. Fars ethnicity associated with lower risk.	Rabei et al.,[1]; Hashemi et al.,[9]
Sex / Hormonal factors	Mixed findings. No significant difference in Shahroud cohort. Higher prevalence in men observed in another population-based study.	Hashemi et al.,[8,9]
Socioeconomic factors	Lower income and educational level significantly associated with increased risk.	Rabei et al.,[1]; Naderan et al.,[18]
Lipid profile	Elevated LDL cholesterol (≥110 mg/dL) associated with KCN.	Mohaghegh et al.,[10]
Sunglasses use	Associated with higher KCN odds in one study.	Jamali et al.,[7]

a key pathway. Yet, studies such as Dehkordi et al.,[19] and Farzadfard et al.,[20] found no pathogenic mutations in VSX1 or MIR184, indicating that the genetic basis is likely polygenic and still incompletely defined.

Environmental and geographic variation also plays a substantial role. Shabani et al.,[5] identified low relative humidity as a global risk factor for KCN, mediated by mechanisms such as dry eye, allergic inflammation, and corneal thinning. Shahram et al.,[22] in their study from Mashhad, observed a younger

age of onset (mean 17.7 years), a female predominance, and strong associations with vernal keratoconjunctivitis, all pointing to distinct regional clinical profiles. Omer [2] emphasized that UV exposure may exacerbate oxidative collagen degradation, particularly in arid climates, which aligns with Iranian data showing clustering of cases in sunny and dry regions.

Sociodemographic factors also modulate risk. Rabei et al.,[1] illustrated that consanguinity, family history, allergic disease, and low socioeconomic status act synergistically in increasing susceptibility. Notably, risk was higher in western provinces and among non-Fars ethnicities. Rafati et al.,[12] reported a relatively late mean age at diagnosis (31 years) in Tehran, possibly reflecting delayed detection or population-specific risk profiles.

Behavioral and inflammatory mechanisms remain central. Eye rubbing and itchy eyes were strongly associated with KCN in studies by Rabei et al.,[1] Naderan et al.,[18] and Jamali et al.,[7].

A meta-analysis encompassing over 15 countries confirmed consistent links between KCN and risk factors such as eye rubbing, allergy, and asthma [23], findings mirrored in Iranian data. Educational attainment also emerged as a modifying factor; lower levels were associated with increased disease risk [18].

Prevalence estimates across Iran range from 0.76 % in Shahroud [8] to 4.0 % in rural regions [9], with 3.3 % reported in Tehran [11]. These disparities likely reflect a combination of ethnic, environmental, and diagnostic differences. Notably, Hashemi et al.,[11] found higher prevalence among non-Persians (OR = 3.33). Sex-related trends were inconsistent: while the Shahroud Eye Cohort[(8)] found no significant difference, rural studies [9] reported higher rates in men (OR = 2.1), suggesting behavioral or environmental modifiers may be at play.

Familial aggregation further supports heritable influences, particularly in rural populations and among siblings [9,18]. However, the absence of definitive mutations in candidate genes such as VSX1 and MIR184 implies a complex polygenic or multifactorial etiology [19,20].

Altogether, the Iranian evidence converges with international literature while adding region-specific insights. To advance the field, future national research should prioritize genome-wide studies, environmental exposure profiling, and standardized diagnostic protocols across provinces. Such efforts will be critical for unraveling the multifactorial nature of KCN and informing tailored public health strategies.

This review is limited by the narrative design, which precludes formal quality assessment or meta-analytic synthesis of findings. Variability in diagnostic criteria, age groups, and imaging modalities across included studies may have introduced heterogeneity that affects comparability. Additionally, regional gaps in data, particularly from central and southeastern provinces, limit national generalizability. Furthermore, the paucity of published studies on keratoconus in Iran (n=20) highlights systemic challenges in regional research infrastructure and prioritization, particularly in underrepresented provinces such as Sistan-Baluchestan and Kerman. While we synthesized all accessible evidence, the limited data availability necessitates cautious interpretation of prevalence estimates and risk factor associations.

Future research should prioritize standardized, multicenter epidemiologic studies with uniform diagnostic protocols. Integration of genomic screening, environmental exposure mapping, and longitudinal follow-up is

recommended to clarify gene–environment interactions and refine early detection strategies. Development of a national KCN registry could facilitate surveillance and targeted public health interventions. The scarcity of studies identified in this review underscores the urgency of collaborative initiatives between Iranian institutions and international consortia to fund large-scale, population-level surveillance. Such efforts should prioritize genetic validation studies, environmental exposure mapping, and equitable representation of Iran's ethnic and geographic diversity.

Conclusion

KCN in Iran exhibits substantial regional, ethnic, and genetic diversity. Gene–environment interactions appear central to disease risk. National-level surveillance, standardized diagnostics, and multicenter genetic studies are needed to improve early detection and guide tailored interventions. The scarcity of available studies underscores the urgent need for expanded epidemiological and genetic research to address regional disparities and refine preventive strategies.

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Footnotes and Financial Disclosures

Conflict of interest:

The authors have no conflict of interest with the subject matter of the present manuscript.