

Age-specific Incidence and Prevalence of Keratoconus: A Nationwide Registration Study



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- **PURPOSE:** To determine the age-specific incidence and prevalence of keratoconus in the modern era of diagnostics.
- **DESIGN:** Epidemiologic study.
- **PARTICIPANTS:** Total of 4.4 million patients from a mandatory health insurance database.
- **METHODS:** Data were extracted from the largest health insurance provider in the Netherlands. Patients aged 10–40 years were defined as the relevant age category for newly diagnosed keratoconus and the annual incidence of newly diagnosed keratoconus was determined. The prevalence of keratoconus was estimated based on the annual incidence, mean age at diagnosis, and average life expectancy. Main outcome measure was the annual incidence and prevalence of keratoconus.
- **RESULTS:** The annual incidence of keratoconus was 1:7500 in the relevant age category (13.3 cases per 100 000, 95% confidence interval [CI]: 11.6–15.2) and the estimated prevalence of keratoconus in the general population was 1:375 (265 cases per 100 000, 95% CI: 260–270). These values are 5-fold to 10-fold higher than previously reported values in population studies. The mean age at diagnosis was 28.3 years and 60.6% of diagnosed patients were male.
- **CONCLUSIONS:** Both the annual incidence and the prevalence of keratoconus were 5-fold to 10-fold higher than previously reported. (*Am J Ophthalmol* 2017;175:169–172. © 2016 Elsevier Inc. All rights reserved.)

KERATOCONUS IS A PROGRESSIVE DISEASE OF THE cornea that leads to a decrease in visual acuity owing to corneal thinning and irregular astigmatism. Although visual acuity can often be restored in most patients through the use of glasses or rigid contact

lenses, complex corneal grafting procedures are ultimately indicated in approximately 10%–20% of keratoconus patients.^{1–3}

The most frequently cited occurrence of keratoconus is 1:2000. This value is based on a registration study in the United States that was conducted from 1935 until 1982. This study reported a prevalence of 54.5 cases per 100 000 individuals.⁴ Estimates of the annual incidence of keratoconus based on epidemiologic studies range from 1:3000 to 1:80 000 per year.^{4,5} This wide range may be attributed to the increased sensitivity of modern diagnostic devices, regional differences with respect to accessibility of health care, and/or differences in study design. Furthermore, ethnic differences with respect to the incidence of keratoconus have also been reported.^{6–8}

Incidence is defined as the number of new cases diagnosed within a specific period of time (usually 1 year), whereas prevalence is the number of existing cases at a given point in time. The onset of keratoconus typically occurs in the second to fourth decade of life (ie, from age 10 through age 40) and the condition affects patients for the remainder of their lives.¹ Therefore, the prevalence of keratoconus is by definition always higher than the annual incidence.

As computer-based technologies and imaging techniques have improved, the ability to diagnose keratoconus has also increased. New treatment options for keratoconus are currently being implemented. Therefore, determining the incidence and prevalence of keratoconus in the modern era will provide a more accurate estimate of the impact of such new treatment options on healthcare costs. We performed a nationwide registration study to determine the annual incidence of keratoconus and to calculate the prevalence of keratoconus in the population. To perform this analysis we used data from the largest health insurance provider in the Netherlands.

All residents of the Netherlands are required to have coverage for the majority of their standard healthcare needs, including primary care and hospital care. Achmea is the largest health insurance provider in the Netherlands, covering 31% of all residents.⁹ In the Netherlands, health insurance providers are required to provide basic health insurance coverage for all applicants who request it. The coverage provided by this basic health insurance plan is determined by the Dutch government and is equal among all health insurance providers.¹⁰ Therefore, populations

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among different healthcare providers are similar, and Achmea provides a representative sample for the population. Given the financial consequences associated with both healthcare providers and insurance providers, health care is monitored carefully using automated systems. Most expenses related to ophthalmic care for keratoconus (such as outpatient visits, diagnostic procedures, contact lenses, and corneal transplants) are reimbursed, regardless of the setting in which it was provided (ie, at a private practice or at a hospital).

METHODS

• **DATABASE AND KERATOCONUS SELECTION:** We used data obtained from the Achmea Health Database (AHD) for this study. Data were extracted from the AHD for patients whose information was entered for the period January 1, 2011 until December 31, 2014. Diagnoses and treatments are assigned a Diagnosis and Treatment Combination (DTC; in Dutch: *Diagnose Behandel Combinatie*). Each DTC includes the diagnosis, the associated medical specialty, and type of care delivered (including whether or not it is a new DTC). Keratoconus is coded as ophthalmologic care under DTC code 457: keratoconus/cornea dystrophy.

The data also included sex, date of birth, date of death (if applicable), and the date the DTC code was assigned (ie, the date of diagnosis). To extract keratoconus cases within DTC code 457, patients aged 10–40 years were defined as the relevant age category based on the pathologic properties of keratoconus; this is the age category in which the majority of new keratoconus cases are diagnosed.¹ Other clinical entities that fall under the DTC code 457 were generally excluded by specifying this age category. These other diagnoses are predominantly found either in older patients (Fuchs endothelial dystrophy) or in younger patients (congenital corneal pathology), although DTC code 457 could contain corneal dystrophies within the specified age category (eg, epithelial basement membrane dystrophy).¹¹ To extract new cases of keratoconus in 2014, patients linked to DTC 457 in a previous year were excluded.

The data provided were anonymized and this study was performed with the permission of the scientific board of Achmea and in accordance with Dutch privacy laws and the Declaration of Helsinki. It was therefore impossible to match insurance records with (electronic) patient charts.

• **DATA ANALYSIS:** The annual age-specific incidence of keratoconus was calculated by dividing the number of new keratoconus cases in 2014 by the total number of insured individuals in the same age category registered in the AHD within the same year. The prevalence of

keratoconus was then estimated based on the age-specific incidence, the total number of individuals registered in the AHD in 2014, mean patient age at the time of diagnosis, and average life expectancy in the Netherlands (based on data from Statistics Netherlands).¹² Calculations were performed using Stata, version 13.1 (StataCorp, College Station, Texas, USA). Data are represented as the annual incidence and prevalence with the corresponding 95% Poisson exact confidence interval (CI).

RESULTS

• **PATIENT CHARACTERISTICS:** There were 4 357 044 individuals registered in the AHD in 2014 and a total of 1 635 517 individuals were within the relevant age category for newly diagnosed keratoconus (ie, 10–40 years). Within this group of eligible individuals, 218 new diagnoses of keratoconus were identified. At the time of the keratoconus diagnosis, the mean age was 28.3 years and 60.6% of the patients were male.

• **INCIDENCE OF KERATOCONUS:** The age-specific annual incidence of keratoconus was calculated by dividing the number of individuals who were newly diagnosed with keratoconus (218) by the number of individuals within the relevant age category (1 635 517), yielding an annual incidence of approximately 1:7500, or 13.3 new cases per 100 000 (95% CI: 11.6–15.2 per 100 000).

• **PREVALENCE OF KERATOCONUS:** The prevalence of keratoconus was estimated based on the annual incidence of keratoconus in the relevant age category (ie, 13.3 new cases per 100 000), the total number of individuals registered in the AHD (4 357 044), the mean age at the time of diagnosis (28.3 years), and the average life expectancy in the Netherlands (81.2 years). Based on these factors, the estimated prevalence of keratoconus in the general population is 1:375, or 265 cases per 100 000 (95% CI: 260–270 per 100 000).

DISCUSSION

THE AIM OF THIS STUDY WAS TO DETERMINE THE ANNUAL incidence and prevalence of keratoconus using health insurance information obtained from approximately 4.4 million individuals in the Netherlands. The age-specific incidence of keratoconus is 1:7500 (13.3 per 100 000) in the relevant age category and the prevalence in the general population is 1:375 (265 per 100 000).

Major strengths of this study are the large sample size and the completeness of the registration. A large sample size is essential in order to accurately determine both the incidence and prevalence of keratoconus. Moreover, as

healthcare providers only get reimbursement of their efforts by using the DTC coding system, the database was previously found to be both accurate and complete.¹² An additional strength of our study is generalizability of the results: Health insurance is mandatory for all residents of the Netherlands and basic health insurance coverage is equal among all health insurance providers. Therefore, populations among different health insurance providers are similar and representative for the Dutch population. Moreover, sophisticated diagnostic devices are widely available throughout the Netherlands and the Dutch hospital system is renowned for its excellent accessibility and high standard of care.¹³ Considering these factors, we feel it is likely that our sample accurately reflects the level of care both needed and provided for patients with keratoconus.

The values for the incidence and prevalence of keratoconus obtained by our study are approximately 5-fold to 10-fold higher than previous reports from population studies.^{4,5} A possible explanation for this difference might be the recent increase in the availability of corneal imaging techniques, resulting in increased accuracy with respect to diagnosing keratoconus. Nevertheless, we believe that our estimates are realistic because the incidence of keratoconus in our study population corresponds with the number of corneal transplants performed annually in the Netherlands. Previous reports indicated that 10%–20% of all keratoconus patients ultimately require a corneal transplant, although advances in rigid gas-permeable contact lenses and scleral lenses might have lowered those rates in the most recent years.^{1–3} Approximately 6.2 million individuals in the Netherlands are 10–40 years of age.¹⁴ Given that the annual incidence of keratoconus in this age category was approximately 1:7500, an estimated 825 new keratoconus cases are diagnosed in the Netherlands each year. Given that approximately 100

corneal transplants are performed for keratoconus in the Netherlands each year,¹⁵ the lifetime chance of receiving a corneal transplant is approximately 12%, which is within the reported range of 10%–20%.

Our study also included possible weaknesses. The incidence calculated in our study may be a slight overestimate, as the diagnostic code that includes keratoconus also includes other conditions (eg, epithelial basement membrane dystrophy). To examine whether this likely affected our analysis, we determined how many patients who received this diagnostic code in our treatment center (a referral center for corneal pathology) were actual keratoconus cases. We found that within the relevant age category (10–40 years), more than 90% of patients with this diagnosis code were indeed keratoconus patients. On the other hand, it is also possible that some patients had late-onset keratoconus and were diagnosed after the age of 40; such patients would not have been included in our analysis and this omission could have led to a slight underestimation.

Previous studies found that Asians have a higher risk of developing keratoconus.^{6–8} The Dutch population consists of 22% immigrants who migrated from Suriname, the former Dutch Antilles, Aruba, Turkey, Morocco, Indonesia, Japan, or other countries.¹⁶ It was impossible to determine the incidence and prevalence among different racial groups because health insurance providers in the Netherlands do not acquire racial information.

In conclusion, our results provide accurate and up-to-date information regarding the annual incidence and prevalence of keratoconus. Obtaining accurate values is essential for policymakers in order to estimate the true impact of this disease on healthcare costs. Importantly, our estimates of the annual incidence and prevalence of keratoconus are 5-fold to 10-fold higher than previous reports, indicating that keratoconus is more common than previously suggested.

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REFERENCES

1. Rabinowitz Y. Keratoconus. *Surv Ophthalmol* 1998;42(4):297–319.
2. Tuft SJ, Moodaley LC, Gregory WM, Davison CR, Buckley RJ. Prognostic factors for the progression of keratoconus. *Ophthalmology* 1994;101(3):439–447.
3. Gordon MO, Steger-May K, Szczotka-Flynn L, et al. Baseline factors predictive of incident penetrating keratoplasty in keratoconus. *Am J Ophthalmol* 2006;142(6):923–930.
4. Kennedy RH, Bourne WM, Dyer JA. A 48-year clinical and epidemiologic study of keratoconus. *Am J Ophthalmol* 1986;101(3):267–273.
5. Ihalainen A. Clinical and epidemiological features of keratoconus genetic and external factors in the pathogenesis of the disease. *Acta Ophthalmol Suppl* 1986;178:1–64.
6. Cozma I, Atherley C, James NJ. Influence of ethnic origin on the incidence of keratoconus and associated atopic disease in Asian and white patients. *Eye (Lond)* 2005;19(8):924–925. author reply 925–926.

7. Georgiou T, Funnell CL, Cassels-Brown A, O'Connor R. Influence of ethnic origin on the incidence of keratoconus and associated atopic disease in Asians and white patients. *Eye (Lond)* 2004;18(4):379–383.
8. Pearson AR, Soneji B, Sarvananthan N, Sandford-Smith JH. Does ethnic origin influence the incidence or severity of keratoconus? *Eye (Lond)* 2000;14(4):625–628.
9. Nederlandse Zorgautoriteit. Zorgverzekeringsmarkt 2014. Available at, https://www.nza.nl/104107/105773/953131/Marktscan_Zorgverzekeringsmarkt_2014_en_Beleidsbrief.pdf. Accessed May 20, 2016.
10. Zorginstituut Nederland. Van goede zorg verzekerd. Available at, [http://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/documenten/rubrieken/pakket/pakketbeheer/1505-van-goede-zorg-verzekerd-hoe-zorginstituut-nederland-adviseert-over-de-inhoud-van-het-basispakket/Van+goede+zorg+verzekerd+\(\).pdf](http://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/documenten/rubrieken/pakket/pakketbeheer/1505-van-goede-zorg-verzekerd-hoe-zorginstituut-nederland-adviseert-over-de-inhoud-van-het-basispakket/Van+goede+zorg+verzekerd+().pdf). Accessed May 20, 2016.
11. Weiss JS, Møller HU, Aldave AJ, et al. IC3D classification of corneal dystrophies—edition 2. *Cornea* 2015;34(2):117–159.
12. Nederlandse Zorgautoriteit. Open data van de Nederlandse zorgautoriteit. Available at, www.opendisdata.nl. Accessed June 18, 2016.
13. Björnberg A. Euro Health Consumer Index 2014. Available at, http://www.healthpowerhouse.com/files/EHCI_2014/EHCI_2014_report.pdf. Accessed June 18, 2016.
14. Dutch Statistics. Bevolkingspyramide. Available at, <https://www.cbs.nl/nl-nl/visualisaties/bevolkingspiramide>. Accessed May 20, 2016.
15. Godefrooij DA, Gans R, Imhof SM, Wisse RP. Trends in penetrating and anterior lamellar corneal grafting techniques for keratoconus: a national registry study. *Acta Ophthalmol* 2016;94(5):489–493.
16. Dutch Statistics. Population; key figures. Available at, <http://statline.cbs.nl/Statweb/publication/?DM=SLLEN&PA=37296eng&D1=0-51,56-68&D2=0,10,20,30,40,50,%28I-1%29-I&LA=EN&VW=T>. Accessed November 13, 2016.