

The Prevalence and Risk Factors for Keratoconus: A Systematic Review and Meta-Analysis

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Purpose: This study was conducted to determine the prevalence and risk factors for keratoconus worldwide.

Methods: In this meta-analysis, using a structured search strategy from 2 sources, 4 electronic databases (PubMed, Web of Science, Google Scholar, and Scopus) and the reference lists of the selected articles were searched from inception to June 2018 with no restrictions and filters. The outcome of the study was the prevalence of keratoconus and its risk factors, including eye rubbing, family history of keratoconus, atopy, allergy, asthma, eczema, diabetes type I and type II, and sex.

Results: In this study, 3996 articles were retrieved, of which 29 were analyzed. These 29 articles included 7,158,241 participants from 15 countries. The prevalence of keratoconus in the whole population was 1.38 per 1000 population [95% confidence interval (CI): 1.14–1.62 per 1000]. The prevalence of keratoconus was 20.6 per 1000 (95% CI: 11.68–28.44 per 1000) in men and 18.33 per 1000 (95% CI: 8.66–28.00 per 1000) in women in studies reporting sex. The odds ratio of eye rubbing, family history of keratoconus, allergy, asthma, and eczema was 3.09 (95% CI: 2.17–4.00), 6.42 (95% CI: 2.59–10.24), 1.42 (95% CI: 1.06–1.79), 1.94 (95% CI: 1.30–2.58), and 2.95 (95% CI: 1.30–4.59), respectively.

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Conclusions: The results of this study, as the most comprehensive meta-analysis of keratoconus prevalence and risk factors, showed that keratoconus had a low prevalence in the world and eye rubbing, family history of keratoconus, allergy, asthma, and eczema were the most important risk factors for keratoconus according to the available evidence.

Key Words: keratoconus, risk factors, meta-analysis

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Keratoconus is the most common cause of corneal transplant in developing countries. It is a noninflammatory, mostly asymmetric, progressive disease, resulting in corneal thinning, irregular astigmatism, and eventually severe vision loss.^{1,2} This multifactorial disease, which is influenced by environmental and genetic factors, usually starts in the second or third decade of life and imposes heavy financial burdens on economically active groups of the society.^{1,3,4} Although many studies have shown that keratoconus affects both sexes with no significant difference,^{5,6} a few studies have reported a sexual predilection.^{3,7–10} It has been shown that eye rubbing,¹¹ atopy,⁸ exposure to sunlight, miscellaneous factors (including the use of environmental and industrial toxins), age, family history of the disease,⁴ ethnic differences,¹² and contact lens use¹³ are the most important environmental risk factors for keratoconus. Moreover, there is evidence of the role of VXX1¹⁴ and SOD1 (1%)¹⁵ in the pathogenesis of keratoconus, highlighting the effect of genetic factors. An autosomal dominant and sporadic pattern is the most common pattern in familial keratoconus.⁴

Moreover, the results of a systematic review revealed the role of cytokines and inflammatory pathways in damage to the corneal tissue.¹⁶

The prevalence of keratoconus ranges from 0.17 in 1000 in the United States¹⁷ to 40 in 1000 in Iran³; this difference could be because of differences in the methodology and design of the studies, genetic factors, geographical locations, environmental exposures, and diagnostic criteria and instruments.¹⁸ Many nonsystematic review studies have been conducted to report the risk factor for keratoconus in recent years,^{4,12,19} but there is no consensus on the total prevalence of keratoconus and the effect size of each risk factor. Therefore, this systematic review and meta-analysis was performed to determine the global prevalence of

keratoconus and some of its most important risk factors using population-based studies.

MATERIALS AND METHODS

Four international databases (Web of Science, PubMed, Scopus, and Google Scholar) were searched for relevant articles until June 2018. All observational epidemiological studies that evaluated the prevalence and risk factors for keratoconus in the world and presented the required information in the body, figures, or tables of the article were accepted with no restrictions.

Search Strategy

A combination of the key words such as “keratoconus,” “KC,” “observational studies,” “cross-sectional studies,” “case-control studies,” “cohort studies,” and “survey” were used to search the databases of Web of Science, PubMed, Google Scholar, and Scopus from inception to June 2018. The text words and MeSh terms of all key words were used during the search. In addition, the reference lists of relevant articles were scanned for articles of interest.

Inclusion Criteria

All stages of the study followed the PRISMA guidelines.²⁰ Observational epidemiological studies including cross-sectional, case-control, and cohort studies that had a population-based design and reported the prevalence and odds ratio (OR) for calculating pooled prevalence and OR were included in this study. If several studies were conducted in a certain population, the study with a higher quality was included in the analysis. Studies which did not meet 1 or more inclusion criteria were excluded from the study. The outcome of the study was the prevalence of keratoconus and its risk factors, including eye rubbing, family history of keratoconus, atopy, allergy, asthma, eczema, sunlight exposure, use of hat and gloves, history of diabetes type I and type II, and sex. To evaluate the prevalence of keratoconus, all studies that reported the total prevalence of keratoconus or its prevalence according to age and sex were included in the study. Few studies reported the prevalence of keratoconus according to age; therefore, the final analysis was not performed according to age. Moreover, because a limited number of studies investigated risk factors such as sunlight exposure and use of hat and gloves, these risk factors were not analyzed because of limitation in the extracted data.

Data Extraction and Statistical Analysis

Two reviewers (E.H. and M.S.) independently screened the search results to ensure each article met the inclusion criteria. After excluding duplicates, the reviewers scanned the titles and abstracts of the retrieved articles for relevance. Then, after applying the exclusion criteria, all remaining articles were read in full. A kappa coefficient of 82% indicated a good interrater agreement. Disagreement was

resolved by discussion or by calling in an expert for arbitration. The variables that were investigated in this study were the first author name, publication year, study location (city and country), mean age and sex of participants, study design, type of study population, eye rubbing, family history of keratoconus, atopy, allergy, eczema, asthma, sunlight exposure, use of hat and gloves, and history of diabetes type I and type II.

The quality of the studies regarding methodology and reporting was evaluated using a STROBE checklist for cross-sectional, case-control, and cohort studies. The following factors were considered for bias assessment: outcome assessment bias, exposure assessment bias, clear description of sample size calculation, information bias, and selection bias. If a study had none of the above, it was considered a high-quality study. A study with 1 bias was considered a medium-quality study, and the presence of at least 2 biases indicated a low-quality study. However, because of the limited number of articles in each subgroup, studies were included in the meta-analysis regardless of their quality.

The Cochran Q-test of heterogeneity at a significance level of 5% was applied to evaluate statistical heterogeneity of the studies, and I^2 was used for quantitative assessment of heterogeneity among the results according to the Higgins classification in which an I^2 value above 75% is indicative of heterogeneity. The Begg and Egger tests were applied to investigate publication bias.

The outcomes of interest, including the prevalence of keratoconus and OR of developing keratoconus after exposure to risk factors, were calculated and reported with a 95% confidence interval (CI). All values of standard errors were calculated using binomial distribution.

The prevalence of keratoconus was reported per 1000 population. Moreover, a meta-regression model was developed to evaluate the effects of sex, sample size, publication year, and keratoconus measurement method as factors contributing to heterogeneity in the prevalence of keratoconus.

Stata version 11 (Stata Corp, College Station, TX) was applied for analysis using a random-effects model at 95% CI.

RESULTS

Our search yielded 3996 articles, 3708 through databases and 288 through manual search of the reference lists of selected articles. After removing duplicates, the titles and abstracts of 3111 articles were scanned. In the next step, 3012 articles were removed considering the exclusion criteria and 99 articles were read in full. Quality assessment of the retrieved articles using the PRISMA guidelines resulted in exclusion of 70 articles; therefore, 29 studies (see Supplemental Table 1, Supplemental Digital Content 1, <http://links.lww.com/ICO/A902>) conducted on 50,358,341 subjects in 15 countries were eventually included in the final analysis (Fig. 1).^{1–3,7,9,17,21–43} Of these 29 articles, 15 reported the total prevalence of keratoconus, according to which the total prevalence of keratoconus in the whole population was 1.38 per 1000 population (95% CI: 1.14–1.62 per 1000) (Fig. 2).

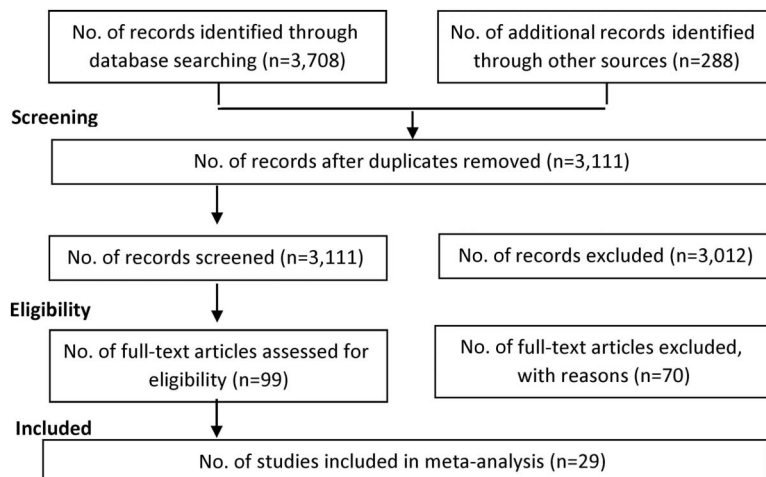


FIGURE 1. Flow of information through different phases of the systematic review.

Because 4 of 5 large studies included in this meta-analysis (Godefrooij, Hobstetter, Merdler, and Reeves) which had the highest weights in analysis did not report the prevalence of keratoconus according to sex, the total prevalence of keratoconus and its prevalence according to sex were estimated using the studies that reported the prevalence in both genders (10 articles). The prevalence of keratoconus was 23.96 per 1000 (95% CI: 15.79–39.13 per 1000) in all subjects, 18.99 per 1000 (95% CI: 9.25–28.83 per 1000) in women, and 21.13 per 1000 (95% CI: 12.01–30.25 per 1000) in men (Fig. 3).

According to the meta-regression results, sex (P value = 0.692), publication year (P value = 0.295), keratoconus measurement method (P value = 0.331), and sample size (P

value = 0.157) had no significant effect on the prevalence of keratoconus. Table 1 presents the OR of risk factors and their CIs.

The OR of keratoconus in men versus women was 1.01 (95% CI: 0.69–1.33).

The OR of eye rubbing (Fig. 4), family history of keratoconus (Fig. 5), atopy, allergy (Fig. 6), asthma (Fig. 7), and eczema (Fig. 8) was 3.09 (95% CI: 2.17–4.00), 6.42 (95% CI: 2.59–10.24), 1.12 (95% CI: 0.40–1.85), 1.42 (95% CI: 1.06–1.79), 1.94 (95% CI: 1.30–2.58), and 2.95 (95% CI: 1.30–4.59), respectively. The OR of developing keratoconus in subjects with diabetes type I and type II was 0.73 (95% CI: 0.26–2.06) and 0.77 (95% CI: 0.50–1.21), respectively.

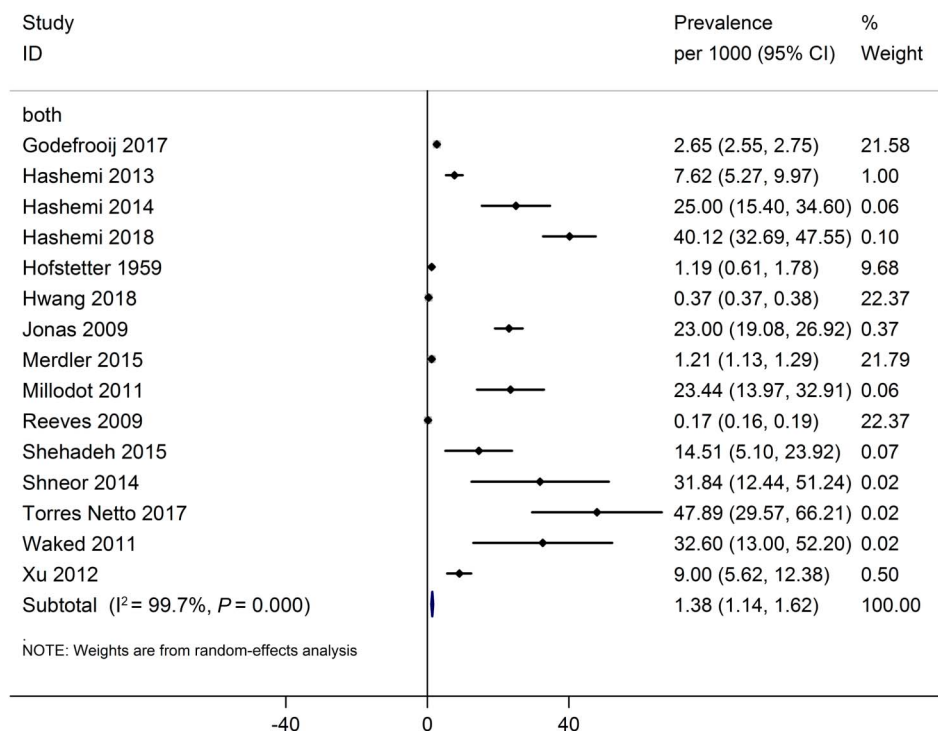


FIGURE 2. Forest plot of the prevalence of keratoconus in the world population.

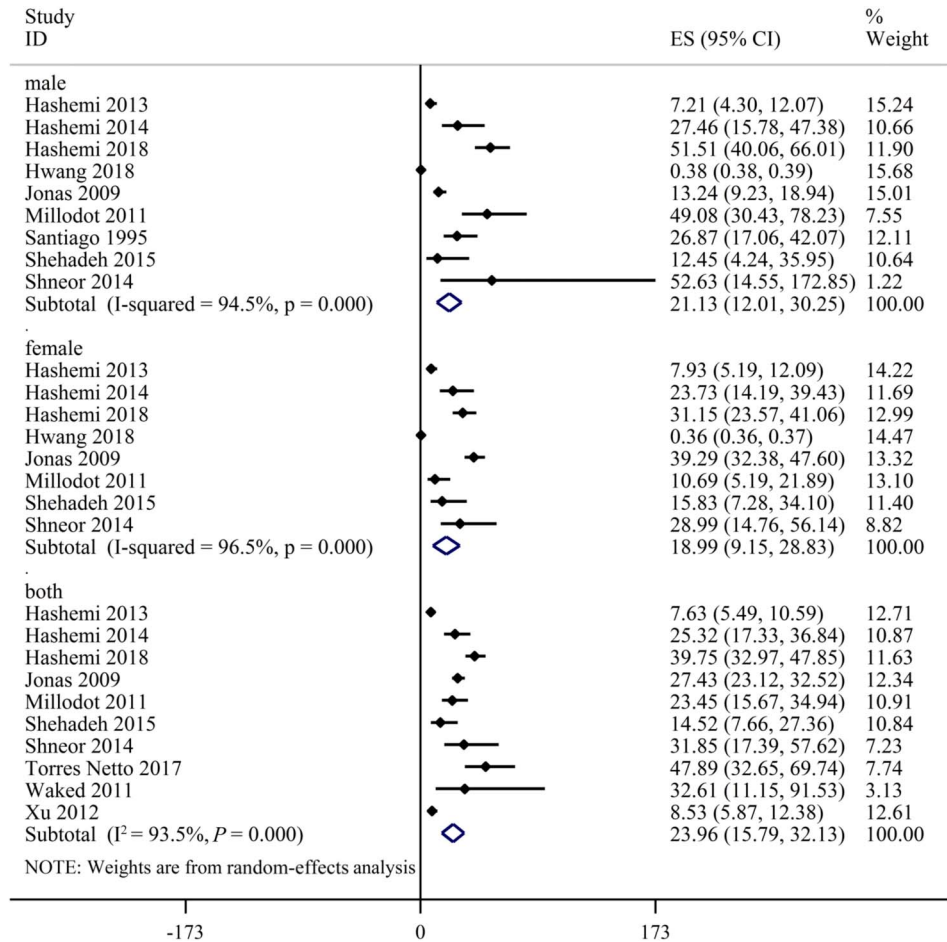


FIGURE 3. Forest plot of the prevalence of keratoconus by sex.

DISCUSSION

As mentioned earlier, approximately 100 articles have investigated the prevalence and risk factors for keratoconus across the world. Although some previous review studies investigated the risk factors for keratoconus in the past, their nonsystematic design,¹⁹ geographical restrictions in the literature search,¹² and focusing on a certain risk factor¹¹ or age group⁴⁴ are some of their weaknesses that limit comparison of the results.

According to our findings, the prevalence of keratoconus was 1.38 per 1000 (95% CI: 1.14–1.62 per 1000) in

the world's population. According to Figure 2, the highest prevalence and lowest prevalence of keratoconus were reported by Torres Netto et al² in a Saudi population and Reeves et al¹⁷ in an American population, respectively. It is important to consider the following factors regarding the wide range of the reported prevalence in population-based studies:

1. Sample size differences: the sample size of the included studies ranged from 92 subjects in a study conducted in Lebanon³⁹ to 47 million subjects in the South Korea National Study.²⁶
2. Inconsistency in the sex ratio of subjects: male subjects comprised 10% to 60% of the study population in different studies.
3. Use of different diagnostic methods including topography, tomography, autorefractokeratometry, clinical examination, and Placido disc: more than 90% of the articles in this meta-analysis used topography methods.
4. Response and nonresponse rates.

Moreover, the wide range of the reported prevalence may be suggestive of the role of genetics and ethnicity in developing this disease. Although the prevalence of keratoconus ranges from 0.5 to 2.3 per 1000 population in Western countries according to Rabinowitz,⁵ it is more than

TABLE 1. Effect of Risk Factors on Keratoconus

Variable	OR	CI 95%
Sex (men)	1.01	0.69–1.33
Eye rubbing	3.09	2.17–4.00
Family history of keratoconus	6.42	2.59–10.24
Atopy	1.12	0.40–1.85
Allergy	1.42	1.06–1.79
Asthma	1.94	1.30–2.58
Eczema	2.95	1.30–4.59
Diabetes type I	0.73	0.26–2.06
Diabetes type II	0.77	0.50–1.21

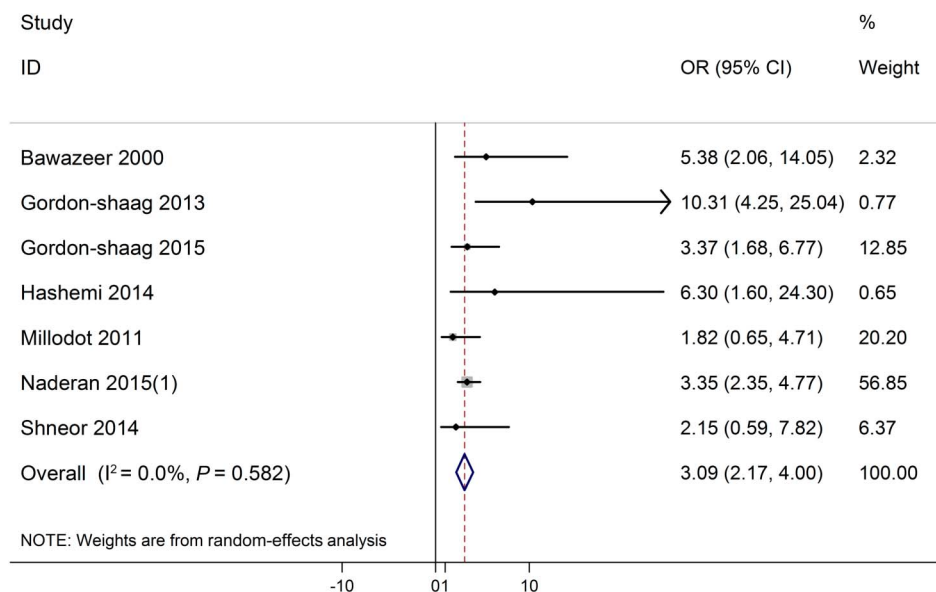


FIGURE 4. Forest plot of OR estimates of keratoconus by eye rubbing.

23 per 1000, that is, 10 times more common, in Jews living in Jerusalem.⁹ Hashemi et al⁴³ also reported that the prevalence of keratoconus was 3 times more common in non-Fars Iranian ethnic groups, such as Turks, Arabs, and Kurds, than the Fars population. Gordon-Shaag reported a prevalence of 0.003 to 23 per 1000 population in a nonsystematic review study; however, many of the studies included in this review were hospital-based and therefore could not provide an accurate estimate of the disease in the general population. Hence, considering all limitations for a meta-analysis of keratoconus prevalence and the weakness of the available review studies, our study showed an estimate of 1.3 per 1000 population for the global prevalence of this disease.

Although animal studies have shown that keratoconus subsets are gender specific,⁴⁵ human epidemiological studies

have reported contradictory results regarding the correlation of sex and keratoconus,^{3,7,27,34} ranging from a 2 to 5 times higher prevalence in men^{9,46} to a higher prevalence in women.⁴² According to our findings, although the odds of developing keratoconus were only 1% higher in men compared with women, indicating a nonsignificant difference, a higher OR for KCN in men in some studies is not an unexpected finding considering more outdoor activities of men resulting in more exposure to environmental factors such as sunlight exposure. On the other hand, some studies have shown that the age of onset of keratoconus differs in male and female patients; therefore, differences in the age range of the study population may be a reason for discrepant results in men and women.

Eye rubbing is one of the most important risk factors for keratoconus according to some epidemiological studies.^{21,24}

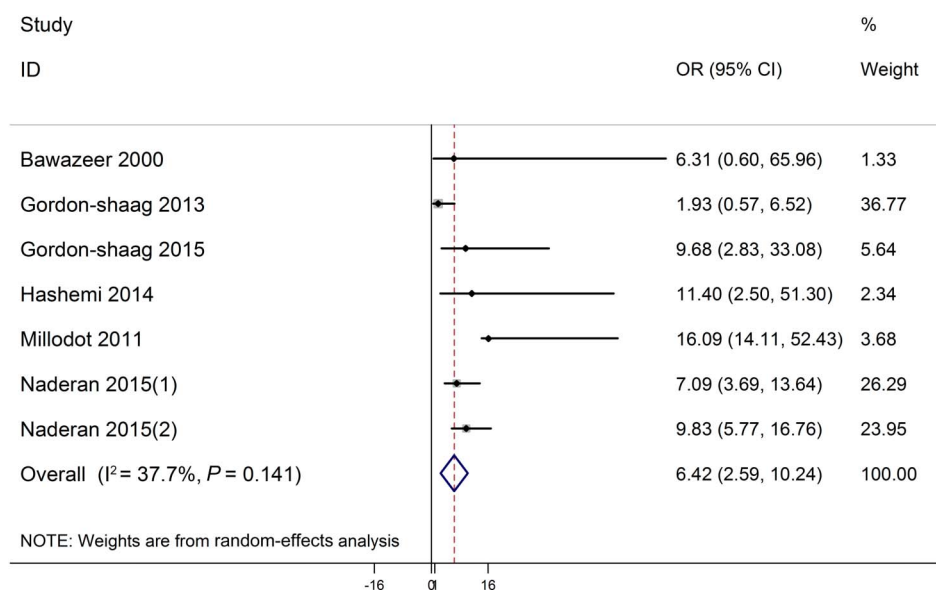


FIGURE 5. Forest plot of OR estimates of keratoconus by family history.

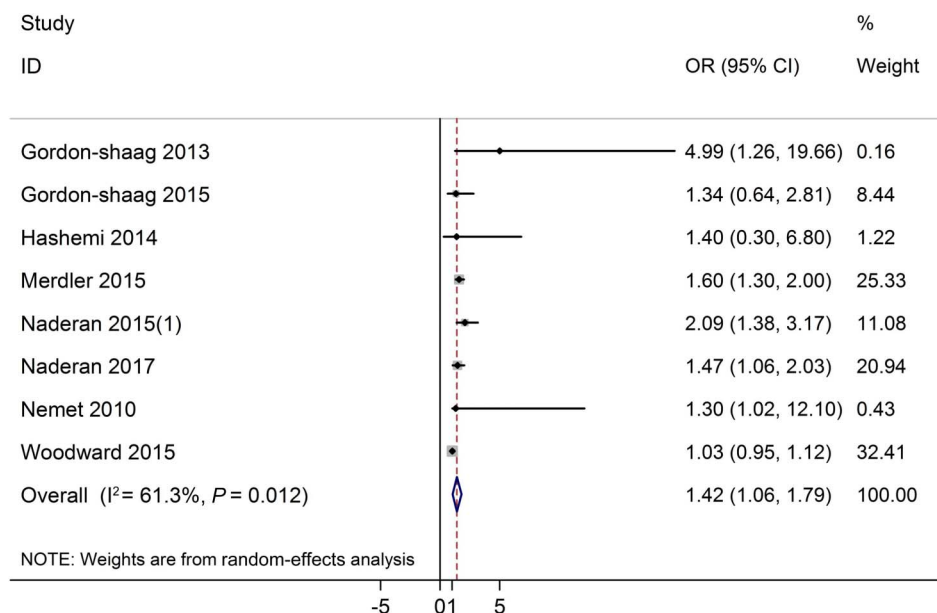


FIGURE 6. Forest plot of OR estimates of keratoconus by allergy.

The results of our study showed that the OR of developing keratoconus was 3 times higher in subjects who had abnormal eye rubbing on a daily basis compared with those who did not have this habit. Except for 2 studies,^{7,9} other studies included in this meta-analysis reported an OR of 3.35 to 10.31 for this risk factor. Use of different definitions and criteria for abnormal eye rubbing is one of the most important challenges of the comparison of different studies.

Among risk factors evaluated in this meta-analysis, family history was identified as the strongest risk factor. An important factor in estimating the effect of family history is the method of collecting the family history data, which is performed either by self-report measures^{7,23} or through valid measurement methods such as videokeratography.^{3,47,48} Family history data were collected through questionnaires, face-

to-face interviews, and telephone interviews in most studies included in our meta-analysis. Gordon-Shaag²³ reviewed studies evaluating the frequency of a positive family history in keratoconus patients from 1974 to 2015 and reported a clear difference in having a positive family history between countries and ethnic groups and higher prevalence of keratoconus among larger households.

Although asthma, allergy, and eczema were all identified as effective risk factors for keratoconus in this meta-analysis, a condition known as atopy did not increase the risk of this disease. There are controversial results about the role of atopy in the literature. Although some large studies have shown a significant correlation between atopy and keratoconus,^{9,44} some other studies have failed to demonstrate a significant difference in the frequency of atopy between

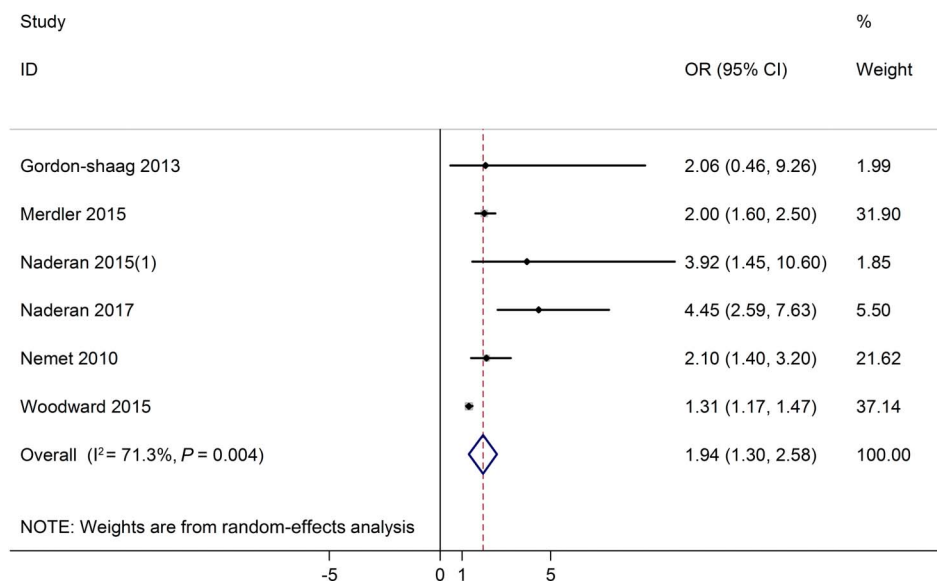


FIGURE 7. Forest plot of OR estimates of keratoconus by asthma.

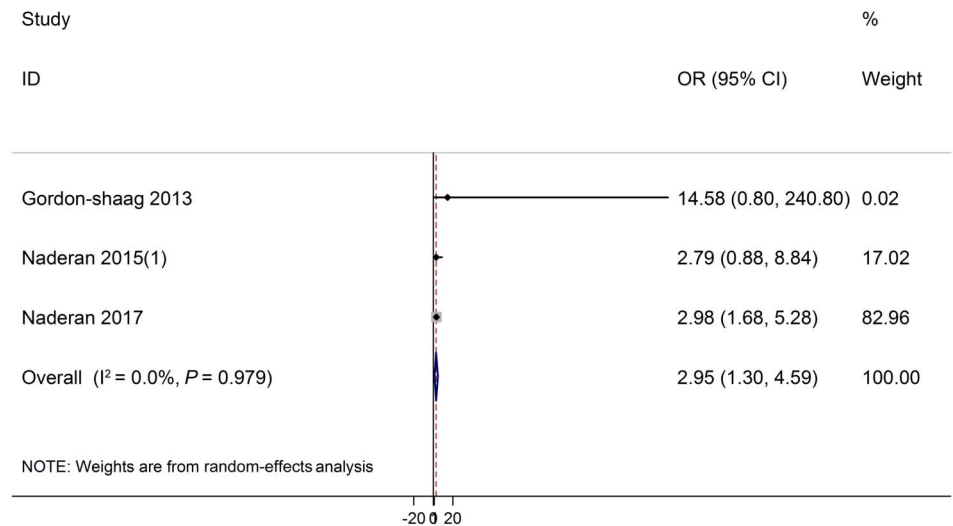


FIGURE 8. Forest plot of OR estimates of keratoconus by eczema.

cases and controls.^{23,30,49} One of the reasons for this discrepancy in results may be because of differences in the definition of atopy. Some studies used allergy alone, some used allergy and asthma, and some other studies only used asthma to define atopy. On the other hand, having an atopic disease such as allergy is the most important cause of eye rubbing, which is one of the most important risk factors for keratoconus. Therefore, atopy is in a causal pathway of keratoconus and can be considered an indirect cause of keratoconus.

Diabetes is another risk factor whose association with keratoconus has been less investigated compared with other risk factors with variable results. Kosker et al²⁸ conducted a large case-control study in more than 5500 subjects to investigate the correlation of diabetes and keratoconus and reported that the prevalence of diabetes was 2% higher in patients with keratoconus; moreover, the odds of developing keratoconus were 1.4 times higher in diabetic versus healthy subjects. This case-control study was clinic-based, and the difference in the prevalence of diabetes between the general population and populations selected from clinics to serve as the control group may be an important reason for these findings. Another important finding of this study was a relationship between diabetes and severity of keratoconus. Although Kuo et al²⁹ found no relationship between diabetes and keratoconus, Seiler et al³⁷ reported that diabetes was a protective factor against keratoconus. To explain this discrepancy, our findings of the meta-analysis of 6 studies (2 reporting the protective effects of diabetes, 1 reporting it as a risk factor, and 3 reporting a nonsignificant relationship) showed that the odds of developing keratoconus were 23% lower in type II diabetic patients, but the relationship was not significant. However, it should be considered that all studies included in our meta-analysis were cross-sectional or case-control studies, which are more prone to information and selection bias compared with cohort studies. Therefore, conducting cohort studies and meta-analysis of their results can provide more reliable information in this regard.

CONCLUSION

The most valid population-based studies were analyzed in this meta-analysis as the most comprehensive meta-analysis of the prevalence and risk factors for keratoconus. We believe that the prevalence of keratoconus is 1.38 per 1000 population in the world according to studies published until June 2018. Moreover, eye rubbing, allergy, asthma, and eczema, and positive family history of keratoconus are the most important risk factors for this disease, and sex, atopy, and diabetes have no correlation with keratoconus. Age, living in places with certain meteorological conditions, and genetic factors may be other important risk factors that were not assessed in this meta-analysis because of a lack of relevant data in the included articles or methodological limitations.

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