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Title

Incidence and prevalence of keratoconus based on Scheimpflug imaging

Authors

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Conflicts of Interest

No conflicting relationship exists for any author.

Running head

Incidence and risk factors for keratoconus in young adults

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Abstract

The prevalence of keratoconus (Belin/Ambrósio Enhanced Ectasia Display Score ≥2.6 on Scheimpflug imaging) in a longitudinal, community cohort study from Western Australia was 3.4% (n=26/755). Keratoconus incidence over an 8-year period was 2.2% (n=15/669).

Keratoconus is a disorder characterized by bilateral corneal thinning, with an onset typically in the first three decades of life.[1, 2] In this study, we report the prevalence of keratoconus among 28-year-old Gen2 participants of the Raine Study in Western Australia, the incidence between 20- and 28-years of age, and risk factors associated with keratoconus.

We have previously reported the prevalence of keratoconus at the 20-year follow-up of the Raine study as 1.2% or 120 cases per 100,000 people.[3] Previous publications based on national health insurance data include a reported keratoconus prevalence of 265 cases per 100,000 and an annual incidence of 13.3 cases per 100,000 in the Netherlands.[2] However, health insurance databases likely underestimate true disease prevalence and incidence.

The Raine Study is a multi-generational cohort study based in Perth, Western Australia. The data in this report were collected from the 20-year (conducted 2010-2012) and 28-year (2018-2020) follow-up visits of the Gen2 cohort, when participants underwent an ophthalmic examination, including Scheimpflug imaging (Pentacam, Oculus, Germany) and completed a health questionnaire.[4] Visual symptoms were not recorded. A full list of ophthalmic and non-ophthalmic examinations, questionnaire and data variables are available online (www.rainestudy.org.au). Differences between active and inactive participants in the Raine study have been published and are unlikely to have an impact on the results of this study.[5] A Belin/Ambrósio Enhanced Ectasia Display (BAD-D) score of ≥2.6 in at least one eye was used to define tomographic-evidence of keratoconus.[6] All scans with a BAD-D ≥2.6 were further analyzed by corneal specialists (EC, EWC) for false positives. Where both eyes of a participant had BAD-D ≥2.6, the eye with the higher score was used for analysis.

Potential ocular and non-ocular risk factors at the 20-year follow-up were investigated, including the sun exposure-related variables serum 25-hydroxyvitamin D concentration [25(OH)D], measured using liquid chromatography tandem mass spectrometry and deseasonalized for month of collection,

and total conjunctival ultraviolet autofluorescence (CUVAF) in both eyes. Apnea-hypopnea index (AHI; events/hour), minimum and mean peripheral capillary oxygen desaturation (%) and T90 (time where peripheral capillary oxygen saturation was <90%) measured at a sleep study performed at the 22-year follow-up were also assessed.[7] The study was conducted in accordance with the tenets of the Declaration of Helsinki. Ethical approval was obtained from the University of Western Australia's Human Research Ethics Committee. All participants provided written informed consent.

Figure 1 shows an overview of participants with Scheimpflug imaging data. Of the 755 participants at the 28-year follow-up available for inclusion in the study, 26 participants were diagnosed with keratoconus. The prevalence of keratoconus at the 28-year follow-up was 3.4% or 1 in 30 people.

Based on the BAD-D threshold of 2.6 at the 28-year follow-up, compared to those without keratoconus, participants with keratoconus were more likely to be male (69.2% vs 48.0%, p=0.045), have a shorter axial length (22.98mm vs 23.70mm, p<0.001, IOLMaster V.5; Carl Zeiss Meditec AG), have poorer visual acuity (0.00 vs -0.09 logMAR, p=0.002) and have higher astigmatism (-1.00D vs -0.50D, p<0.001) and myopia (-1.67D vs -0.30D spherical equivalent, p=0.01) on cycloplegic autorefraction (ARK-510A autorefractor, Nidek, Japan). Additionally, there were significant differences in multiple parameters including keratometric and pachymetric indices on Scheimpflug imaging (Table 1, available at www.aaojournal.org).

After excluding 8 participants who were diagnosed with keratoconus at the 20-year follow-up, 669 participants had Scheimpflug imaging data at both the 20- and 28-year follow-up visits (Figure 1) and were available for analysis of keratoconus incidence (representing 52.0% of the 1,303 participants who had Scheimpflug imaging at 20-years). Mean follow-up time was 8.3 years (range 6.6-9.8 years or 5,526 person-years). From this group, 15 participants (8 bilateral, 7 unilateral cases) were

identified as having new onset of keratoconus. The incidence of keratoconus over the 8-year period was therefore 2.2% (95% CI: 1.12, 3.36) or 271 per 100,000 person-years.

We did not identify any association between keratoconus and self-reports of allergic diseases (asthma, allergic rhinitis or ocular allergies) or body mass index. In univariable analysis, we found an association between higher risk of keratoconus and smaller CUVAF area, and higher AHI. In multivariable analysis, after adjusting for age, we found that sex (odds ratio [OR]=3.23, p=0.048), CUVAF (per 10mm^2 increase, OR=0.72, p=0.007) and AHI (per 10 events/hour increase, OR=2.93, p=0.001) were significant risk factors for keratoconus. Analysis of AHI by categorizing into no OSA (AHI <5), mild OSA (AHI 5-14), moderate OSA (AHI 15-29) and severe OSA (AHI ≥30)[7] resulted in odds ratios of 3.16 (p=0.09), 7.98 (p=0.02) and 29.25 (p=0.007), respectively (Tables 2 and 3 available at www.aaojournal.org). CUVAF area may be a biomarker for long-term UV exposure which may result in a natural corneal cross-linking, thus reducing the risk of keratoconus. However, arguing against such a relationship is the lack of association between 25(OH)D concentration, a short-term measured of sun exposure, and keratoconus. The association between AHI and keratoconus is unlikely due to hypoxia, as associations were not seen with either capillary oxygen saturation nor T90.

To examine ocular associations for incident keratoconus, we selected parameters that are commonly performed during a standard ocular examination. On univariable analysis, astigmatism, K1, K2 (mean simulated keratometry reading in the flattest and steepest meridian, respectively), central corneal thickness (CTcentral) and axial length were significantly associated with incident keratoconus (Table 4, available at www.aaojournal.org). On multivariable analysis, only steeper K2 and thinner CTcentral remained significant. While K2 and CTcentral are established features of keratoconus, the Global Delphi Panel of Keratoconus and Ectatic Diseases considered central pachymetry as the least reliable indicator for diagnosing keratoconus.[1] Our findings reinforce the value of K2 and CTcentral in

assessing both current and future risk of keratoconus in individuals undergoing routine ocular examinations.

In a population of young adults in Western Australia, our study reports one of the highest prevalence and incidence of keratoconus in the world. This study emphasizes the importance of early screening for keratoconus in individuals aged 20- to 28-years, especially males and those with steeper K2, higher astigmatism, and thinner corneas and who spend less time outdoors or have sleep apnea.

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Figure 1: Flow chart of the Gen2 Raine study participants included in this study.