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Faculty of Health and Social Sciences
–
Master's Thesis
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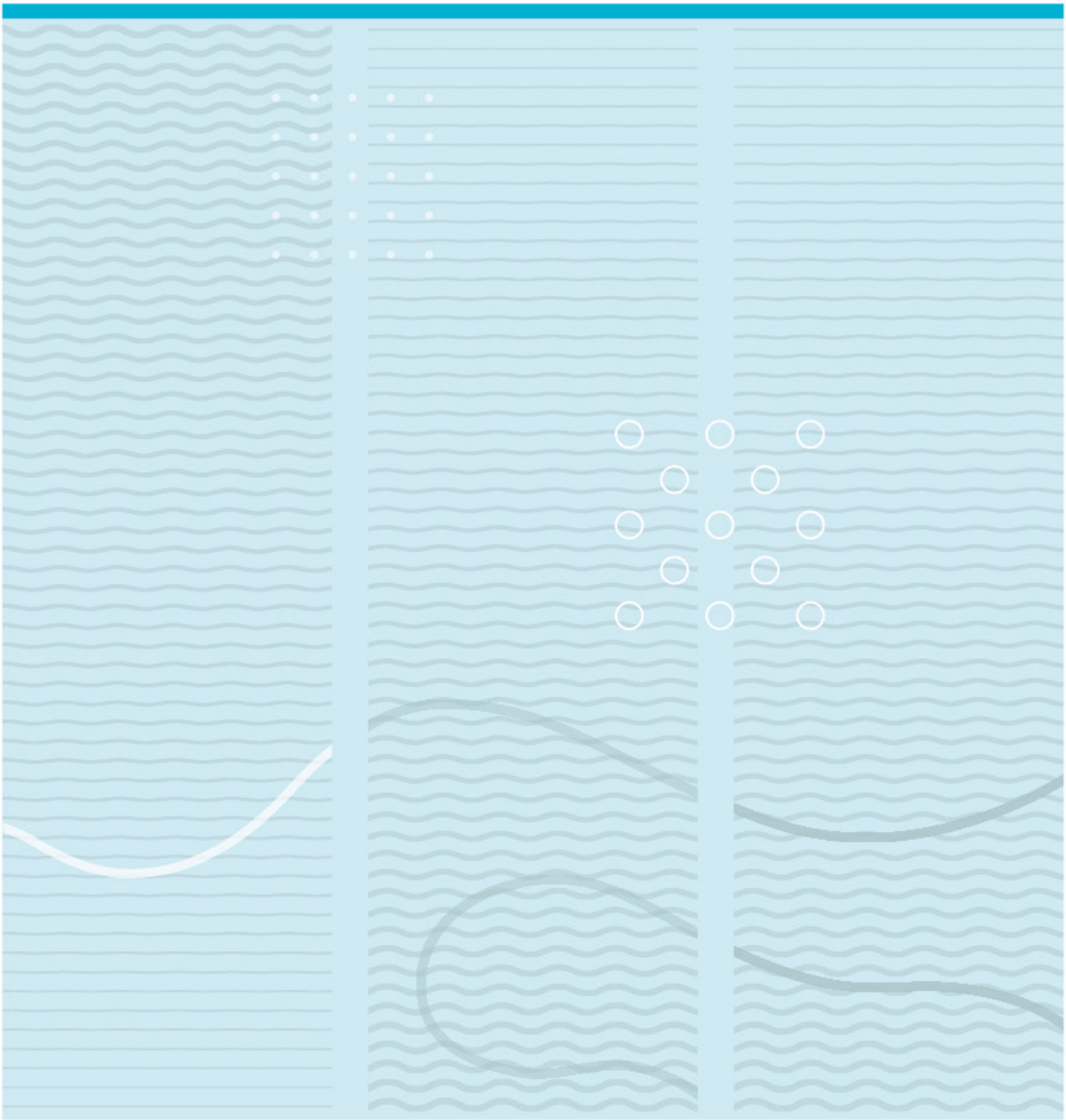
Jonathan Binder

Prevalence and incidence of keratoconus in Sweden

A nationwide register study between 2010 to 2020



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This thesis is worth 30 study points

Contents

1 Foreword

This master thesis was designed into two separate parts, an article and an extended abstract. It is recommended to read the article “Prevalence and incidence of keratoconus in Sweden – A nationwide register study between 2010 to 2020” first and then the extended abstract thesis to get a continuous understanding. These two are partially overlapping, but has separated reference list, annexes, figures and tables. Further, this master thesis assumes some knowledge of eye care and the optometrist´s role in Sweden.

I would also take some time to show my gratitude to my supervisor Vibeke Sundling for all the help and support to navigate me to the finish line. I would also like to say thank you for all support to my lovely partner Ida Quint. At last, thanks to all, Caroline Hansson, Susanne Johansson, Kenneth Knoblauch and Trine Stendal Olsen for the help with the master thesis.

2 Aim

The purpose with the article was to obtain data from the Swedish Patient Register and present the occurrence of keratoconus in Sweden between 2010 to 2020. Further, in the extended abstract present how many Swedes that was treated with cornea crosslinking and corneal transplantations due to keratoconus.

To manage this, the study was based on following research question:

1. How many in Sweden have keratoconus?
2. How many in Sweden are yearly diagnosed with keratoconus?
3. What age and sex do the patients have at the first time of diagnosis?
4. How many are treated with corneal crosslinking due to keratoconus?
5. How many are treated with corneal transplantation due to keratoconus?
6. What was the age of the treated patients?
7. What was the yearly rate of corneal crosslinking and corneal transplantation in the period 1 January 2010 to 31 December 2020?

3 Article

Title page with author details

Prevalence and incidence of keratoconus in Sweden

A nationwide register study between 2010 to 2020

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3.1 Abstract

Purpose:

To estimate the prevalence and incidence of keratoconus in Sweden.

Methods:

The study had a cross-sectional descriptive design using register data from the Swedish Patient Register. Data about keratoconus registered from January 1, 2010, to December 31, 2020 were analyzed. Prevalence was estimated from the total number of patients registered. Incidence was estimated from the annual first-time registrations stratified by age and for the age group 0 to 40 years.

Results:

In 2010 to 2020, 16 055 patients were registered with keratoconus in the Swedish Patient Register, giving an estimated prevalence of 169.5 per 100 000 (95% CI: 144.9-194.1), 74.2% were males. The prevalence of keratoconus was highest in age group 21 to 30 years with a prevalence of 348.4 (95% CI: 313.2-383.6). The average incidence of keratoconus was 11.8 per 100 000 (95% CI: 5.1-18.5). The incidence was highest in age group 21 to 30 years, 26.1 per 100 000 (95% CI: 16.1-36.1). For age group 0 to 40 years, the estimate incidence was 22.5 per 100 000 (95% CI: 13.7-32.3).

Conclusion:

This register study present prevalence and incidence of keratoconus in Sweden between 2010 to 2020. The prevalence and incidence were higher than reported in earlier studies, but comparable to recent Scandinavian studies. This may be explained by modern diagnostic tools and treatments like corneal crosslinking. The true prevalence may be even higher due to under registration in older age groups and keratoconus should not be regarded as a rare condition.

Keywords:

Keratoconus, Prevalence, Incidence, Epidemiology.

3.2 Introduction

Keratoconus was first described in 1854 as a non-inflammatory and chronic corneal ectasia (Gordon-Shaag et al., 2015). Keratoconus is a corneal ectasia characterized by progressive steepening and thinning of the cornea and can lead to visual impairment (Bowling, 2016, p. 213; Mukhtar & Ambati, 2018). Corneal ectasia also consists of pellucid marginal degeneration and keratoglobus but keratoconus is the most common (Bowling, 2016, pp. 214, 216; Gomes et al., 2015).

Two decades ago, corneal collagen crosslinking (CXL) was introduced to the field and has been proven to be a revolutionizing treatment to prevent progression of keratoconus (Gregor et al., 2003; Vardhaman-P et al., 2013). Further, in some reports CXL has demonstrated visual and topographic improvement by reducing the irregularity of astigmatism (Gregor et al., 2003; Vardhaman-P et al., 2013). Since CXL was implemented in the management of keratoconus, corneal transplantation has reduced in number, up to 25% in some register studies (Godefrooij et al., 2016; Gregor et al., 2003).

It has been reported that family history can be a risk factor of developing keratoconus (Romero-Jiménez et al., 2010). Further, keratoconus often debuts as unilaterally, but within 16 years more than 50% of the unaffected eyes develop keratoconus and in an early stage of keratoconus, the patients are often asymptomatic (Mukhtar & Ambati, 2018; Vardhaman-P et al., 2013). Myopia and irregular astigmatism present decreased visual acuity during progression of keratoconus (Gordon-Shaag et al., 2015). Keratoconus is therefore often detected in the course of an eye examination and the patient is unaware of the disease (Gordon-Shaag et al., 2015).

The diagnosing of keratoconus has increased the last decade because of more advanced diagnostic tools to monitor corneal ectasis (Flynn et al., 2016). The best and most sensitive method of detecting, confirming and supervision keratoconus is corneal topography based on the principles of the Placido disc, Scheimpflug imaging, and optical coherence tomography (OCT) (Gordon-Shaag et al., 2015). A commonly used grading system of keratoconus is Amsler-Krumeich system (AK) and in 2015 a new grading system was introduced (Belin & Duncan, 2016). Belin ABCD take into consideration anterior radius of curvature (ACR), posterior radius of curvature (PCR), thinnest pachymetry, best corrected visual acuity at distance (BCVA) and corneal scarring (Belin & Duncan, 2016).

Recently, keratoconus has been found to be more common than previously reported (Godefrooij et al., 2017a). Previous studies estimate the prevalence of keratoconus to be 50 to 54 per 100 000 worldwide, however, in the last decades studies have shown a higher prevalence rate in many parts of the world (Gomes et al., 2015; Kennedy et al., 1986; Romero-Jiménez et al., 2010). A study from the Netherlands present an estimated prevalence of 265 per 100 000 (Godefrooij et al., 2017a). In Scandinavia, the prevalence of keratoconus is sparsely described and a register study in Norway present a prevalence of 192.1 per 100 000 and for patients Down syndrome 5481 per 100 000 (Kristianslund & Drolsum, 2021; Kristianslund et al., 2020). Using data from national patient register in Denmark, the prevalence was estimated to 44 per 100 000 (Bak-Nielsen et al., 2019). The annual incidence of keratoconus in Norway was 19.76 per 100 000 and the highest rates of new cases (36.7 per 100 000) were in the age group of 21 to 30 years (Kristianslund et al., 2020). Between 1977 to 2015 the incidence of keratoconus in Denmark was estimated at 3.6 per 100 000 (Bak-Nielsen et al., 2019).

No epidemiology studies of keratoconus have previously been reported in Sweden and due to the established public healthcare in Sweden with a wide national patient register, we think a register study was appropriate to present the occurrence of keratoconus in Sweden. The aim for this study was to present an estimated prevalence and incidence of keratoconus in Sweden between 2010 to 2020.

3.3 Methods

The study had a cross-sectional, descriptive design analyzing data obtained from the Swedish Patient Register. The register is administered by the Swedish National Board of Health and Welfare and reporting to the register has been mandatory since the last decades for all public hospitals and for private practices with a public contract in the Swedish health care.

The study population was all men and women with keratoconus in Sweden regardless a secondary diagnosis, and the sample population was all men and women diagnosed with keratoconus and registered in the Swedish Patient Register between 2010 to 2020. Further, it is the National Board of Health and Welfare who approved the use of the anonymous data. Due to the anonymity in the present data, the Swedish Ethical Review do not need to do an appraisal.

The present study analyze data for patients registered with specific International Classification of Disease and Related Health Problems (ICD-10) codes the last decades. The specific ICD-10 code for keratoconus is H18.6 and each patient in the data have a personal identification number to ensure that each patient only counts once. The data were obtained in the period of the 1 January 2010 to 31 December 2020 to estimate the annual incidence. In the same period annual incidence was also calculated for the age group 0 to 40, this because we consider these patients to be in a risk group to develop keratoconus and also according to similar studies (Godefrooij et al., 2017a; Kristianslund et al., 2020).

The prevalence was estimated from the total number of registrations with ICD-10 H.18.6 in the Swedish Patient Register between 2010 to 2020. Further, prevalence and incidence were stratified by sex and in age groups 0-20, 21-30, 31-40, 41-50, 51-60, 61-70, +71 years. Further, the size of the age groups was determined so the data remained anonymous. Therefore, were some age groups in larger intervals.

The data about the Swedish population was obtained from the open, digital archive at the Central Bureau of Statistics categorized both gender, age, and years (www.scb.se). This data includes all inhabitants that was registered and lived in Sweden which includes immigrants with a unique coordination number. Total number of inhabitants for each of the eleven years were obtained to increase the accuracy and reliability of the present study.

The data were analyzed using the free software program R-commander (version 2.8.1) and was presented per 100 000 inhabitants, with a 95% confidence interval (CI). This results in a clear conclusion and will be easily comparable with similar studies from Scandinavia (Bak-Nielsen et al., 2019; Kristianslund et al., 2020). This study adhered to the Declaration of Helsinki.

3.4 Results

In 2010 to 2020, 16 055 patients were registered with ICD-10 H18.6 Keratoconus in the Swedish Patient Register, 74.2% were males. During the same period the average number of Swedish inhabitants was 9 886 365. The estimated prevalence of keratoconus was 169.5 per 100 000 (95% CI: 144.9-194.1) or conforming to 1 per 590. Table 1 present the age-stratified prevalence of keratoconus and the average prevalence. The prevalence was highest in the age group 21 to 30 with a prevalence of 348.4 per 100 000 (95% CI: 313.2-383.6).

The estimated annual incidence of keratoconus was 11.8 per 100 000 (95% CI: 5.1-18.5) and is presented in Figure 2. The highest incidence rate, 26.1 per 100 000 (95% CI: 16.1-36.1) was in the age group 21 to 30 years and the lowest, 5.2 per 100 000 (95% CI: 0.8-9.7) in the age group 71 year and older. The gender distribution for first-time registration is presented in Figure 1. The estimated incidence in the age group 0 to 40 years was 22.5 per 100 000 (95% CI: 13.7-32.3) and is shown in Figure 3.

3.5 Discussion

Keratoconus has been reported as an uncommon condition but in the last decades more studies has presented an increased prevalence (Godefrooij et al., 2017a; Kristianslund et al., 2020) and to our knowledge, the prevalence and incidence of keratoconus in Sweden has not previously been reported.

The estimated prevalence of keratoconus in Sweden was 169.5 per 100 000, that is the only and highest rate reported from the general population in Sweden, whereas earlier worldwide studies report a lower prevalence of 50 to 54 per 100 000 (Godefrooij et al., 2017a; Kennedy et al., 1986). This large difference can be related to several factors such as study design, access to health care, diagnostic criteria, and diagnostic tools. In Norway and the Netherlands, the estimated prevalence is similar to our study, 192.1 per 100 000 and 265 per 100 000 respectively (Godefrooij et al., 2017a; Kristianslund et al., 2020). Both these studies are register studies, undertaken during the same period as our register study, and our study supports these numbers. Denmark presents a prevalence of 44 per 100 000 for keratoconus which reflect the world-know prevalence and this could be due to criterial like Down Syndrome, corneal laser refractive surgery were excluding in the data analysis (Bak-Nielsen et al., 2019).

Three of four patients registered with keratoconus in Sweden were male, this is also in line with findings from Norway, Denmark, the Netherlands and other studies (Aylin & Orkun, 2008; Bak-Nielsen et al., 2019; Godefrooij et al., 2017a; Kristianslund et al., 2020) and is showing a clear overrepresentation of keratoconus among male patients. There are no explanations for the possible gender difference in keratoconus, although there is hypothesis that hormonal factors can be an explanation (Gordon-Shaag et al., 2015). However, this difference of gender is not found in some studies, these presenting no or small sex difference for keratoconus and this can be due the difference of population and ethnicity in the study (Hwang et al., 2018; Kennedy et al., 1986; Xu et al., 2012).

The present study estimates an average keratoconus incidence of 11.8 per 100 000, with the highest incidence in the age group 21 to 30 (26.1 per 100 000) and the second highest incidence was in the age group 31 to 40 (16.9 per 100 000). These results are supported by the study from Norway that present similar distribution in the same age groups (Kristianslund et al., 2020). In the age group 0 to 20 the incidence was low, compared to age groups 21 to 30 and 31 to 40, and it is known that keratoconus debuts around puberty to young adulthood. We do not know if the majority of the keratoconus diagnosis was in age group 0 to 10 or in 11 to 20. Nevertheless, this will not change that incidence was low in the first twenty years of life compared to the third and fourth decades of life. Further, the lower incidence in the age group 0 to 20 may reflect that keratoconus takes some years to progress to have visual impact and therefore leads to a diagnosed at an older age. Moreover, this can also reflect that eye examinations by optometrists are done at an older age because of requirements for the driving license, work, or school. Nevertheless, it is important to screen for keratoconus in young patients as keratoconus can lead to reduced visual acuity, negatively affecting educational and social development (Mukhtar & Ambati, 2018).

We assume that the patients with first-time registration in late adulthood has been undiagnosed in the greater part of life, so to adjust for these aspects and estimate a more reliable incidence, we did a secondary estimation of incidence for only patient aged 0 to 40. The estimated incidence in the age group 0 to 40 was 22.5 per 100 000 and therefore higher than average incidence and are comparable to the incidence in Norway and Netherlands, 19.76 per 100 000 and 13.3 per 100 000 in age group 0 to 40 respectively 10 to 40 in the Netherlands (Godefrooij et al., 2017a; Kristianslund et al., 2020).

In the time period of the present study, the number of first-time registrations has increased over the years, this is also in line with reports from Norway (Kristianslund et al., 2020). We believe the contributing factor to the increased incidence of keratoconus can be to higher awareness due to more modern diagnostic tools like Scheimpflug camera and optical coherence tomography (OCT) and the implementations of CXL as a treatment to reduce progression. Further, research about keratoconus has resulted in modern grading system like Belin ABCD, which has made it easier to detect and follow patient with progression of keratoconus (Belin et al., 2020). This enhanced system of grading has also been implemented in the software in Pentacam from Oculus GmbH, Wetzlar, Germany to facilitate grading of keratoconus (Belin et al., 2020).

A contributed factor that we believe has increased the incidence of keratoconus is the increasing number of refractive laser surgery that can lead to progression of corneal ectasia. Further, a pre-examination can also lead to a detection of keratoconus. Furthermore, it is unclear if all clinics classify progression of refractive laser surgery as keratoconus or as other specific changes in the cornea in Sweden. This may have increased the total number of patients that was diagnosed with keratoconus.

The present study does not take in consideration ethnicity or immigration which has described to be factors to impact the prevalence of keratoconus. Kristianslund et al (2020) discussed that the increased prevalence of keratoconus may also be a result of immigration from regions with a higher prevalence of keratoconus. The study in Denmark present a lower incidence of keratoconus when immigrants were excluded from the analysis (Bak-Nielsen et al., 2019). Moreover, a population study from the Netherlands present a high prevalence and reports that approximately 22% of the general population was immigrants. Due to the lack of statistics about immigrants in Sweden, we do not know how this affect the prevalence. Therefore, we suggested that further epidemiological studies, including ethnicity should be carried out to improve the knowledge of keratoconus in Sweden.

In the present study the data were obtained with help of ICD-10 codes, where keratoconus has a specific one (H18.6). There are other corneal ectasias with separate ICD-10 codes that was excluded from the study. Nevertheless, we believe that other corneal ectasia has been coded as keratoconus and is included in this study. We suspect that the number is limited compared to the number of keratoconus and therefore have limited impact on the findings of the present study.

The choice of grading system will determine when the first-time diagnosis of keratoconus was made. To our knowledge, in the Swedish health care there are no general guidelines for diagnostics and management of keratoconus. Therefore, we do not know the criteria for diagnosis of keratoconus in Sweden. Nevertheless, we do not believe this have a significant impact for the present study.

ICD-10 codes can be used when a general practice or another health personnel suspect keratoconus and referrals to an ophthalmologist who later may contradict the diagnosis. This first ICD-10 code will be reported in the Patient Register. This will contribute to an overestimation of keratoconus. However, we believe this will have a limited impact on the outcome of the present study, but it represents as an unreliability in the data.

We do not know if the patients with keratoconus were diagnosed in a hospital of private practice, but it is mandatory for healthcare personnel to report in the nationwide Swedish Patient Register. Therefore, we believe that the present study reflects the occurrence of keratoconus in the general population in a chosen time period of eleven years in Sweden.

In the first ten years of the present study, there was an increasing occurrence of keratoconus, but in 2020, there was a slightly decreasing of occurrence. We suspect this is due to the Covid-19 pandemic leading to delayed management of keratoconus. Delayed management of keratoconus can lead to reduced visual acuity and quality of life. Therefore, this knowledge is important for the clinicians and policy makers that are allocating healthcare personnel in an ongoing pandemic or under normal circumstances. This is also highlighting as an important topic in a Norwegian population study (Kristianslund et al., 2020).

The data for prevalence are obtained if the patient has been in the health care systems between 2010 to 2020 even if they have not got the first-time diagnosis during this period. Further, because of the low numbers of patients with keratoconus in the age group 0 to 10 and 11 to 20, the Swedish National Board of Health and Welfare merged the age group 0 to 10 and 11 to 20 when provided the data to maintain the anonymity. This does not affect the result of this study, part from the absolute, relative numbers of keratoconus in the youngest age.

This study did not obtain first time diagnostic records, like pachymetry, k-value or visual acuity that could have described the stage of keratoconus at the time of diagnosis. A more in-depth study including this data could described if keratoconus was diagnosed at an early stage or if there are place for improvement of detecting and management of keratoconus.

The study presents credible results of the prevalence and incidence of keratoconus in Sweden and the results show similar prevalence and incidence as in other Scandinavian countries. This indicates that keratoconus is more common than previously described. Further, early diagnosis and early treatment like CXL are beneficial for patients' vision and quality of life and has also a positive societal and economical effect (Godefrooij et al., 2017b; Lindstrom et al., 2021).

To our knowledge, there has been non epidemiology studies to established keratoconus in Sweden and the aim for this study was to present an estimated prevalence and incidence of keratoconus in Sweden between 2010 to 2020. The prevalence and incidence were higher than reported in earlier studies, but comparable to recent Scandinavian studies. The presented results may in part be explained by the modern management like, diagnostic tools, grading system and treatments to prevent a progression. The true prevalence may be even higher due to under registration in older age groups. The present study indicated that keratoconus appears to be more prevalent than earlier known and should not be regarded as a rare condition in Sweden. This study contributes with important knowledge about keratoconus for the Swedish eye care.

3.6 References

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3.7 List of tables

Table 1. The estimated average prevalence of keratoconus and prevalence of keratoconus stratified by age, per 100 000 with 95% confidence interval (CI).

Age groups (years)	Prevalence per 100 000 (95% CI: lower and higher)
0–20	90.0 (71.8–108.2)
21–30	348.4 (313.2–383.6)
31–40	255.3 (225.2–285.4)
41–50	183.8 (158.3–209.3)
51–60	133.5 (111.8–155.2)
61–70	111.5 (91.7–131.3)
71+	63.8 (48.8–78.8)
Average	169.5 (144.9–194.1)

3.8 List of figures

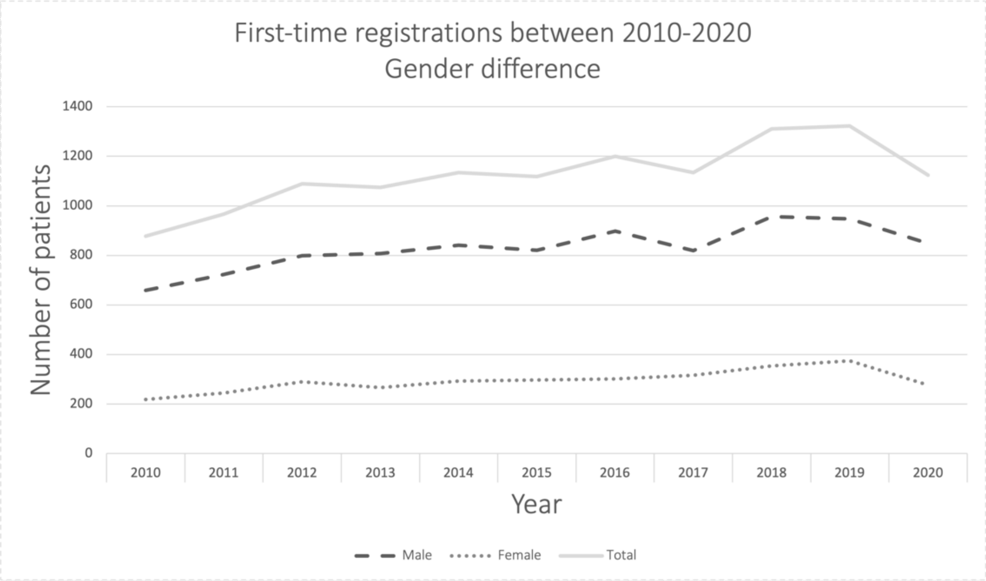

Figure 1. Total number of first-time registrations by year in 2010 to 2020. The data were from Swedish Patient Registry and data prior 2010 were excluded. There is three lines representing males (dashed), females (dotted) and total (solid).

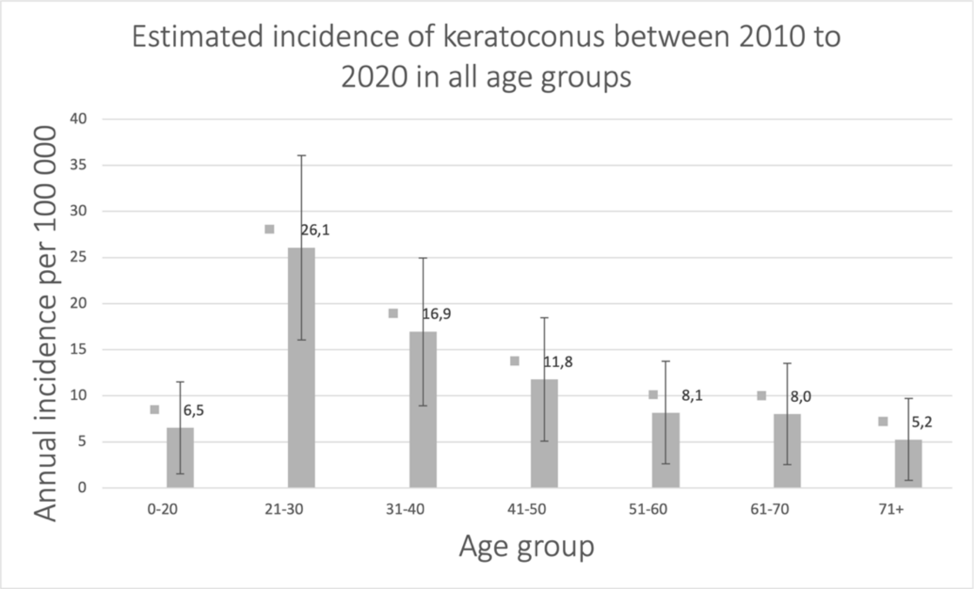

Figure 2. The estimated age-stratified average annual incidence of keratoconus per 100 000 in 2010 to 2020.

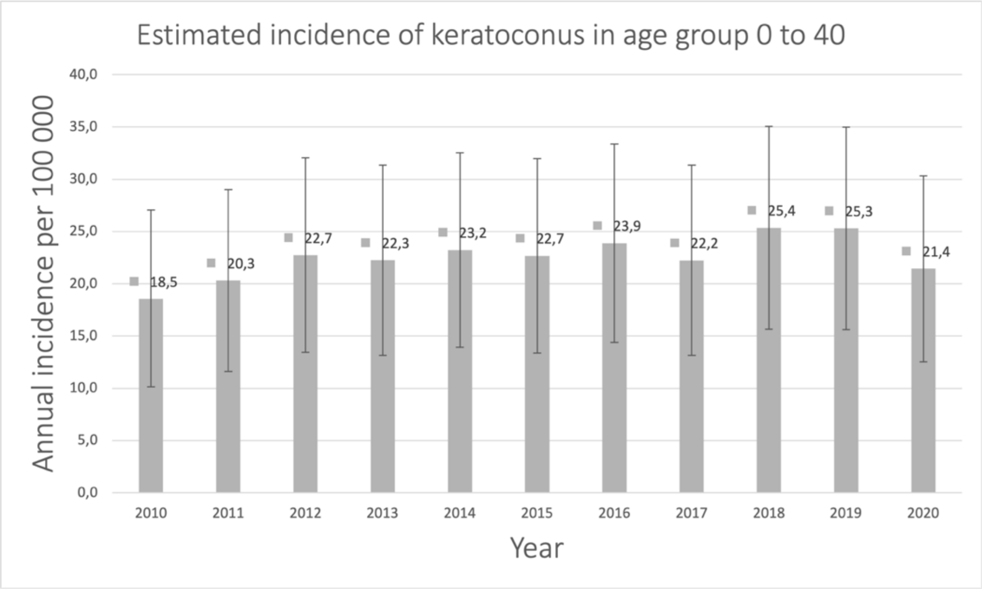

Figure 3. Estimated annual incidence of keratoconus per 100 000 for age group 0 to 40.

3.9 Acknowledgement

The article has been presented as a master thesis at the University of South-Eastern Norway in April 2022. The authors declare no interest of conflict and will not gain economical on this article. No financial founds has been given to this study. The study did not require ethical approval from the Swedish Ethical Review. The obtained data from Swedish Patient Registry is administrated of the National Board of Health and Welfare and the analysis of these data are the authors responsibility.

3.10 Annexes

Annex 1: Author guidelines

Author guidelines can be read on the next page or online:

https://onlinelibrary.wiley.com/page/journal/17553768/homepage/ForAuthors.html

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4 Extended abstract

4.1 Abstract

Purpose:

To estimate the prevalence and incidence of keratoconus in Sweden and present total number of corneal crosslinking and corneal transplantations.

Methods:

The study had a cross-sectional descriptive design using register data from the Swedish Patient Register. Data about keratoconus registered from January 1, 2010, to December 31, 2020, were analyzed. Prevalence was estimated from the total number of patients registered. Incidence was estimated from the annual of first-time registrations stratified by age and for the age group 0 to 40 years. Corneal crosslinking and corneal transplantation were estimated from total number of patients registered with keratoconus and the chosen treatment.

Results:

In 2010 to 2020, 16 055 patients were registered with keratoconus in the Swedish Patient Register, giving an estimated prevalence of 169.5 per 100 000 (95% CI: 144.9-194.1), 74.2% were males. The prevalence of keratoconus was highest in age group 21 to 30 years with a prevalence of 348.4 (95% CI: 313.2-383.6). The average incidence of keratoconus was 11.8 per 100 000 (95% CI: 5.1-18.5). The incidence was highest in age group 21 to 30 years, 26.1 per 100 000 (95% CI: 16.1-36.1). For age group 0 to 40 years, the estimate prevalence was 22.5 per 100 000 (95% CI: 13.7-32.3). In 2010 to 2020, 909 corneal crosslinking was registered, which was an average of 82.6 per year. In the same period 4071 corneal transplantation was registered, which was an average of 370.1 per year. In all, 5.1% of all patients with keratoconus were corneal crosslinked and 10.6% were corneal transplanted. The estimated mean from first-time registration to corneal crosslinking was 3.3 years and 8.4 years for corneal transplantation.

Conclusion:

This register study present prevalence and incidence of keratoconus in Sweden between 2010 to 2020. The results were higher than reported in earlier studies, but comparable to recent Scandinavian studies. The higher result could be explained due to modern diagnostic tools and treatments like corneal crosslinking. The present study indicated that keratoconus appears to be more prevalent than earlier known and males in age group 21 to 30 has higher risk to develop keratoconus. Between 2010 to 2020, corneal transplantation was a more common treatment than corneal collagen crosslinking for all age groups. This statistic contributes with important knowledge for the Swedish eye care. Nevertheless, true prevalence may be even higher due to under registration in older age groups.

Keywords:

Keratoconus, Prevalence, Incidence, Epidemiology, Corneal crosslinking, Corneal transplantation.

4.2 Abstrakt

Syfte:

Att uppskatta prevalensen och incidensen av keratokonus i Sverige och presentera antal korneal krosslinking och hornhinnetransplantationer.

Metod:

Studien var en tvärsnittsstudie med registerdata från Svenska Patientregistret. Statistiken om keratokonus som blev analyserad var registrerad från 1 januari 2010 till 31 december 2020. Prevalensen uppskattades från det totala antalet registrerade patienter. Incidensen uppskattades från det årliga antalet förstagångsregistreringar stratifierade efter ålder om tio och för en åldersgrupp från 0 till 40 år. Korneal krosslinking och hornhinnetransplantation uppskattades från det totala antalet patienter registrerade med keratokonus och den specifika behandlingen.

Resultat:

Mellan 2010 och 2020 registrerades 16 055 patienter med keratokonus i Svenska Patientregistret. Den estimerad prevalens var 169.5 per 100 000 (95 % KI: 144.9–194.1) och 74.2% av dessa var män. Prevalensen av keratokonus var högst i åldersgruppen 21 till 30 år med en prevalens på 348.4 (95 % KI: 313.2–383.6). Den genomsnittliga incidensen av keratokonus var 11.8 per 100 000 (95 % KI: 5.1–18.5). Incidensen var högst i åldersgruppen 21 till 30 år, 26.1 per 100 000 (95 % KI: 16.1–36.1). För åldersgruppen 0 till 40 år var den estimerade prevalensen 22.5 per 100 000 (95 % KI: 13.7–32.3). Mellan 2010 till 2020 registrerades 909 korneala krosslinkingar, vilket motsvarar 82.6 per år. Under samma tidsperiod registrerades 4071 hornhinnetransplantationer, vilket motsvarar 370.1 per år. Totalt 5.1% av alla registrerade patienter med keratokonus blev behandlade med korneal krosslinking och 10.6% blev hornhinnetransplanterade. Medelvärdet från förstagångsregistrering till korneal krosslinking var 3.3 år och för hornhinnetransplantation var det 8.4 år.

Slutsats:

Denna registerstudie visar prevalensen och incidensen av keratokonus i Sverige mellan 2010 och 2020. Resultaten var högre än tidigare studier, men jämförbara med nyare skandinaviska studier och kan förklaras på grund av modernare diagnostikverktyg och behandlingar som korneal krosslinking. Studien indikerat att keratokonus är vanligare än tidigare känt och män i åldersgruppen 21 till 30 har förhöjd risk att utveckla keratokonus. Mellan 2010 och 2020 var hornhinnetransplantation vanligare behandling för keratokonus än korneal krosslinking i alla åldrar. Studiens resultat bidrar med viktig kunskap för svensk ögonsjukvård och keratokonus ska inte ses som en sällsynt hornhinneförändring. Vidare, den verkliga prevalensen kan vara ännu högre på grund underregistrering i äldre åldersgrupper.

Nyckelord:

Keratokonus, Prevalens, Incidens, Epidemiologi, Korneal krosslinking, Hornhinnetransplantation.

4.3 Introduction

This master thesis was designed into two separate parts, an article, and an extended abstract. It is recommended to read the article “Prevalence and incidence of keratoconus in Sweden – A nationwide register study between 2010 to 2020” first and then the extended abstract to get a continuous understanding. These two are partially overlapping, but has separated reference lists, annexes, figures, and tables.

The article was completed first and the aim of the article was to estimate prevalence and incidence of keratoconus in Sweden during a specific period. The ambition is to publish the article, therefore the article follows Acta Ophthalmologist author guidelines. The article will be sent to Acta Ophthalmologist after successful completion of the thesis.

The extended abstract explained more thoroughly the method and theory for prevalence and incidence of keratoconus. The results are compared to a similar study from Norway. Moreover, new results are presented and discussed in the extended abstract. The extended abstract follows the University of South-Eastern Norway guidelines for a Master Thesis.

4.3.1 Background of the chosen theme

The optometrist profession is the primary eye care and has obligations to screen for ocular pathology in an eye examination. Also, in Sweden there is no national data for the prevalence and incidence of keratoconus and due to the lack of this knowledge, this topic was chosen.

4.3.2 Excluding criteria for the master thesis

Due to the large, obtained material, the findings did not fit in one article and therefore was the result of treatment presented in the extended abstract. To make an essential, first study to present occurrence of keratoconus within the scope of a master´s thesis, demographic and ethnicity data were not collected. Further, according to other studies Intracorneal Ring Segments (ICRS) is the least used treatment for keratoconus (Bak-Nielsen et al., 2019) and therefore was this treatment excluded from the present study.

4.3.3 The purpose for the master thesis

The main focus of the article was to present the prevalence and incidence of keratoconus in Sweden and the results were compared to other studies in Scandinavia and Northern Europe. The master thesis further aims was also to estimate the total number of corneal crosslinking (CXL) and corneal transplantation in Sweden.

This study can increase the knowledge for an optometrist, for example, how often a keratoconus patient will appear and the typically age and gender for these patients. Also, what is the probability that the patient needs treatment like CXL or corneal transplantation.

4.4 Method

In the article the method was briefly described. In this section the method will be more explained in-depth. First will the research design, literature and the study population be presented and then will the register study be described. The method for the present study has been submitted as a Research Protocol in an earlier course, Research Methods and Project Description (MRES) and assessed passed. The Research Protocol, method section is provided in Annex 3.

4.4.1 Research design

The study had a quantitative- and cross-sectional, descriptive design and analyzing data obtained from the Swedish Patient Register. A quantitative study is based on systematic obtained quantitatively data that is analyzed and often used in natural and social science (Nygaard, 2017, pp. 155-157). A cross-sectional study is an observational study that will analyze statistic data and are often used in medical research to present prevalence and incidence (Befring, 2020, pp. 112-118). A cross-sectional study is a form of epidemiological study (Befring, 2020, pp. 52-55).

4.4.2 Literature

In an early stage, a literature search was done to acquainted in what type of research that was available and if there has been a resembling study in Sweden. The literature search was performed in University of South-Eastern Norway online library which includes databases like: AMED, BMJ best practice, EMBASE, Scopus and PubMed (University-of-South-Eastern-Norway, 2022). The search resulted in similar, modern studies from Norway, Denmark and the Netherlands but non from Sweden.

After the literature search it has been clear that there was a large amount of research on keratoconus. Due to data like prevalence and incidence can change with time, I chose the most modern research, but I also compared to older research.

To increase and share the knowledge a journal club was started at the beginning of the master thesis. Together with the supervisor and students with similar topic we discussed and analyzed articles and research about keratoconus (Bowles et al., 2013).

4.4.3 Study population

The study population was all men and women with keratoconus in Sweden regardless a secondary diagnosis, and the sample population was all men and women diagnosed with keratoconus and registered in the Swedish Patient Register.

4.4.4 Data collection

The register is administered by the National Board of Health and Welfare and the reporting to the register has been mandatory since 2001 for all public hospitals and for most of the private practices, this because they commonly have a public contract (Patientregister hos Socialstyrelsen, 2001).

The first stage of this study was to contact the National Board of Health and Welfare to confirm the possibility to obtain this type of data. When that was confirmed, I compiled the statistic order with right International Classification of Disease and Related Health Problems (ICD-10) codes that is presented in Table 2. After three months I got a contact person at the National Board of Health and Welfare and together we summarized the statistical data. The period of the present study was chosen since it was closest in time. This master thesis and study was financed with private funds.

The data about the Swedish population was obtained from the open, digital archive at the Central Bureau of Statistics categorized both gender, age, and years (Statistikmyndigheten, 2022). This data includes all inhabitance that was registered and lived in Sweden which includes immigrants with a unique coordination number. Total number of inhabitances for each of the eleven years were obtained and used to increase the accuracy and reliability of the present study.

4.4.5 Data analyze

The present study analyze data with help of ICD-10. The data were obtained in the period of the 1 January 2010 to 31 December 2020 to estimate the annual incidence. In the same period incidence was calculated a second time for age up to 40 years old because it is considering these patients to be in a risk group to develop keratoconus. The data was divided in gender and age groups and each patient has a personal identification number to ensure that each patient only counts once during the selected period. The prevalence was estimated from the total number of registrations with ICD-10 according to the table 2 in the Swedish Patient Register between 2010 to 2020, and the first-time registration for these patients starts from 1998 and goes up to 2020. Further, prevalence and incidence were stratified by sex and age-groups 0-20, 21-30, 31-40, 41-50, 51-60, 61-70, +71 years. Due to low number of registrations in age group 0-10 and 11-21 the National Board of Health and Welfare merge this into one larger age group to not risk expose the patients. The National Board of Health and Welfare reported that no data was excluded because of low credibility.

The data were delivered as a Microsoft Excel file and analyzed in the free software program R-commander (version 2.8.1) and was presented per 100 000 inhabitants, with a 95% confidence interval (CI). The figures were done in Microsoft Excel. This results in a perspicuous conclusion and will be easily comparable with similar studies from Scandinavia (Bak-Nielsen et al., 2019; Kristianslund et al., 2020).

4.4.6 Ethic

It is the National Board of Health and Welfare who approved the use of the anonymous data. Due to the anonymity in the present data, the Swedish Ethical Review do not need to do an appraisal. This study adhered to the Declaration of Helsinki.

4.5 Theory

In this section the theory about keratoconus and the theory that was the foundation for the chosen topic will be presented. Further, this will later be used as a theoretical framework in the discussion section.

4.5.1 Knowledge of keratoconus

Keratoconus is a condition that has considered too be uncommon and for two decades ago, there was no good or effective treatment to reduce keratoconus progression (Godefrooij et al., 2017a; Godefrooij et al., 2017b). Further, corneal transplantation was the solution when glasses or contact lenses cannot increase visual acuity (Kristianslund et al., 2020). Keratoconus can develop at an early age and is known to be more aggressive in younger ages. Further, keratoconus often debuts as unilaterally, but within 16 years more than 50% of the unaffected eyes develop keratoconus (Mukhtar & Ambati, 2018; Vardhaman-P et al., 2013).

The best and most sensitive method of detecting, confirming and supervision keratoconus is with corneal topography based on the principles of the Placido disc or Scheimpflug imaging. Both these has been known as the gold standard, but Scheimpflug imaging has later on been proven to be a more accurate method to estimate the corneal surface and pathogens progression (Gordon-Shaag et al., 2015). Diagnosing of keratoconus has increased the last decade because of more advanced devices to monitor corneal ectasis (Flynn et al., 2016).

Asians and Arabians has a higher risk to develop keratoconus and in some studies the incidence was 4.4 to 7.5 higher in Asian ethnicity compared to Caucasian ethnicity (Gomes et al., 2015; Gordon-Shaag et al., 2015; Romero-Jiménez et al., 2010). Genetic factors have shown to increase the risk for developing keratoconus, if a close relative had keratoconus (Romero-Jiménez et al., 2010).

Visual impairment because of keratoconus may affect educational and social development negatively (Mukhtar & Ambati, 2018). In an early stage of keratoconus, the patients are often asymptomatic. Myopia and irregular astigmatism present decreased visual acuity during a progression so keratoconus is often detected in the course of an eye examination and the patient is unaware of the condition (Gordon-Shaag et al., 2015).

The etiology is until today unknown, but what is proven is that genetic and environmental factors affect the development of keratoconus (Shneor et al., 2013). Mechanical risk factors have long been described as a risk factor like atopic dermatitis, asthma, floppy eyelid syndrome and eye rubbing which can be related to ocular allergy (Bak-Nielsen et al., 2019; Gomes et al., 2015; Romero-Jiménez et al., 2010). In some studies over 65% of the patient with keratoconus rub their eyes (Shneor et al., 2013). Keratoconus is associated with multitude of disease like Ehlers-Danlos syndrome, Down Syndrome, Leber's congenital amaurosis, osteogenesis imperfecta and connective tissue disorder (Gomes et al., 2015; Shneor et al., 2013). Hormonal changes due to pregnancy may affect corneal biomechanics in a negative way and induce a keratoconus progression (Bilgihan et al., 2011).

Corneal transplantation was the only treatment for keratoconus with low visual acuity due to severe keratoconus (Kristianslund et al., 2020). Further, due to research and science in the last decades, CXL has developed as a treatment to reduce the progression of keratoconus (Godefrooij et al., 2017b; Kristianslund et al., 2020). CXL has reported to be a gold standard to prevent progression which also has reported to reduce number of corneal transplantations (Godefrooij et al., 2016; Godefrooij et al., 2017b).

The Swedish Corneal Register is a nationwide quality register and reports annual number of corneal transplantations since 1996 and in the first years, 30% of all corneal transplantation was due to keratoconus (Svenska Cornearegistret & Svensk Cornealkirurgisk Förening, 2020). Further, according to the Corneal Register, keratoconus has been the leading cause to corneal transplantation but since a couple years back Fuchs's endothelia dystrophia is the most common cause (Svenska Cornearegistret & Svensk Cornealkirurgisk Förening, 2020). In 2020, 2.63% of all corneal transplantation was due to keratoconus, according to the Swedish Corneal Register, and the reduced number was explained due to CXL (Svenska Cornearegistret & Svensk Cornealkirurgisk Förening, 2020).

4.5.2 The optometrist role in the management of keratoconus

An optometrist is after the education legitimized by the National Board of Health and Welfare and to prescribe contact lenses, the optometrist requires to have a second legitimation (Socialstyrelsen, 2019). Scleral and Rigid Gas Permeable (RGP) contact lenses can increase visual acuity in a severe keratoconus and therefore reduce the number of corneal transplantation (Koppen et al., 2018). CXL is a treatment to reduce the progression of keratoconus and corneal transplantation reduced the irregularity in the cornea (Sandvik et al., 2015). Nevertheless, can it be needed to prescribe medical contact lenses post-operative CXL treatment (Koppen et al., 2018).

An optometrist clinic always has an autorefractor, often with Placido disc and with a biomicroscopic examination, keratoconus can be detected. Nevertheless, clinical diagnostic tools like Topography, Scheimpflug camera and Optical Coherence Tomography (OCT) is started to be more common in these clinics and these tools can detect keratoconus in an earlier stage (Belin et al., 2020). Further, these tools can also be helpful when fitting Scleral contact lens or RGP (Rathi et al., 2013).

Optometrist in Sweden can use ICD-10 in the system of journal or when referral to an ophthalmologist to clarify the main reason to the referral. Moreover, an optometrist has no obligation and cannot registry to the Swedish Patient Registry and it is the primary health care and specialists like ophthalmologist that is responsible to report to the Swedish Patient Registry (Socialstyrelsen, 2020).

4.6 Result

The results from the article

In 2010 to 2020, 16 055 patients were registered with ICD-10 H18.6 Keratoconus in the Swedish Patient Register, 74.2% were males. During the same period the average number of Swedish inhabitants was 9 886 365. The estimated prevalence of keratoconus was 169.5 per 100 000 (95% CI: 144.9-194.1) or conforming to 1 per 590. Table 1 present the age-stratified prevalence of keratoconus and the average prevalence. The prevalence was highest in the age group 21 to 30 with a prevalence of 348.4 per 100 000 (95% CI: 313.2-383.6).

The estimated annual incidence of keratoconus was 11.8 per 100 000 (95% CI: 5.1-18.5) and is presented in Figure 2. The highest incidence rate, 26.1 per 100 000 (95% CI: 16.1-36.1) was in the age group 21 to 30 years and the lowest, 5.2 per 100 000 (95% CI: 0.8-9.7) in the age group 71 year and older. The gender distribution for first-time registration is presented in Figure 1. The estimated incidence in the age group 0 to 40 years was 22.5 per 100 000 (95% CI: 13.7-32.3) and is shown in Figure 3.

Extended results that were not presented in the article

The prevalence was higher in Norway compared to Sweden in all age groups and the largest difference was in age group 0 to 21, this is presented in Figure 4. The incidence of keratoconus was higher in all age groups in Norway compared to Sweden and is presented in Figure 5.

Between 2010 to 2020, 909 CXL was registered due to keratoconus, that is an annual average of 82.6. In the same period 4071 cornea transplantation was register due to keratoconus and that gives an annual average of 370.1 and is presented in Figure 7. Between 2010 to 2020 5.1% were corneal crosslinked and 10.6% were corneal transplanted of all registered patients with keratoconus.

Most CXL were registered within the age group 21 to 30 followed by age group 0 to 20. Corneal transplantations were registered most in the age group 31 to 40 followed by age group 41 to 50 and is presented in Figure 6. An estimated average of mean from first-time registration to CXL was 3.3 years and for corneal transplantation it was 8.4 years.

4.7 Discussion

In this section the choice of the method and the new results will be discussed. Further, a more in-depth discussion of the article results focusing on the optometrist profession in the management of keratoconus will be provided.

4.7.1 Research design

The variation of the results from other studies can be related to the type of study design, access to health care in the country, exclude criteria and the conditions criteria and what type of diagnostic tools that was used. Moreover, this type of register study has been used in similar studies to present prevalence and incidence of keratoconus (Bak-Nielsen et al., 2019; Godefrooij et al., 2017a; Kristianslund et al., 2020). Therefore, where register study used to present the prevalence and incidence of keratoconus in Sweden.

A different way to estimate prevalence is a screening study and this type of study could report a truer prevalence due to actual patients testing. Further, this study design is very time consuming and requires diagnostic tools on a clinic with large among of patients.

4.7.2 Study population

The study population in the present study was all men and women in Sweden regardless a secondary diagnosis. It is known there are conditions that has increased risk to develop keratoconus (Gomes et al., 2015), but in this study the aim was to estimate keratoconus for all inhabitants regardless other diagnosis.

4.7.3 Ethic

In this registry study all data was anonymous for the project manager and the patients. Therefore, no one can be asked if they do not want to participate, and the patient will not be contacted and get information about this study from the National Board of Health and Welfare. Due to the study´s anonymous data, the present study does not required approval from the Swedish Ethical Review nor the Norwegian Center of Research (NSD). Further, this shortened the waiting time to obtain the data.

4.7.4 Data collection

The data from the Swedish Patient Register were obtained with a special order which is required when more than one ICD-10 codes collate to each other, otherwise the register is an open, digital archive. A special order entails a cost that was hourly charged. During the time I did the Research Protocol the waiting time was four weeks but due to the Covid-19 pandemic the waiting time increased to twelve weeks. During this waiting time I prepared for the data analysis and wrote the Introduction and method sections.

4.7.5 Data analyze

ICD-10 codes can be used when a general practice or another health personnel suspect keratoconus and referrals to an ophthalmologist who later rejected the diagnosis. This first ICD-10 code will be registered in the Patient Register and not disappear after the diagnosed was rejected. This will contribute to an overestimation for first-time registration of keratoconus and was a disadvantage to a register study. However, I do not believe it was a high number and will not have a larger impact on the outcome on the present study. Nevertheless, it needs to be represented as an unreliability in the data.

The data of prevalence was obtained if the patient has been at the health care between 2010 to 2020 even if the patient does not have the first-time diagnosis during this time period, the prevalence data goes back to 1998. This improves the quality of this present study. Year 1998 was three years earlier than when it started to become mandatory for Swedish healthcare personnel to report to the Swedish Patient Register, and I expect that the first years of reporting to be unreliable due to the uncertainty how to report. However, I do not believe this has an effect to the outcome of this study results.

The data were delivered as a large Microsoft Excel file with eight columns and 34 549 rows. Due to the large file, it was not possible to do the statistic analyze by hand, instead R commander where used. The calculated data was then exported back to Excel to design the graphs and tables. The graphs were presented to be similar to other population studies, and this made to comparison easier.

4.7.6 The choice of publisher

The choice of publisher was Acta Ophthalmologica (Acta Ophthalmologica, 2022). Acta Ophthalmologica are a peer-reviewed international journal, manage by the Acta Ophthamologica Scandinavia Foundation. Further, Acta Ophthalmologica are well-known in the field and has published the present studies main reference from Norway, the Netherlands and Denmark (Bak-Nielsen et al., 2019; Godefrooij et al., 2017a; Kristianslund et al., 2020). I believe that the present article covers a relevant topic for this Scandinavian publisher and due to that they already have published similar articles, I believe the interest of the present study is high. After successful completion of the Master thesis the article will be submitted to Acta Ophthalmologica in an attempt to get it published and the cost to get the article published will be with private funds.

4.7.7 Prevalence and incidence of keratoconus

Keratoconus is a bilateral non-inflammatory condition but debuts as unilateral and between 2010 to 2020 the total number of 16 055 were diagnosed with keratoconus. With this present data, can we not know if the patient has been diagnosed in one or two eyes and we cannot know in which eye the patient has been treated.

The results presented a clear overrepresentation of keratoconus among male sex, that was similar results from other population studies (Bak-Nielsen et al., 2019; Godefrooij et al., 2017a; Kristianslund et al., 2020). However, it is unclear why there is a different between gender (Bilgihan et al., 2011) but these results indicate that gender should be seen as a risk factor to develop keratoconus. Moreover, some of the risk factors for keratoconus can an optometrist manage, like diagnose ocular allergy and recommend right sorts of eyedrops without a prescription. Further, it is important with follow-ups, because if there was no improvement, a referral to an ophthalmologist or general practitioner for further examination is needed.

The present study includes all patients with keratoconus in Sweden but in a study from Denmark, Down Syndrome were excluded and in Norway the prevalence was for patient with Down

Syndrome 5481 per 100 000 (Bak-Nielsen et al., 2019; Kristianslund & Drolsum, 2021). Further, this indicates that Down Syndrome has an increased risk to develop keratoconus and therefore it is highly relevant to screen all patients with Down Syndrome for keratoconus as an optometrist.

The result reported a decreased prevalence in higher age, and it was assumed that the prevalence decreasing with the age due to increased level of the deceased. Nevertheless, I believe that the prevalence in older age was underestimated. This due to lack of better diagnostic tools and knowledge of keratoconus in the past, the older generation remained undiagnosed which resulted to under registration.

4.7.8 The results compared to other studies

The prevalence was higher in Norway compared to Sweden in all age groups. There was a large difference in the age group 0 to 21. Further, this indication also applies to incidence of keratoconus. The optometrist in Norway can examinate patients in younger ages than a Swedish optometrist and in Norway the optometrist have the legal right to use diagnostic drugs such as Cyclopentolate, which could result in uncertain refractive error. Further, a Swedish optometrist need a second education in forms of a Master to have the rights to use diagnostic drugs. This can be a contributed factor to the difference in occurrence of keratoconus.

The incidence of keratoconus in Sweden and Norway was highest in age group 21 to 30, and this can be a result of optometrist examinations. This was something (Gordon-Shaag et al.) also discussed. In the second decade of life a larger part of the inhabitants takes driving license or start an education. Some educations require good visual acuity for example police and military. It is the optometrist that approves the certificate of vision, and it can be in these examinations conditions like keratoconus occur. Therefore, I believe that optometrist has an important role to screens after pathology.

4.7.9 Treatments for keratoconus

In the present study most CXL were registered in the age group 21 to 30 followed by age group 0 to 20. The result reports that CXL was rarely indicated in a patient over 40 years old and that was similar to other studies reports (Godefrooij et al., 2017a; Gomes et al., 2015). Moreover, most of the corneal transplantations were registered in the age group 31 to 40 followed by next age group. This can be explained that corneal transplantation was performed when keratoconus has developed into a severe stage and resulting in low visual acuity.

There was an increasing number of CXL comparing year 2010 to 2020. Nevertheless, it was low numbers compared to corneal transplantation. In other studies, it has been reported that the total number of corneal transplantations has decreased since CXL was introduced as a treatment of keratoconus (Godefrooij et al., 2016; Sandvik et al., 2015). This outcome seems not to correspond to Sweden. Further, a hypothesis can be due to corneal rejections which resulted in a necessary re-corneal transplantation, and these re-transplantations was reported in the present register. Also, it is unusual for a second CXL treatment. Nevertheless, the knowledge of the long-term outcome of CXL is unknown and it is unclear if a patient with post-CXL needs a corneal transplantation later in life which also could be an explanation to the high number of corneal transplantations.

One of ten has been corneal transplanted compared to one of twenty has been corneal crosslinked in Sweden and in Denmark it was more common with corneal transplantation as a treatment for keratoconus (Bak-Nielsen et al., 2019). However, in a study from the Netherlands present a reduction of corneal transplantation up to 25% since CXL where introduced as a treatment (Godefrooij et al., 2016). Even if the present study does not present mean age, the mean age of first-time diagnosis in Denmark was 38.2 and in Norway 37.5 (Bak-Nielsen et al., 2019; Kristianslund et al., 2020). Further, this was a high age of first-time diagnosis if keratoconus stops progression around 40 years old. This could explain the low number of CXL. Another theory can be that due to the colder climate in Scandinavia contribute to a reduced progression, which results in that the mean age was higher, and that the progression only lasts for a shorter time period.

The average time from first-time registration to CXL was estimated to 3.3 years. This time can indicate to be the progression time when CXL was necessary, or it can also be the waiting time for an CXL. Due to the lack of first diagnostic records like pachymetry, k-value, biomicroscopic findings and visual acuity, I cannot say in which stage keratoconus was when first examined. Moreover, the data do not present which eye that was diagnosed and which eye that was treated. For corneal transplantation the average mean was higher than CXL which seems to be reliable since corneal transplantation is the last way out for a patient with low visual acuity due to severe keratoconus. Further, to our knowledge it was unclear if there was any private practice that preform CXL or corneal transplantations in Sweden. However, I believe these cases are few and will not affect the results of the present study.

In this present study there was a larger number of corneal transplantations in all age groups compared to CXL, even in the younger age groups. This can be an indication of a late first-time diagnosis. The delayed diagnosis can be a result of an ignorance of decreased visual acuity from the patients, or it can be that the optometrist does not screen or noticed the symptoms and signs for keratoconus in an eye examination.

Further, it has been established that CXL is cost-effectiveness due to reduced number of corneal transplantations (Godefrooij et al., 2017b; Lindstrom et al., 2021) and it was only a few precent that gets treated with CXL compared to corneal transplantation in Sweden. Therefore, from a cost-effective perspective, increased number of CXL due to an earlier diagnosis will reduce the cost. Moreover, the high number of corneal transplantations indicates that these patients had low vision acuity, and it is the optometrist responsibility to fit right type of correction if possible. Therefore, can the optometrist reduce the number of corneal transplantations due to more accurate prescribing, something Koppen et al (2018) also discuss. An optometrist may need to prescribe medical contact lenses after CXL and corneal transplantation due to the irregular shape of cornea. Therefore, has the optometrist profession an important role to management before and after a diagnosis and treatment.

Treatments for keratoconus is a major topic and I have the data, so my expectation is to get a second article published on this topic, and I also consider to obtained more in-depth data through an approval from the Swedish Ethical Review Authority to get a better knowledge of the management of keratoconus.

4.7.10 Implementation for optometrist profession

This study reporting the prevalence and incidence for keratoconus in Sweden and important risk factors like gender and age. With this knowledge the optometrist can be more prepared when doing an eye examination. Due to these results, we now know more about the risk factors than before. Further, I also believe that this article will increase the awareness of keratoconus for optometrist and ophthalmologists in Sweden due to the higher outcome of prevalence and incidence than previously thought. The results of treatment that was left out from the article will be presented in a second article in the future and I believe that will have a significant impact on the management of keratoconus, particularly for the ophthalmologists who treat keratoconus.

4.8 Conclusion

To our knowledge, there has been non epidemiology studies to established keratoconus in Sweden nor present the total number of CXL and corneal treatment. The aim for this study was to present an estimated prevalence and incidence of keratoconus and the total number of treatments in Sweden between 2010 to 2020.

This register study present prevalence and incidence of keratoconus in Sweden between 2010 to 2020. The results were higher than reported in earlier studies, but comparable to recent Scandinavian studies. The higher result could be explained due to modern diagnostic tools and treatments like corneal crosslinking. The present study indicated that keratoconus appears to be more prevalent than earlier known and males in age group 21 to 30 has higher risk to develop keratoconus. Between 2010 to 2020, corneal transplantation was a more common treatment than corneal collagen crosslinking for all age groups. This statistic contributes with important knowledge for the Swedish eye care. Nevertheless, true prevalence may be even higher due to under registration in older age groups.

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4.10 List of tables

Table 2. The International Classification of Disease and Related Health Problems (ICD-10) that were used to obtain the data from the Swedish Patient Register.

Variable	ICD-10
Keratoconus	H18.6
Corneal crosslinking (CXL)	CGG99
Corneal transplantation	Z94.7

4.11 List of figures

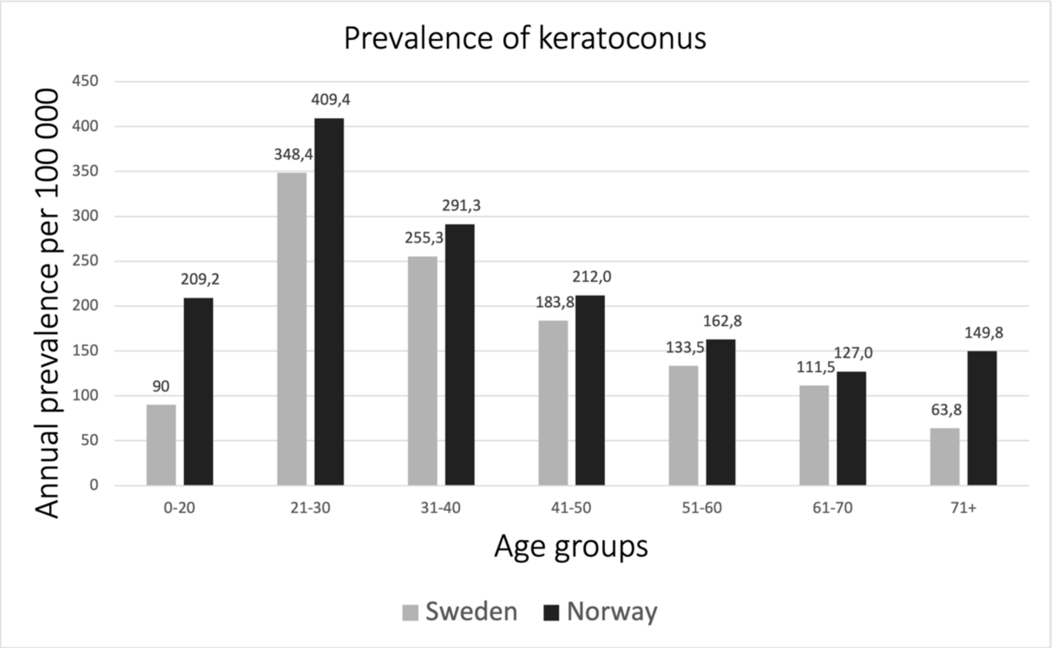

Figure 4. Prevalence of keratoconus in Sweden (grey) and Norway (black) without error bars between 2010 to 2020. Divided into age groups per 100 000.

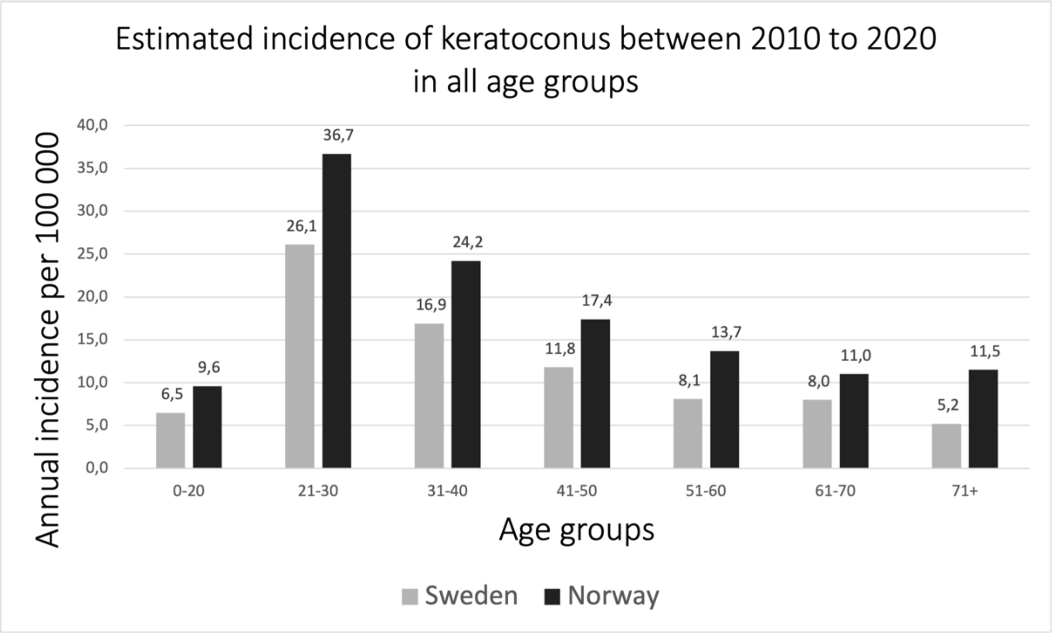

Figure 5. The estimated incidence of keratoconus in Sweden (grey) and Norway (black) divided into age groups, per 100 000 without error bars.

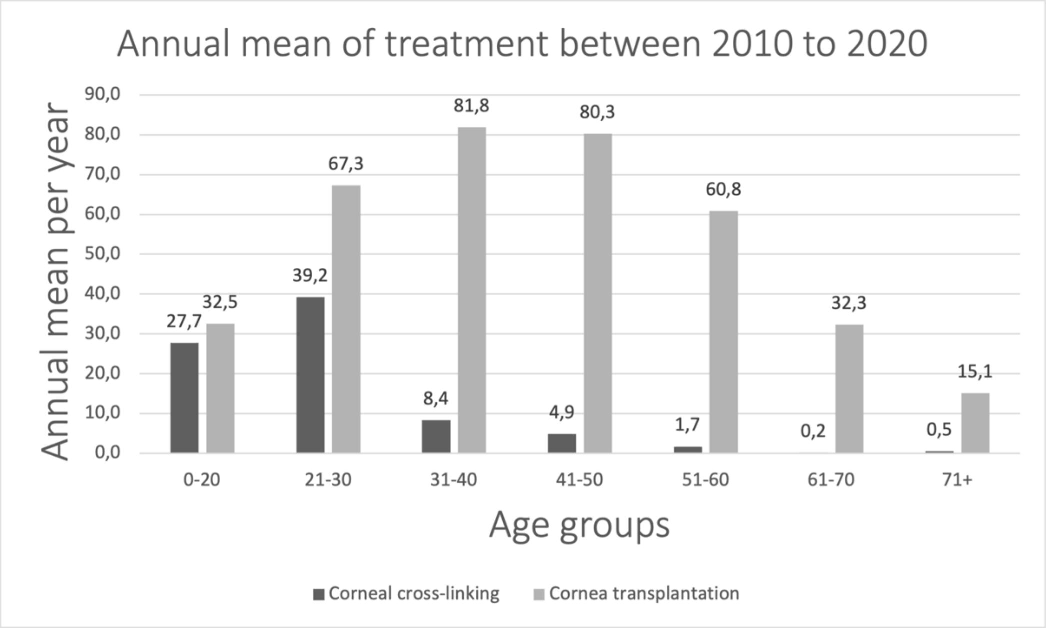

Figure 6. The estimated age-stratified mean of corneal cross-linking (black) and corneal transplantation (grey) between 2010 to 2020.

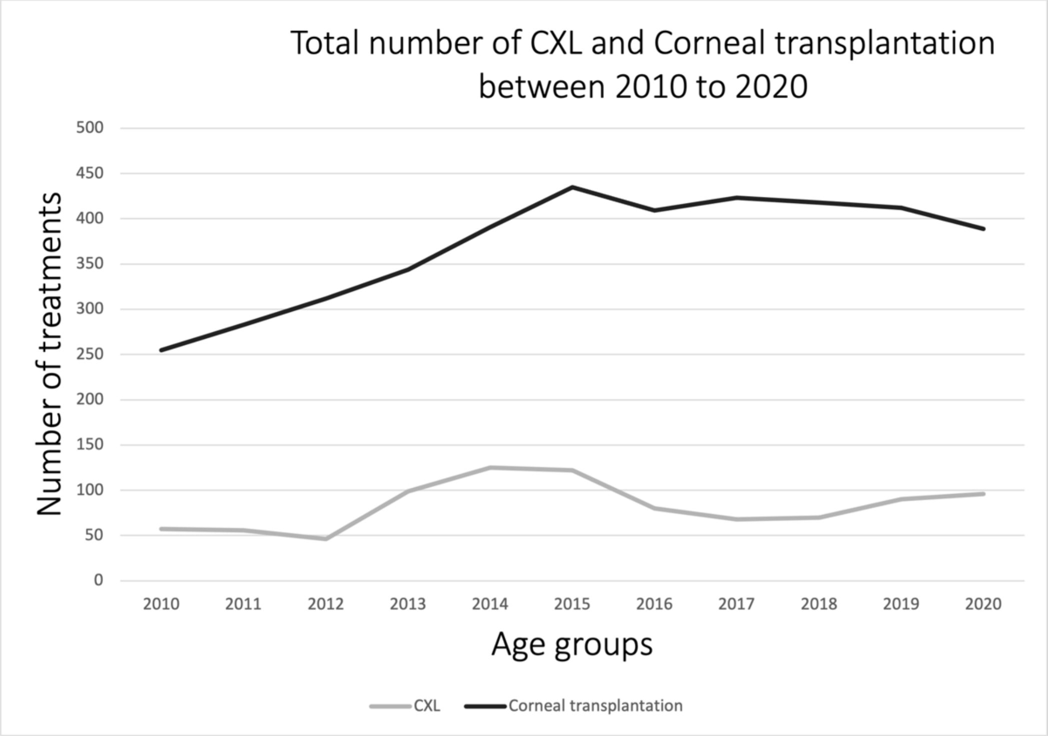

Figure 7. The annual total number of CXL (grey) and corneal transplantation (black) in Sweden between 2010 to 2020.

4.12 Annexes

Annex 3: Research Protocol – Method section

Research objectives and significance

The main objective of this study is to estimate the national prevalence and incidence of keratoconus in Sweden and estimate the patients age of onset based on data at the Swedish Patient Register at the Swedish authority the National Board of Health. Secondary aims are to understand when and on what indication treatment with corneal crosslinking (CXL) and/or corneal transplantation is initiated.

This will be obtained by the following research question:

1. How many Swedes have keratoconus?
2. How many Swedes are yearly diagnosed with keratoconus?
3. How old are the patients at the time of diagnosis?
4. Who are treated with corneal crosslinking (CXL) and how long after diagnosis?
5. Who are treated with corneal transplantation and how long after the diagnosis?
6. What is the yearly rate of CXL and corneal transplantation in the period 2010 to 2019?

Research question one to three are the primary research question and will show how common keratoconus is in Sweden. Research question four to six are secondary and provide in-depth knowledge about surgical treatment.

The study will improve the understanding of how common keratoconus is in Sweden. This will help the primary healthcare how often a keratoconus patient will show up in the clinic or practice and the most common age of onset at the diagnosis. When a patient discovers that he or she has poor visual acuity, will they contact their optometrist. So, if this optometrist has a better knowledge about the epidemiology of keratoconus an early diagnosis and referral will reduce the risk of visual impairment. The optometrist’s role is also to help to provide visual correction for a keratoconus patient and because of the irregularity in the corneal surface, a more advanced correction can be needed in forms of medical contact lenses.

Study design

The study has a descriptive quantitative cross-sectional design based on register data from the Swedish Patient Registry between 2010 to 2019.

Study sample

Anonymous data will be obtained from the Swedish Patient Register at the Swedish Authority the National Board of Health.

Target population

Target population is all Swedish citizens, when estimated prevalence of keratoconus in Sweden and the sample population is patients that is registered with keratoconus between 1 January in 2010 to 31 December in 2019.

Study population

The study population is all men and women between 0-40 years, in Sweden diagnosed with keratoconus by an ophthalmologist during the period between year 1 January of 2010 to 31 December in 2019.

Exclusion criteria

Age limit of 40 years old when calculated incidence is set because, the study considered the patients to be the ones at risk of developing keratoconus.

The Swedish version of ICD-10 is called ICD-10-SE and have been updated several times but, it was first introduced in Sweden 1997 (Socialstyrelsen, 2021). To delimit the study and have a modern study the chosen years is between 2010 to 2019.

Outcome variables

The primary outcome of this study is the prevalence and incidence of keratoconus in Sweden between 2010 to 2019. Secondary outcome are the mean age at keratoconus onset and how many that are treated with CXL and corneal transplantation because of keratoconus. Also, how old are the patient at the time of treatmeant.

Prevalence

Prevalence is in epidemiology the proportion of a particular population that is affected by a medical condition at a specific time and prevalence is a proportion that indicates how much of the whole has a certain disease (La-Torre, 2010, pp. 7-9). Prevalence will present how many Swedes that are registered with keratoconus during 2010 to 2019.

Incidence

In epidemiology, incidence present a measure of the probability or risk of occurrence of a medical condition in a certain population swithin a specific time frame. Incidence are often used to discribed number of new cases of a disease or number of symptomes during a clinical trail (La-Torre, 2010, pp. 7- 9). Incidence will present how many Swedes that yearly diagnosed with keratoconus between 2010 to 2019.

Predictor and other variables

Age and gender are predictor variable to CXL and corneal transplantation and also duration of keratoconus is a predictor variable. Geography is a predictor variable for keratoconus.

Table 1 - outcome and predictor variables

Variables	Variable type	Unit	ICD–10
Gender / Sex	Nominal / Dichotomous	0 = female, 1 = male	
Age	Continuous	Years	
Age of onset	Continuous	Years	
Age of treatment	Continuous	Years	
Age of CXL treatment	Continuous	Years	
Age of corneal transplant	Continuous	Years	
Duration of keratoconus	Continuous	Years	
Geography location	Continuous	Years	
Keratoconus	Nominal / Dichotomous	0 = no, 1 = yes	H18.6
Corneal transplantation	Nominal / Dichotomous	0 = no, 1 = yes	Z94.7
Corneal crosslinking (CXL)	Nominal / Dichotomous	0 = no, 1 = yes	CGG99

Methods

The Swedish Patient Register gathers information from all publicly funded specialists care in Sweden and it is mandatory to reporting for these groups (Socialstyrelsen, 2021). The population statistic of Swedish citizens for the selected years will be obtained at an open archive on an authority website (SCB, 2021). An application will be submitted to Swedish patient registry at the Swedish authority the National Board of Health to get out the requested data according to table 1 and the processing time are estimated six to eight weeks (Socialstyrelsen, 2020a). Based on the statistic collected (see table 1), a calculated diagram will show the annual rate and mean age of CXL and corneal transplantation.

The data from table 1 will be used to answer all the research question. Prevalence will be calculated as equation 1 and multiplied with 100̋ 000 so prevalence will be presented with a unit per 100̋ 000 citizen. This will be done for each year in the chosen period and also an average prevalence will be calculated. Incidence will be calculated as equation 2 and multiplied with 100̋ 000 so the incidence will be the same unit as prevalence. If using the same unit makes it possible to compare the result with similar studies.

Equation 1

$$\frac{\text{Number of keratoconus patients}}{\text{Population}} \times 100\,000$$

Equation 2

$$\frac{\text{New cases of keratoconus}}{\text{Total population}} \times 100\,000$$

Data collection

This is a be observational quantitative- & cross sectional- study. The main data will be obtained from the Swedish authority the National Board of Health and Welfare and will not contain any information that is traceability to a specific patient. All statistical data will be confidential and anonymous.

First step is to obtain the statistical data from the National Board of Health and Welfare and Central Bureau of Statistics. The statistical data from the National Board of Health and Welfare you have to apply and being approved to get access, this take between six to eight weeks (Socialstyrelsen, 2020b). In this data no social security number, names or anything else where the patient’s identity will be present (Socialstyrelsen, 2020a).

The collected data all data will be stored on a password protected private computer that will be stored safe in one place as the data is anonymous. The statistical data from the Central Bureau of Statistics is an open archive at a website and do not need a apply for. This data will contain the population of Swedish citizen, categorized male, female and age (SCB, 2021). When all data is collected, prevalence and incidence will be calculated with the help of equation 1 and 2 and how many that gets treated with CXL and corneal transplantation because of keratoconus. Also, what is the mean age when the patient gets treated. All data will be deleted at the closure of the study, at the latest on 31. June 2022.

Analyses

This study will take place at a distance between 1. August 2021 to 1. June 2022. All data will be delivered as a Microsoft Excel format and will also be processed with spreadsheet in Microsoft Excel and will be presented with diagrams. Prevalence and incidence between 2010 to 2019 will be analyzed and the significance, confidence interval (CI) and P-value will strive to be 95%. Prevalence and incidence will be presented with unit “per 100́ 000 citizen”. To understand how long time the patient needs to wait for an CXL treatment and how long a patient have keratoconus before an corneal transplantation is needed the duration of keratoconus from first diagnosis to a treatment (CXL and corneal transplantation) will be analyzed.

Project management and organization

Principal investigator and supervisor: Vibeke Sundling.
Project manager and Master ́s student: Jonathan Binder.

Resources, equipment and physical facilities

Computer: Private owned laptop.
Statistical data: Procure from the Swedish authority the National Board of Health.
Program: Microsoft Office Excel (private license) and Microsoft Office Word (private license).

Budget and financial plan

All cost that is shown in table 2 will be paid directly by the project manager. There will not be any sponsors to this project.

Table 2

Post		Credit	Comment
1	Statical data	5 000	Procurement of the data from the Swedish Authority the National Board of Health.
2	Poster	500	Presentation poster
3	Total	5 500	Total cost of the study

Project plan

After research protocol the data collection will be done and the statistical data from the National Board of Health and Welfare take between six to eight weeks to obtain and meanwhile the study will begin to be written. It is estimated that 810 workhours will be spent on this study and 15 hours of individual supervision with the principal supervisor divided into two semesters. In figure 1 an estimated timeline is shown over the project. The project will be presented and exanimated in June 2022.

Figure 1. An estimated timeline is presented from Research protocol to Examination

Dissemination

This is a master thesis and will be oral presented with a poster in June 2022. There will be an attempt to get this study published at an international conference, ARVO Annual meeting and as a paper in a scientific peer review journal. Whenever possible, first author of published data will be the project manager, Jonathan Binder.

Ethical considerations and Privacy protection

This study is a register study and does not involve clinical examination of patients. The Swedish National Board of Health is responsible for the data handling and the delivery of anonymous data set for analysis. The data that are obtained will be shown in five-year groups. Furthermore, the register requires a minimum number of cases in each group when reporting anonymous data, thus if there is any group of age with low number of cases the data will report in wider intervals in these ages. National Board of Health and Welfare will not hand out data that are too detailed so there is a very low risk that the patient can be identified (Socialstyrelsen, 2020a).

In a previous study from Norway, the Data Protection Officer at the research institute of Norway waived the for the study approval because the data were anonymous and aggregated group level so no patient could not be identified (Kristianslund et al., 2020). In this registry study all data is anonymous for the project manager and the participants, so no one can be asked if they do not want to participate, and the patient will not be contacted and get information about this study from the National Board of Health and Welfare or the author of this study.

In a similar study from Denmark that were approved by the Danish Protection Agency, all data were stored on a secure server on the Statistic Denmark. This data contains non anonymized data for the population in Denmark and could therefore identified individuals (Bak-Nielsen et al., 2019). In this study all data will be stored on a password protected private computer that will be stored safe in one place as the data is anonymous. All data will be deleted at the closure of the study. The study will follow the direction of the Declaration of Helsinki and the Health Research Act of Norwegian Center of Research. The study do not required approval from the Reginal Ethics Committee in Norway or review by the Data Protection Officer, Norwegian center of research (NSD) as anonymous data are used for analysis.