Original Article | Clinical Studies

Ten-year incidence of keratoconus in relation to sex, age, and thyroid gland dysfunction: a nationwide population-based cohort study (2009–2018)

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Background: Keratoconus is a corneal ectatic disorder that often leads to visual impairment and may require corneal transplantation. However, its age and gender-based incidence and potential association with thyroid gland dysfunction (TGD) remain poorly understood. This study aims to clarify these aspects and investigate the possible connection between keratoconus and TGD.

Methods: We conducted a nationwide population-based cohort study using data from the Korean National Health Insurance Service database. A retrospective chart review was conducted on 4,059,021 patients aged over 20 without underlying corneal diseases in 2009. The end of the review period was at ten years, or until the onset of keratoconus. To evaluate the association with TGD, multivariate Cox regression analysis was used with adjustment of confounding variables such as sex and age.

Results: During the review period, 2,334 patients developed keratoconus before the 10-year mark. Females exhibited a higher keratoconus incidence (7.101 per 100,000 person-years) compared to males (5.559) (P<0.001). After adjusting for age, the hazard ratio (HR) for keratoconus was 1.295 times higher [95% confidence interval (CI): 1.193–1.406] in females compared to males. Age groups were stratified in 10-year intervals. The highest incidence of keratoconus was observed in the 20 to 29-year age group (10.695 per 100,000 person-years). All other age groups had significantly lower HR values, with the lowest at 50–59 years (0.508, 95% CI: 0.447–0.577). Keratoconus incidence per 100,000 person-years was 6.227 in subjects without TGD, 6.019 in the hypothyroidism group and 8.287 in the hyperthyroidism group, respectively. Although not statistically significant, individuals with hyperthyroidism showed a higher HR (1.290, 95% CI: 0.939–1.771) for keratoconus when compared to those without TGD, after adjusting for age and sex.

Conclusions: This study emphasizes a female predominance in keratoconus incidence and suggests a possible connection between hyperthyroidism and keratoconus. Furthermore, it affirms a higher incidence of keratoconus among young individuals.

Keywords: Keratoconus; thyroid gland dysfunction (TGD); incidence

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Introduction

Keratoconus is a bilateral corneal ectatic disorder characterized by progressive thinning and steeping of the cornea that causes irregular astigmatism and eventually visual impairment (1,2). Typically, mild cases are managed with glasses or contact lenses, cross-linking but about 20% of keratoconus patients require corneal transplantation (3). Conventional penetrating keratoplasty (PK) or deep anterior lamellar keratoplasty (DALK) may be conducted in the late or advanced stage of protrusion (4).

Keratoconus usually develops in the second or third decade of life. In many cases, it progresses until the third to fourth decade (1). It has historically been considered as a multifactorial disease caused by a combination of genetic components and environmental factors (1,3). The reported associated factors for keratoconus include ocular allergy, atopic dermatitis, connective tissue disease, and trisomy 21 (5-7). Furthermore, hormonal imbalances affect corneal metabolism and may be associated with keratoconus (8).

Recent literature suggests that there is a possible association between the thyroid gland dysfunction (TGD) and keratoconus (8). TGD is also frequently associated with ocular diseases such as Graves' eye disease (9). A previous study indicated a prevalence of TGD of 13.6% in keratoconus patients (10). In contrast, other studies did not show keratoconus to be attributable to hypothyroidism alone (11,12). However, study design choices may have limited the ability to find a strong relationship between TGD and keratoconus (8,10-12).

Epidemiological studies so far have shown wide variation globally in prevalence and incidence of keratoconus (1,13). It has been estimated to be 1.5 to 22.3 per 100,000 persons/year, respectively (14,15). Keratoconus also affects all ethnicities and both sexes (1,16). Though a higher prevalence in men was shown in some recent studies (17-19), there was no sex predisposition in a previous population-based study in South Korea (13).

Recently, the Korean National Health Insurance Service (KNHIS) database has become available for medical research in South Korea. The KNHIS includes a complete set of health data covering approximately 50 million of the South Korean population (20). Thus, we analyzed a nationwide representative sample of 4,059,021 patients using the KNHIS claims database from 2009 through 2018. This study aimed to identify gender differences in the development of keratoconus and determined the incidence of clinically diagnosed keratoconus in patients with TGD in South Korea. We present this article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-23-1906/rc).

Highlight box

Key findings

- This study revealed a gender disproportion in keratoconus incidence, indicating a higher prevalence among females (7.101 per 100,000 person-years) compared to males (5.559). Moreover, the peak incidence is observed within the 20–29 age group (10.695), followed by a discernible decline with advancing age.

What is known and what is new?

- Keratoconus causes visual impairment and may require corneal transplantation.
- A pronounced female predominance was found in keratoconus incidence, and an examination of potential associations with hyperthyroidism adds novel insights.

What is the implication, and what should change now?

- Attention to clinical awareness, especially targeting young females, is crucial. Additionally, there is a proposal to integrate thyroid screening in keratoconus cases and advocate for prioritized research on the thyroid-keratoconus link to formulate preventive strategies.

Methods

Data source

The Korean National Health Insurance Service is a government organization that manages a national insurance system in Korea, covering approximately more than 95% of the Korean population (21-23). Detailed information on the KNHIS is provided elsewhere (20,24). In this retrospective cohort study, we used data from health insurance claims in the KNHIS Database from 2009 to 2018 in which diagnoses are recorded using the Korean Classification of Disease (KCD).

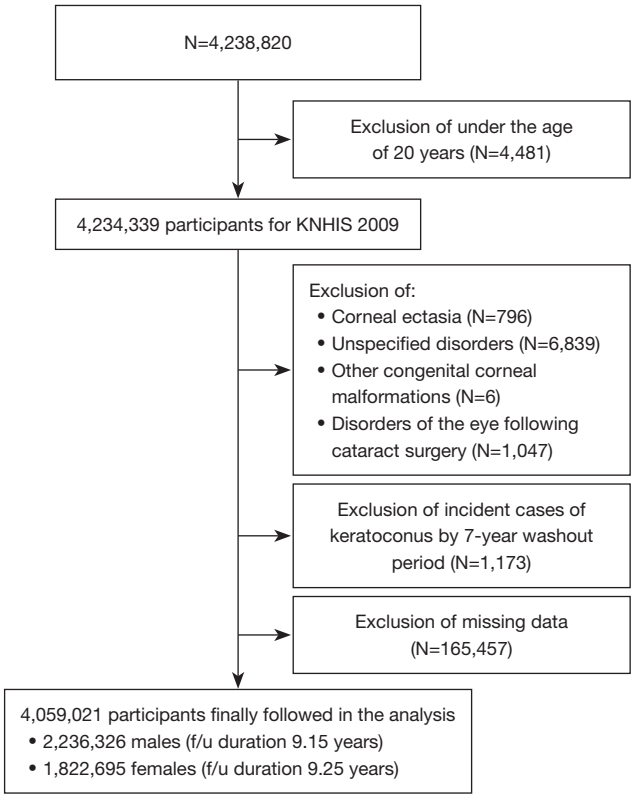

Figure 1 The flowchart used to identify cases of keratoconus in national claims database. KNHIS, Korean National Health Insurance Service; f/u, follow-up.

We collected a nationally representative cohort sample of 4,238,820 by selecting a random sample (40%) of the entire population enrolled in KNHIS who underwent a health check-up in 2009. Stratified random sampling was performed according to sex and age in 2009. The present study utilized this data set, and each patient's identification number was anonymized to protect the individual's privacy. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Baekseok University (IRB No. BUIRB-202007-HR-009). Informed consent was waived for this retrospective study.

Study population

The flowchart depicting the overall study design is described in *Figure 1*. The index year was set at 2009, and data was initially reviewed from a total of 4,238,820 medical claims in the KNHIS database, of which 4,234,339 were adults (subjects aged 20 years and older in 2009). From the 4,234,339 subjects, we excluded those who had other corneal disorders such as corneal ectasia (n=796) (H187), unspecified disorders (n=6,839) (H189), other congenital corneal malformations (n=6) (Q134), or disorders of the eye following cataract surgery (n=1,047) (H590). Among the remaining subjects, we used a 7-year wash-out period to remove any potential preexisting cases of keratoconus. We excluded those who were diagnosed with keratoconus in 2002 and 2008 and only included those who were first diagnosed with keratoconus after 2008 (e.g., in 2009). We further excluded subjects with missing data (n=165,457). Therefore, 4,059,021 eligible individuals were followed up for this study through 2009 until 2018.

Identification of keratoconus and TGD cases

Keratoconus cases were designated as patients over 20 years of age with newly diagnosed keratoconus (H186) between January 1, 2009, and December 31, 2018, as diagnosed by an ophthalmologist. For the patients with multiple events recorded on different dates, only the first chronological event was included in the analysis. The incidence of keratoconus per 100,000 person-years for 2009 through 2018 was calculated as the number of people who developed keratoconus divided the number of the total population during the study period. Hence, these cases were regarded as new incident cases of keratoconus.

TGD was classified into the following two categories. Hyperthyroidism was defined as KCD-code E05, and hypothyroidism was defined as KCD-code E02 or E03.

Statistical analysis

Data is presented as frequency and percentage (categorical) or mean ± standard deviation (continuous variables). The baseline characteristics between groups with and without keratoconus were compared using Student's *t*-test and chi-square. Incidence for keratoconus per 100,000 person-years was calculated. Kaplan-Meier curves were used to calculate the incidence of keratoconus between male and female using probability. To examine the hazard ratio (HR) of keratoconus for the incidence of age or sex and TGD, the Cox proportional hazard model was used to perform crude or adjustment models. HR was calculated with a 95% confidence interval (CI). Statistical tests were performed using SAS Version 9.4 (SAS Institute, Inc., Cary, NC, USA). P values <0.05 were considered statistically significant.

Table 1 The distributions of socio-demographic and clinical characteristics in the 4,059,021 adults of the current study

Characteristics	Total (n=4,059,021)	Keratoconus (n=2,334)	No keratoconus (n=4,056,687)	P value
Age, years				<0.001
20–29	497,102 (12.2)	495 (21.2)	496,607 (12.2)	
30–39	776,329 (19.1)	456 (19.5)	775,873 (19.1)	
40–49	1,066,982 (26.3)	380 (16.3)	1,066,602 (26.3)	
50–59	860,656 (21.2)	441 (18.9)	860,215 (21.2)	
60–69	550,615 (13.6)	407 (17.4)	550,208 (13.6)	
≥70	307,337 (7.6)	155 (6.6)	307,182 (7.6)	
Sex				<0.001
Male	2,236,326 (55.1)	1,137 (48.7)	2,235,189 (55.1)	
Female	1,822,695 (44.9)	1,197 (51.3)	1,821,498 (44.9)	
Income, low 25%	870,489 (21.4)	531 (22.8)	869,958 (21.5)	0.13
Diabetes	357,166 (8.8)	246 (10.5)	356,920 (8.8)	0.003
Hypertension	198,307 (27.1)	647 (27.7)	1,097,660 (27.1)	0.47
Body mass index, kg/m^2	23.7±13.23	23.6±43.69	23.7±13.22	0.28
Thyroid gland dysfunction				
Hyperthyroidism	51,267 (1.3)	39 (1.7)	51,228 (1.3)	0.04
Hypothyroidism	70,512 (1.7)	39 (1.7)	70,473 (1.7)	0.91

Data are expressed as n (%) or mean ± standard deviation.

Results

Baseline characteristics of the study population

Of the 4,059,021 participants in the study, 2,334 participants (0.057%) were clinically diagnosed keratoconus cases in the analysis period of 2009 to 2018. The baseline characteristics of the participants are shown in *Table 1*. There were no significant differences in income, hypertension, body mass index, and hypothyroidism between the groups with and without keratoconus. However, there were significant differences in age, sex, the presence of diabetes, and the presence of hyperthyroidism between the two groups. Patients with keratoconus, as compared to those without, were more likely to be younger, female, with diabetes and hyperthyroidism (*Table 1*).

Incidence of keratoconus according to age or sex

Table 2 shows the incidence and HR for keratoconus during the 10-year follow-up period using cox proportional hazard model. The keratoconus incidence per 100,000 person-year was 10.695, 6.321, 3.837, 5.533, 8.104, and 6.034 among those 20 to 29 years of age, 30 to 39 years of age, 40 to 49 years of age, 50 to 59 years of age, 60 to 69 years of age, and more than and equal 70 years of age, respectively (P<0.001). Individuals 20 to 29 years of age had the highest gender-adjusted HR of keratoconus. It was 0.623 (95% CI: 0.548–0.709) in 30 to 39 years of age, 0.359 (95% CI: 0.314–0.410) in 40 to 49 years of age, 0.508 (95% CI: 0.447–0.577) in 50 to 59 years of age, 0.739 (95% CI: 0.648–0.842) in 60 to 69 years of age, 0.560 (95% CI: 0.467–0.671) in more than and equal 70 years of age times lower that than in 20 to 29 years of age (P<0.001) (*Table 2*).

Females had a higher keratoconus incidence at 7.101 per 100,000 person-year compared to 5.559 in males (P<0.001). The age-adjusted HR of keratoconus in females was 1.295 (95% CI: 1.193–1.406) times higher than in males (P<0.001) (*Table 2*). *Figure 2* displays the cumulative incidence of keratoconus in male and female groups. Moreover, log-rank testing showed a significant difference in the incidence of keratoconus between the gender groups (P<0.001), and the incidence calculated using probability was linearly related to

Table 2 The incidence of keratoconus according to age or sex

Characteristics	Number	KC event	Duration (person-years)	IR	Adjusted HR (95% CI)	P value
Age, years						<0.001
20–29	497,102	495	4,628,270.64	10.695	1 (ref.)	
30–39	776,329	456	7,213,700.27	6.321	0.623 (0.548, 0.709)	
40–49	1,066,982	380	9,904,404.88	3.837	0.359 (0.314, 0.410)	
50–59	860,656	441	7,971,040.69	5.533	0.508 (0.447, 0.577)	
60–69	550,615	407	5,022,174.16	8.104	0.739 (0.648, 0.842)	
≥70	307,337	155	2,568,922.51	6.034	0.560 (0.467, 0.671)	
Sex						<0.001
Male	2,236,326	1,137	9.15	5.559	1 (ref.)	
Female	1,822,695	1,197	9.25	7.101	1.295 (1.193, 1.406)	

KC, keratoconus; HR, hazard ratio, IR, incidence rate (person-year per 100,000); CI, confidence interval; Adjusted HR, hazard ratio adjusted for sex and age.

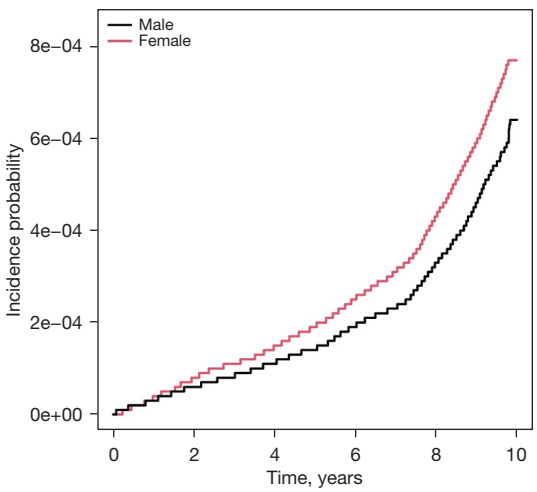

Figure 2 Kaplan-Meier curve of keratoconus patients among male and female at least a 10-year population based follow up (log-rank test P value, P<0.001).

the duration of keratoconus.

Demographics of the subjects with TGD

Subjects with TGD were classified into two groups: hyperthyroidism (n=51,267) and hypothyroidism (n=70,512). There are significant differences between two groups according to age group and gender (both P<0.001). In subjects with hypothyroidism, the frequency of older age and female gender was higher than that of subjects with hyperthyroidism (*Table 3*).

Incidence of keratoconus according to TGD

During a follow-up of 10 years, 39 of 70,512 subjects with hypothyroidism and 51,267 subjects with hyperthyroidism were newly diagnosed with keratoconus. The keratoconus incidence per 100,000 person-year was 6.019 in hypothyroidism group, and 8.287 in hyperthyroidism group, respectively (*Table 4*).

The crude HR of hypothyroidism for keratoconus was not significantly lower than that of participants without TGD [HR (95% CI): 0.962 (0.701–1.321)]. Sex and age-adjusted HR of hypothyroidism for keratoconus was also not significantly lower than those without TGD [HR (95% CI): 0.920 (0.670–1.265)]. In contrast, the crude [HR (95% CI): 1.326 (0.966–1.820)] or sex and age-adjusted HR [HR (95% CI): 1.290 (0.939–1.771)] of hyperthyroidism for keratoconus were generally higher than that of participants without TGD, although there was not a statistically significant difference (*Table 4*).

Discussion

The present study used a nationwide sample of Korean adults to elucidate the differences of gender and thyroid gland function in the development of keratoconus. We found that the development of keratoconus in females was 1.295 times higher (95% CI: 1.193–1.406) than in males

Table 3 Demographics of thyroid gland dysfunction patients

Characteristics	Thyroid gland dysfunction		P value
	Hyperthyroidism (n=51,267)	Hypothyroidism (n=70,512)	
Age, years			<0.001
20–29	3,476 (6.8)	2,947 (4.2)	
30–39	6,244 (12.2)	6,393 (9.1)	
40–49	13,261 (25.9)	18,350 (26.0)	
50–59	14,019 (27.3)	20,998 (29.8)	
60–69	9,387 (18.3)	14,897 (21.1)	
≥70	4,880 (9.5)	6,927 (9.8)	
Sex			<0.001
Male	17,174 (33.5)	14,841 (21.0)	
Female	34,093 (66.5)	55,671 (79.0)	

Data are expressed as n (%).

Table 4 The incidence of keratoconus according to thyroid gland dysfunction

Thyroid gland dysfunction	N	KC event	Duration (years)	IR	Crude		Adjusted	
					HR (95% CI)	P value	HR (95% CI)	P value
None	3,930,771	2,250	36,130,445.6	6.227	1 (ref.)	0.82	1 (ref.)	0.61
Hypothyroidism	70,512	39	647,934.06	6.019	0.962 (0.701, 1.321)		0.920 (0.670, 1.265)	
Hyperthyroidism	51,267	39	470,631.39	8.287	1.326 (0.966, 1.820)		1.290 (0.939, 1.771)	

KC, keratoconus; IR, incidence rate (person-year per 100,000); CI, confidence interval; Adjusted HR, hazard ratio adjusted for sex and age.

after controlling for age. Although there was no significant difference, the HR of keratoconus after controlling sex and age was higher [HR (95% CI): 1.290 (0.939–1.771)] in those with hyperthyroidism than in those without TGD.

The gender difference in the incidence of keratoconus was an issue of debate in previous literature (3,13,18,25-29). Unlike our results some previous studies have been reported that keratoconus showed preponderance over female in male (18,25). In their studies, the male to female ratio reported 1.54 from 4.4 million patients using a mandatory health insurance database in the Netherlands by Godefrooij *et al.* (18) and 1.11 from 990,818 population in a province in the central Iran by Ziaei *et al.* (15). In a more recent study, it was documented 2.33 among high school students in New Zealand (19). Fatima *et al.* (25) from India and Ota *et al.* (26) from Japan, have found a greater prevalence for keratoconus in males, while other researchers have not found differences in the genders (27,28). Hwang *et al.* (13) reported that the overall male to female incidence ratio was 1.00, meaning there was no sex predisposition in Korean. In their study, age distribution of keratoconus was different according to sex, and early (age <20 years) onset has been reported to occur more frequently in males. However, we examined only those older than 20 years of age. In addition, it is known that males develop that disease earlier rapidly than females (29).

A few previous studies reporting gender differences have suggested a role of sex hormones (13,30,31). Zhao *et al.* (30) compared the level of specific sex hormones in 62 and 120 patients with keratoconus and myopia, respectively. They analyzed the plasma concentrations of estriol, estradiol, progesterone and testosterone and reported low testosterone levels in both sexes with keratoconus and high estradiol in males with keratoconus. From these results, they suggested that sex hormones may influence the cornea even within a normal range. Also, Escandon *et al.* (31) suggested that estrone, estriol, and sex hormone receptors are involved in keratoconus pathobiology. Despite

extensive clinical investigations and basic research, the pathophysiological mechanisms underlying keratoconus have not been fully established (10). Further studies on hormonal differences are required to clarify the gender difference in the pathobiology of keratoconus.

In our research, we demonstrated that although the statistical significance was not established, there was a higher incidence of keratoconus in patients with hyperthyroidism. The association between thyroid disease and keratoconus is a subject of controversy in the literature. However, there is a growing body of evidence suggesting an association between hyperthyroidism and keratoconus, rather than hypothyroidism, which aligns with our findings. Previous studies implicated a crucial role of thyroxine in keratoconus pathology, revealing increased T4 level in keratoconus patients' tear as well as the aqueous humor of keratoconus (10,32,33). Moreover, Kahán *et al.* (32) reported that the tear thyroxine levels of patients with keratoconus were higher during the progression of keratoconus. Additionally, a positive correlation between tear thyroxine and serum thyroxine value was reported as well. The association between hyperthyroidism and keratoconus is not surprising given the thyroxine's important role in corneal development and collagen synthesis (34). Similarly, a study has shown that the collagen expression is increased in parallel to an increasing thyroxine concentration in monkey corneas. By binding to its receptor, thyroxine is thought to regulate the homeostasis between collagen degradation and synthesis, thus provoking keratoconus (10). The formation of collagen is influenced by thyroid hormones through the transforming growth factor-β (TGF-β) signaling pathway, or through a direct effect on TGF-β (35,36). The TGF-β signaling pathway plays a crucial role in the secretion and assembly of the extracellular matrix in various tissues, including the anterior part of the eye, and there is evidence linking alterations in TGF-β signaling to the progression of keratoconus (37). However, there has also been a report indicating that thyroxine administration had no effect on TGF-β1, collagen I, and V expression in keratoconus keratocytes (38). Keratoconus is a multifactorial disease and the mechanism of thyroid hormone in keratoconus needs to be further clarified.

There is growing evidence that keratoconus is an immune-mediated inflammatory disorder (39). A strong association has been reported between keratoconus and immune disorders such as rheumatoid arthritis, ulcerative colitis, asthma, and irritable bowel syndrome (40). Our finding regarding the association with TGD aligns with those associations, as Graves' disease is the most common cause of hyperthyroidism induced by circulating autoantibodies. Local changes in the microenvironment of the eye may reflect the systemic activity of the immune system (39). Likewise, a positive association between type 2 DM and the presence of keratoconus has been reported, as demonstrated in our study (41). Diabetes has been noted to exhibit an underlying systemic inflammation that influences multiple organs. The distinct systemic factors associated with each disease may have diverse impacts on the cornea's cellular response, consequently affecting the regulation of collagen expression and deposition (42).

The age-specific incidence of keratoconus in the present study showed the highest incidence in people in the age group ranging from 20 to 29 years, which is congruent with results of previous studies (3,13,43). Typically, keratoconus has its usual onset at a younger age and, in many cases, stabilizes by the fourth decade of life (3,13). An interesting point about the age-specific incidence examined in the present study is that it trended downward with age until a slightly increased peak in the age group ranging from 60 to 69 years old. Another chart review study from Korea showed similar results to ours. Hwang *et al.* (13) speculated that the incidence had second peak as patients visiting for cataract treatment assessed corneal topographic measurements. In addition, because the development of corneal topography has made it possible to detect early keratoconus, it is assumed that patients who visited the ophthalmology clinic for cataract surgery may have found keratoconus in a mild state compared to the past.

The strengths of our study in determining the 10-year incidence of keratoconus include using a nationwide representative sample of the Korean adult population; exclusion of other corneal disorders; exclusion of any potential pre-existing cases with keratoconus; and classification of participants by hyper- or hypothyroidism. To the best of our knowledge, this study is the first nationwide analysis to the risk of keratoconus in patients with co-morbid TGD using big data analytics. Unlike cohort studies previously published in Korea, we focused on the development of keratoconus in patients with TGD. In the present study, our large sample size of over 4 million people is advantageous, while previous studies on the relationship between thyroid and keratoconus have used small samples (8,10,11). Since all citizens in South Korea are obliged to register for health insurance at birth, this data is ideal for epidemiological research (13). Also, we only included patients coded as H18.6 (KID-10) and not patients

with other corneal disorders such as corneal ectasias with other diagnosis codes, and it seems likely that the number of registered patients is accurate and representative of the Korean population. Furthermore, we used a 7-year wash-out period when analyzing the incidence of keratoconus, which can have removed any pre-existing keratoconus diagnoses. Previous studies mainly used a 1-year wash-out period, and among the cohort studies analyzed to date (13,44), we used the longest wash-out period.

There are some limitations in this study. First, since the cohort data we used in this study is comprised only of residents of South Korea, it may be difficult to generalize these results to other populations. Second, age and sex were adjusted but other variables that may affect the development of keratoconus such as allergic conjunctivitis (44), atopy (45), environmental factors (46,47) were not considered. Third, although corneal topography is used in the diagnosis of keratoconus, devices from different manufacturers and software were used, which may not have the same sensitivity in detecting early stages of the disease (46). Despite these limitations, this study has strength that longitudinal cohort big data of nationwide Korean population.

Conclusions

The present study showed a higher age-adjusted prevalence of keratoconus in females. Furthermore, a higher incidence of keratoconus in patients with hyperthyroidism was observed, suggesting a possible role of thyroid hormones in the occurrence of keratoconus.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-23-1906/rc

Peer Review File: Available at https://atm.amegroups.com/article/view/10.21037/atm-23-1906/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-23-1906/coif). Y.S.Y. reports that this work was supported by grants from the Catholic Medical Center Research Foundation made in the program year of 2022. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy of integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Baekseok University (IRB No. BUIRB-202007-HR-009). Informed consent was waived for this retrospective study.

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