Nationwide epidemiological approach to identify associations between keratoconus and immune-mediated diseases

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ABSTRACT

Background The aetiology of keratoconus (KC) remains poorly understood. KC has typically been described as a non-inflammatory disorder of the cornea. Nonetheless, there is increasing presumptive evidence for the role of the immune system in the pathogenesis of KC.

Aim To evaluate the association between KC and immune-mediated diseases on a population level. We hypothesise that KC is immune-mediated rather than a predominantly degenerative disease.

Methods Data were obtained from the largest health insurance provider in the Netherlands. Dutch residents are obligatorily insured. The data contained all medical claims and sociodemographic characteristics from all KC patients plus all those data from a 1:6 age-matched and sex-matched control group. The primary outcome was the association between KC and immune-mediated diseases, as assessed by conditional logistic regression.

Results Based on our analysis of 2051 KC cases and 12 306 matched controls, we identified novel associations between KC and Hashimoto's thyroiditis (OR=2.89; 95% CI: 1.41 to 5.94) and inflammatory skin conditions (OR=2.20; 95% CI: 1.37 to 3.53). We confirmed known associations between KC and atopic conditions, including allergic rash (OR=3.00; 95% CI: 1.03 to 8.79), asthma and bronchial hyperresponsiveness (OR=2.51; 95% CI: 1.63 to 3.84), and allergic rhinitis (OR=2.20; 95% CI: 1.39 to 3.49).

Conclusion Keratoconus appears positively associated with multiple immune-mediated diseases, which provides a population-based argument that systemic inflammatory responses may influence its onset. The identification of these particular diseases might shed light on potential comparable pathways through which this proinflammatory state is achieved, paving the way for pharmacological treatment strategies.

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INTRODUCTION

Keratoconus (KC) is an eye disease characterised by progressive thinning and cone-shaped protrusion of the cornea, resulting in a decrease in visual acuity due to myopia and irregular astigmatism. The disease usually manifests during the puberty or early adulthood. KC has an estimated annual incidence of 1:7500 and prevalence of 1:375 KC patients based on the same dataset used for this article.[1] This corresponds with approximately 16 500 patients in the Netherlands.

The classic triad of histopathological features found in KC eyes are the thinning of the corneal stroma, breaks in Bowman's layer and deposition of iron in the basal layers of the corneal epithelium.[2] The aetiology of KC, however, remains poorly understood. It appears to be of a multifactorial origin with involvement of both genetic and environmental factors.[2] Most commonly, KC is presented as an isolated disorder without the presence of any systemic or ocular disease. However, KC has also been reported to be associated with other conditions such as atopy, sleep apnoea and numerous genetic disorders, including Down's syndrome.[3] Although no specific KC genes have been reported up to now, genome-wide association studies (GWAS) have identified genes associated with central corneal thickness and corneal curvature.[4] Environmental factors as contact lens wear and eye rubbing seem to influence the progression of the disorder in genetically predisposed individuals.[2 5]

KC has typically been described as a noninflammatory disorder of the cornea.[2] Nonetheless, there is increasing presumptive evidence for the role of the immune system in the pathogenesis of KC. Compelling evidence has been supplied for an upregulation of proinflammatory mediators in KC eyes and the involvement of Toll-like 2/4 receptors as a systemic inflammatory mediator for KC development.[6 7] Furthermore, allergic conjunctivitis, which invariably results in a chronic inflammation of the ocular surface, has long been associated with KC.[8 9]

We hypothesise that KC is an immune-mediated inflammatory disorder (IMIDs), and that local changes in the microenvironment of the eye are a reflection of the systemic activity of the immune system. Typically, different systemic inflammatory diseases are characterised by uniform, common pathways and networks.[10] Consequently, diseases with immune-mediated pathogeneses occur with increased frequency in patients with a history of another immune-mediated disease.[11] If an underlying systemic autoimmune pathway in the pathogenesis of KC exists, one would expect significantly higher odds of being diagnosed with immune-mediated diseases in KC patients, when compared with a control group. Evaluating these disease associations may help to better understand the pathophysiology of KC.

The aim of this study was to investigate the association between KC and immune-mediated diseases using a healthcare insurance database containing all

medical claims from KC patients and a control sample matched by age and sex. We used data from the largest health insurance provider in the Netherlands (Achmea), covering 4.3 million people; approximately 33% of all residents of the Netherlands (years 2010–2015).[12]

METHODS
Case–control study design
We performed a case–control study with six randomly selected age-matched and sex-matched controls for every KC patient. Data for this study were obtained from the Achmea Health Database (AHD). The AHD contains all medical claims and patient characteristics, including sex, postal code, date of birth and date of death (if applicable). An individual enrolee was characterised by a unique pseudoidentification number. For each enrolee, the database included all medical claims submitted over 6 years; between 1 January 2010 and 31 December 2015. Diagnoses and treatments in hospital care are assigned a specific code; the Diagnosis and Treatment Combination (DTC; in Dutch: *Diagnose Behandel Combinatie*). Each registered claim contains this DTC. Every medical specialty, diagnosis and type of care delivered has its own unique combination. KC is coded in the ophthalmology DTC-listing under code 457: 'KC/cornea dystrophy'. In the Netherlands, this code can only be registered after evaluation by an ophthalmologist. In our data set, patients with a registered claim with this code were defined as cases. Both pre-existing and new registrations were included. Code 457 is a registration code that includes more clinical entities than KC. To select solely patients with KC within this group of records, the study population was limited to patients aged 10–40 years. This is the age category in which the vast majority of KC patients are diagnosed. Other disorders within DTC code 457 are predominantly found either in older patients (ie, Fuchs endothelial dystrophy) or in younger patients (congenital corneal pathology).[13]

Definitions of sociodemographic characteristics
Every person who lives or works in the Netherlands is legally obliged to arrange health insurance. Health insurance plans in the Netherlands always last one calendar year, so any individual can switch to another insurance company only at the end of each year. 'Years of enrolment in the plan' is based on the total years a record was insured by Achmea between 2010 and 2015. More disease registrations are available in the database when an individual has been enrolled for a longer period of time.

Socioeconomic status and urbanisation status were estimated by linking the four-digit postal codes of our records to data from the Statistics Netherlands.[14] Socioeconomic status is a well-known determinant for health status in general. It is represented by a score that included a neighbourhood's average income, level of unemployment, percentage of low-income households and percentage of people with a low level of education. Urbanisation status is associated with allergic conditions and IMIDs. These diseases have been reported to be more common in urban areas, driven by environmental factors, such as air pollution and a reduced early-life exposure to microbe diversity.[10] The degree of urbanisation is based on households per km². Urban and rural areas are defined as ≥1000 and <1000 households per km², respectively.

Selection of diseases of interest
The dataset contained all reimbursed healthcare per enrolee, and as such also DTCs covering IMIDs and atopic diseases. These diseases of interest were manually identified, based on current insights on disease biology and expert opinion (JK, see the acknowledgments section). The diseases with established immunological pathways were selected in order to explore our primary objective.[2 3 15 16] Subsequently, sleep apnoea, a condition that had been reported in previous research to be associated with KC, was also included in order to validate our methodology.[17 18] If similar conditions appeared in multiple listings, these were combined; for example, sarcoidosis is defined by three different DTC codes; for rheumatologists, internal medicine and pulmonologists. If a condition was registered multiple times, this variable was only counted once. Consequently, all studied disease registrations in the database were binary variables.

Statistical analysis
Conditional logistic regression was used to test our hypotheses about possible associations between immune-mediated diseases and the diagnosis of KC. This extension of logistic regression allows one to take into account matching and stratification.[19] The dependent variable in this model was a diagnosis of KC and the explanatory variables were the diseases of interest. Disease associations were studied by univariate analyses with adjustment for age, sex, socioeconomic status and urbanisation status. Data are represented as ORs with 95% CIs for having been diagnosed with KC. For all analyses, a $p < 0.05$ was considered statistically significant. Statistical analyses were performed with IBM SPSS Statistics V.25 (IBM).

RESULTS
Patient characteristics
From a pool of approximately 4.3 million enrollees, a database with 10 646 KC patients and 63 876 controls (age and sex matched by ratio 1:6) was provided. Our analysis, within the relevant age group 10–40 years, included 14 357 records, of which 2051 KC and 12 306 controls. The characteristics of these KC cases and controls can be found in table 1. The mean age of KC cases and controls was 30 years (±6.5 SD) and the majority was male (62.8%). Most individuals were enrolled in the insurance plan for multiple years. The distribution of socioeconomic status was comparable among both groups, with the majority of enrollees scoring 'average' (50.6% of cases and 55.5% of controls). The proportion of enrollees living in urban areas was slightly higher in the KC group than in the control group (79.7% vs. 71.4%).

Associations of diseases with KC
Table 2 shows the diseases of interest that we selected, the frequencies of these diseases in our study population and their associations with KC. The results of the univariate conditional logistic regression analyses with adjustment for age, sex, socioeconomic status and urbanisation status show a positive association between KC and Hashimoto's thyroiditis, between KC and inflammatory skin conditions, between KC and several atopic conditions, and between KC and obstructive sleep apnoea. No negative associations were identified in our analyses. Univariate conditional multiple logistic regression without adjustment for potential confounders did not materially alter the results.

KC was positively associated with Hashimoto's thyroiditis (OR=2.89; 95% CI: 1.41 to 5.94, p=0.004) and with inflammatory skin conditions (OR=2.20; 95% CI: 1.37 to 3.53, p=0.001). As expected, we found a statistically significant positive association between KC and atopy. There were positive associations for the following registrations: allergic rash (OR=3.00; 95% CI: 1.03 to 8.79, p=0.045), asthma/bronchial hyper-responsiveness

Table 1 Characteristics of keratoconus patients and age-matched/sex-matched control group of the Achmea Health Database

Characteristics	Keratoconus cases	Controls	Total
No. of enrollees (%)	2051 (14.3)	12 306 (85.7)	14 357
Years of enrolment in plan, no. (%)			
1 year	45 (2.2)	973 (7.9)	1018 (7.1)
2 years	101 (4.9)	956 (7.8)	1057 (7.4)
3 years	183 (8.9)	1217 (9.9)	1400 (9.8)
4 years	218 (10.6)	1304 (10.6)	1522 (10.6)
5 years	205 (10.0)	1146 (9.3)	1351 (9.4)
6 years	1299 (63.3)	6710 (54.5)	8009 (55.8)
Age in years, mean (SD)	29.7 (6.5)	29.8 (6.4)	29.8 (6.5)
Sex, no. (%)			
Male	1289 (62.8)	7734 (62.8)	9023 (62.8)
Female	762 (37.2)	4572 (37.2)	5534 (37.2)
Socioeconomic status, no. (%)			
Below average	688 (33.5)	3227 (26.2)	3915 (27.3)
Average	1038 (50.6)	6824 (55.5)	7863 (54.8)
Above average	277 (13.5)	1708 (13.9)	1985 (13.8)
Unknown	48 (2.3)	1546 (4.4)	594 (4.1)
Urbanisation status, no. (%)			
Urban	1635 (79.7)	8790 (71.4)	10 425 (72.6)
Rural	378 (18.4)	3050 (24.8)	3428 (23.9)
Unknown	38 (1.9)	466 (3.8)	504 (3.5)

Data are no. (%) or mean (SD).
Socioeconomic status and urbanisation status are based on 'postal codes'-related data from the Statistics Netherlands.[14] Socioeconomic status is determined by a neighbourhood's average income, level of unemployment, percentage of low-income households, and percentage of people with a low level of education. Urban and rural areas are defined as ≥1000 and <1000 households per km^2, respectively.

(OR=2.51; 95% CI: 1.63 to 3.84, p=2.50×10^{-5}) and allergic rhinitis (OR=2.20; 95% CI: 1.39 to 3.49, p=0.001) Additionally, we found a positive association of KC with obstructive sleep apnoea (OR=2.33; 95% CI: 1.12 to 4.83, p=0.023). Other hypothetical associations did not reach statistical significance

DISCUSSION

The aim of this study was to investigate the association between KC and immune-mediated diseases. Based on our analysis, KC is positively associated with Hashimoto's thyroiditis, with inflammatory skin conditions, and with several atopic conditions. The latter is in line with the current body of evidence. We also confirmed the known association between KC and obstructive sleep apnoea. The immune system is highly involved in the positively associated diseases. Even though we did not demonstrate a causal relationship between KC and the associated immune-mediated diseases, we believe that the associations with these diseases suggest that activity of the immune system contributes to the development of KC.

Major strengths of this study are the large sample size and the accuracy of our dataset. The database is expected to be complete and accurate because of the financial consequences of medical claims registrations. Healthcare providers fully rely on these registrations to be reimbursed for their work. The enrollees in the database are expected to be a representative sample of the general population since all residents of the Netherlands are obliged to have a medical insurance provider that covers the majority of their healthcare needs, including primary care and hospital care. Since coverage provided by a health insurance plan is largely determined by the government, insurance plans are comparable among the different providers. In particular, KC care is completely reimbursed (hospital consultations, medically prescribed visual aids, lasers and surgery). As a result, our database includes enrollees from all socioeconomic classes. A limitation of the reimbursement data is that only hospital care is registered and that health expenditures for optometrists practicing outside hospitals are not entered. However, in the Netherlands, virtually all KC patients will regularly visit ophthalmologists, so we do not expect this to highly impact the generalisability of our outcomes.

Another limitation of our study is that the DTC code for KC also includes registration of other corneal dystrophies, leading to a possible dilution of the observed associations. This effect

Table 2 Frequencies and conditional logistic regression model estimating associations of diseases with keratoconus compared with matched controls of the Achmea Health Database

	OR (95% CI)	P values	Keratoconus cases, no. (%)	Controls, no. (%)
IMIDs and atopic diseases				
Allergic rash	**3.00 (1.03 to 8.79)**	**0.045**	5 (0.2)	10 (0.1)
Hashimoto's thyroiditis	**2.89 (1.41 to 5.94)**	**0.004**	11 (0.5)	23 (0.2)
Asthma/BHR	**2.51 (1.63 to 3.84)**	**2.50×10^{-5}**	30 (1.5)	74 (0.6)
Allergic rhinitis	**2.42 (1.06 to 5.49)**	**0.035**	8 (0.4)	20 (0.2)
Rheumatoid Arthritis	2.22 (0.71 to 6.97)	0.173	4 (0.2)	11 (0.1)
Inflammatory skin conditions*	**2.20 (1.37 to 3.53)**	**0.001**	24 (1.2)	66 (0.5)
Psoriasis and psoriatic arthritis	1.60 (0.89 to 2.89)	0.116	14 (0.7)	53 (0.3)
Diabetes mellitus	1.60 (0.85 to 3.03)	0.149	12 (0.6)	46 (0.4)
Ulcerative colitis	1.46 (0.54 to 3.86)	0.463	5 (0.2)	21 (0.2)
Crohn's Disease	0.94 (0.33 to 2.70)	0.942	4 (0.2)	26 (0.2)
Graves' disease	0.92 (0.21 to 4.07)	0.910	2 (0.1)	13 (0.1)
Multiple sclerosis	0.63 (0.15 to 2.72)	0.538	2 (0.1)	19 (0.2)
Ankylosing spondylitis	0.59 (0.76 to 4.62)	0.617	1 (0.0)	10 (0.1)
Sarcoidosis	0.42 (0.06 to 3.16)	0.396	1 (0.0)	15 (0.1)
Other diseases				
Obstructive sleep apnoea	**2.33 (1.12 to 4.83)**	**0.023**	10 (0.5)	26 (0.2)

Univariate analysis with adjustment for age, sex, socioeconomic status and urbanisation status. An uncorrected analysis of disease associations did not materially differ from presented outcomes above (data not shown). Bold values represent statistically significant outcomes.
*Inflammatory skin conditions include contact dermatitis, hives/urticaria and other non-specified inflammatory dermatoses.
BHR, bronchial hyperresponsiveness; IMIDs, immune-mediated inflammatory diseases.

was mitigated by limiting the study population to people aged 10–40 years old. A previously published sensitivity analysis of the Achmea insured cases from our own institution (a referral centre for corneal pathology) found that more than 90% of patients within this age category were indeed KC patients.[1] Other disorders within DTC code 457 are predominantly found either in older patients (i.e. Fuchs endothelial dystrophy) or in younger patients (congenital corneal pathology).[20] A weakness of not including patients older than 40 years of age is that late onset/diagnosis of KC or IMIDs will be missed. The typical age of onset of both these conditions is at a younger age, however, so the impact of this omission is considered limited.

Interestingly, the overall prevalence of the immune-mediated diseases is relatively low. Even though our dataset is of reasonable size and derived from a pool of 4.3 million enrollees, true associations might have been missed due to a lack of statistical power. In addition, we manually selected diseases of interest: associations with diseases that have not been studied may still exist.

A positive association between KC and Hashimoto's thyroiditis has been reported before, in line with our findings.[21 22] To some extent this association might be indirect, since KC and thyroid dysfunction are both more prevalent in patients with Down's syndrome.[23] Down's syndrome is not identified in our database as there is no specific DTC-code for this syndrome. Considering the size of the Dutch Down syndrome population (est. 13 000 in 2016),[24] we estimate that the AHD contains approximately 860 Down syndrome patients aged 10–40 year old. On a total of 14 357 enrollees, we expect the effect of this potential confounder (6%) to be limited.

Alterations of histopathological skin characteristics in KC patients have been described before. Most notable is the increased prevalence of connective tissue disorders, such as Marfan's syndrome or Ehlers-Danlos syndrome, among KC patients.[25] Interestingly, the association between inflammatory skin conditions and KC has not extensively been described before. Inflammatory skin conditions are characterised by a T-cell-mediated inflammation of the skin. An appropriate balance of T helper (Th) and regulatory T (Treg) cells is essential for immune tolerance and host defence. A number of immune-mediated diseases, including Hashimoto and immune-mediated skin conditions, are characterised by a disruption of the Th17-Treg cell balance.[26] This imbalance is caused by a dysregulation of the insulin-like growth factor (IGF) system. Recent novel therapies, such as teprotumumab (an IGF-1 inhibitor) have initiated a revolution in the treatment of Graves' orbitopathy.[27] Based on our found associations and suggestion that KC is immune mediated, it could be hypothesised that KC patients benefit from (future) biological treatments.

KC and rheumatoid arthritis have been reported to be strongly associated by Nemet et al.[22] Yet, we did not reproduce this finding. It should be noted that the study populations differ because Nemet et al assessed one hospital database, and our study is based on a more representative sample of the general population. Importantly, we only considered individuals up to 40 years of age. The onset of rheumatoid arthritis can be at any age but the disorder is most typical in elderly people.[28] This might explain the low number of registrations of rheumatoid arthritis in our database. It is plausible that the association was not identified in our study, but the KC patients will still develop rheumatoid arthritis later in life.

Our study did not find a significant association between KC and diabetes mellitus (DM). It is important to note that the DTC-code does not distinguish between type 1 or type 2 DM.

Type 1 DM is the condition we are interested in by reason of its immune-mediated aetiology. We expect the great majority of our studied disease registrations to be type 1 DM, since the study population is limited to patients aged 10–40 years old. Previous studies on the associations between DM and KC have found conflicting results. Both positive and negative associations have been reported.[3 29] It has been suggested that glycosylation, which occurs in hyperglycaemic states, strengthens the cornea by collagen crosslinking, thus slowing down corneal damage. A study supporting this hypothesis reported no significant association between KC and DM, but did report that having DM decreases the odds of having more severe KC.[30] An effect of the DM on the severity of KC cannot be demonstrated by our dataset, since information on KC severity is lacking.

Our study did not find a positive association for KC and ulcerative colitis or for KC and Crohn's disease, contrary to Nemet et al.[22] In their study, the positive association between KC and ulcerative colitis was statistically significant, though the number of patients was very small in both the KC and the control groups (3 and 1, respectively). This is also true for the identified cases in our dataset: small differences can swing the ORs. We cannot completely rule out a possible association between KC and these inflammatory bowel diseases.

Atopic conditions have long been reported to be associated with KC.[2 8 31] A recent study by Mazzotta et al identified similar associations as the present study.[32] Importantly, a high correlation between severity of allergy and KC progression was reported. Atopy provokes eye rubbing by local irritation, resulting in mechanical corneal damage. Besides, increased levels of proteases and inflammatory mediators (Matrix metallopeptidase 13, Interleukin 6 and Tumor Necrosis Factor α) in the tear film, exacerbating KC, have been described after eye rubbing, even in healthy individuals.[33]

It is important to note that association does not necessarily imply causality. We propose that chronic systemic inflammation influences KC onset and progression both directly and indirectly. Directly, systemic inflammatory pathways may lead to periocular inflammation and changes in the tear film in KC eyes. Indirectly, local inflammation may trigger a variety of ocular surface and anterior segment diseases which are directly associated with the development and progression of KC. Any comorbidity that is inflammatory in nature (e.g. dry eye syndrome or ocular rosacea) may add synergistically to other forms of KC-related inflammation, and hence lead to KC progression.[34] In this association study, the independent effects of confounding ocular comorbidities are not distinguishable.

In conclusion, the present observational study identifies that KC is associated with several immune-mediated diseases on a population level. We found positive associations between KC and Hashimoto's thyroiditis, inflammatory skin conditions, and several atopic diseases. We did not identify a significant association with DM or other systemic IMIDs. However, due to the low prevalence of the studied diseases in our database, we cannot rule out possible associations with these diseases. The positively associated diseases involve systemic activity of the immune system, which suggests that KC onset is partly favoured by a chronic, systemic proinflammatory state. This may help clinicians in better understanding the course of KC and contribute to future research investigating novel treatment options, such as biologicals.

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