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Editorial

## **“Aye, there’s the rub” – ocular allergy and keratoconus**

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Affecting approximately 1 in 725 individuals worldwide<sup>1</sup> and up to 1 in 84 Australian young adults,<sup>2</sup> keratoconus is the most common corneal ectatic disorder. It is characterised by progressive, bilateral though often asymmetric thinning of the central or paracentral cornea, leading to cone-shaped corneal protrusion and irregular astigmatism. Risk factors classically described have included systemic disorders such as Down syndrome, Ehlers-Danlos syndrome and osteogenesis imperfecta; atopy and ocular allergy; mechanical factors such as eye rubbing and floppy eyelid syndrome; and family history and ethnicity.<sup>3</sup>

We congratulate Seth et al.<sup>4</sup> for the publication of “The association between keratoconus and allergic eye diseases: A systematic review and Meta-analysis” in this issue of *Clinical and Experimental Ophthalmology*. The authors screened 361 titles and abstracts to include 15 observational studies (10 case-control, 5 cross-sectional) with 708,225 participants (20,336 of which had keratoconus) in quantitative meta-analyses; and 7 studies (6 cross-sectional, 1 basic science) with 899 participants (709 of which had keratoconus) in descriptive analyses. Three meta-analyses were performed to synthesise the associations between keratoconus and allergic eye diseases (13 studies, pooled odds ratio (OR) 1.03, 95% confidence interval (CI) 0.96-1.11), eye rubbing (10 studies, pooled OR 1.59, 95% CI 0.70-3.63), and atopy (3 studies, OR 1.08, 95% CI 0.80-1.44); no significant association was found in all three analyses, although ORs were in the positive direction. The authors assessed included studies to be moderate to high quality, and interestingly deemed heterogeneity as not significant, in contrast to previous meta-analyses pooling similar original articles on this topic. The authors did not provide a table of included studies with variables, measures of interest and definition of outcome measures to allow the readers to independently assess the degree of clinical heterogeneity and the appropriateness of pooling of results. The authors rightly identified that their study results should be interpreted with limitations. While it is true that a randomised controlled trial (RCT) on this topic would be impractical, the low number of prospective cross-sectional and case-control studies and the low sample size of 3 studies in the meta-analysis of keratoconus and atopy limits the certainty of study conclusions. The extremely large confidence intervals of some

included odds ratios (with upper bounds of up to 188,752) further highlights the impreciseness and potential methodological limitations of some included studies. As the authors note, with the higher than average prevalence of ocular allergy estimated to be between 11 to 30% of individuals with keratoconus, future high-quality studies are needed to corroborate these meta-analysis findings.

Atopy and allergic eye diseases have been linked to chronic habitual eye rubbing. Postulated mechanisms of progression to corneal ectatic disorders, such as keratoconus, have included rubbing-induced frictional microtrauma, elevations in corneal temperature and intraocular pressure, as well as release of inflammatory mediators such as matrix metalloproteinases, interleukins, interferon gamma, and tumour necrosis factor alpha leading to corneal thinning with subsequent remodelling and increased curvature.<sup>5</sup> Other less common anterior segment complications of eye rubbing include acute corneal hydrops, intraocular pressure spikes, and intraocular lens dislocation, to name a few.<sup>5</sup> Clarifying these potential modifiable risk factors of keratoconus is particularly important to prevent ongoing progression and visual loss.

Eye rubbing, in particular, is an exposure which is notoriously difficult to measure consistently. There exists no uniform way of eye rubbing – differences arise in style (rubbing with the knuckles, finger pads, fingernails, palms, or otherwise), location (on the globe, below the globe, above the globe, or otherwise), duration, pressure, rhythm, intensity, and frequency. In the context of measurement and reporting error, accurate assessment of rubbing poses understandable challenges, and these differences may lead to differences in outcomes. Observational studies generally utilise self-reporting on questionnaires or history taking as a gross measure eye rubbing; such approaches rely on patient awareness and memory. Many patients do not remember, realise, or gauge accurately their eye rubbing. From our clinical experience, many patients with keratoconus report that they only realised that they do rub their eyes after it was highlighted to them. This is a limitation of cross-sectional and case-control analyses. Additionally, such measures do not account for subconscious eye rubbing during sleep, or night-time pillow rubbing. For these

reasons, detailed assessment of included study characteristics in meta-analyses concerning eye-rubbing is needed to confirm validity.

In addition, the diagnosis of keratoconus across institutions globally is subject to significant clinical heterogeneity. In the absence of unifying diagnostic criteria, individual studies may use clinical examination criteria such as stromal thinning and Munson's sign (late signs of keratoconus), Vogt's striae, and Fleischer's ring, and/or topographical indices to reach a diagnosis of keratoconus. Differences in diagnostic criteria lead to systematic differences in study population characteristics beyond sampling variability, adding a further dimension of complexity to the interpretation of inter-study comparisons and syntheses.

Eye rubbing and associated atopic risk factors for keratoconus have received considerable attention in recent years, with two other systematic reviews and meta-analyses published on this topic since 2020. In 2020, Hashemi et al.<sup>1</sup> analysed 29 studies including 7,158,241 participants from 15 countries, and found that eye rubbing (7 studies (4 case-control, 3 cross-sectional), pooled OR 3.09, 95% CI 2.17-4.00), family history of keratoconus (7 studies (5 case-control, 2 cross-sectional), pooled OR 6.42, 95% CI 2.59-10.24), allergy (8 studies (6 case-control, 2 cross-sectional), pooled OR 1.42, 95% CI 1.06-1.79), asthma (6 studies (5 case-control, 1 cross-sectional), pooled OR 1.94, 95% CI 1.30-2.58), and eczema (3 case-control studies, pooled OR 2.95, 95% CI 1.30-4.59) were significantly associated with keratoconus. In 2021, Sahebjada et al.<sup>6</sup> pooled data from 6 case-control studies including 2,150 participants to find that eye rubbing was significantly associated with keratoconus (pooled OR 6.46, 95% CI 4.12-10.1), with included studies being substantially heterogeneous ( $I^2=71.69\%$ ). Although four identical original articles<sup>7-10</sup> measuring eye rubbing and keratoconus were included by all three systematic reviews,<sup>1,4,6</sup> pooled ORs and associated inter-study heterogeneities were highly variable across these separate reviews. The discordant pooled results between the reviews may arise from differences in search strategy, with some searches picking up studies which others did not, differences in choice of meta-analysis models (fixed vs random effects) and individual study weightings within those models, possible

inclusion of unpublished data in some reviews but not others, and other variations in data processing. Interestingly, two<sup>4,6</sup> of the three systematic reviews meta-analysed ORs and 95% CIs that were different to those reported by their included studies, resulting in different final conclusions. *Clinical and Experimental Ophthalmology* should be commended for inviting further discussion on this topic. It should be highlighted that the previously published two systematic reviews<sup>1,6</sup> demonstrated a significant association between eye rubbing and keratoconus, and while Seth et al.'s<sup>4</sup> pooled OR did not reach statistical significance for eye rubbing, it was in a positive direction. Eye rubbing should continue to be strongly discouraged, and allergic eye conditions appropriately treated, in patients with keratoconus.

Whilst existing systematic reviews have addressed the association between eye rubbing and keratoconus through cross-sectional and case-control studies, such study designs do not lend themselves to analyses of temporal causation and keratoconus progression. Prospective cohort studies with long-term follow-up are needed. Corneal collagen crosslinking (CXL) has been shown in randomised trials to halt the progression of keratoconus with sustained improvements in topographic and wavefront indices enduring for up to seven year post procedure.<sup>11,12</sup> In the context of ocular allergy induced corneal itch, the decrease in corneal sensation post CXL may be a further therapeutic benefit, resulting in less stimuli for eye rubbing and offering an opportunity to unlearn learnt habits. Allergic eye diseases and persistent habitual eye rubbing appeared to be key modifiable risk factors for progression after CXL in three retrospective cohort studies with 42,<sup>13</sup> 130,<sup>14</sup> and 676<sup>15</sup> patients followed-up over a mean of 26, 29, and 37 months respectively. Even following CXL, eye rubbing should be strongly discouraged.

With high clinical heterogeneity between original articles and conflicting results reached by different attempts at synthesis, definitive conclusions of the magnitudes of eye rubbing and allergic eye disease's associations with keratoconus remain to be drawn. Clinicians should continue to advise patients against eye rubbing, and treatment of allergic eye disease in patients with keratoconus should be optimised.

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