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Philanthropic Ophthalmology

Two teams, two towns, one mission: bringing sight to Ugandans

Higher Myopia Risk in Firstborns

A recent study on risk factors for myopia show it doesn't always pay to be the eldest child…

As we've previously reported (1), rates of myopia are huge and rising – but the reasons for this remain, largely, a mystery. A range of potential causes, such as genetic factors, close work, and time spent outside have been identified as likely contributors. But another is birth order – the theory is that parents invest more time and resources in the education of their firstborn, increasing their exposure to close work (and possibly reducing time outdoors), and therefore their risk of myopia, when compared with younger siblings.

A recent study, published on World Sight Day in *JAMA Ophthalmology*, has explored the link between myopia and birth order further, using data from 89,000 UK Biobank participants. Those included were aged between 40 to 69 years, self-reported white ethnicity, and had no history of eye problems, such as cataracts or serious eye trauma. After adjusting for variables, including gender, age, and the Townsend Deprivation Index score, the authors found that first-born children were around 10 percent more likely to have myopia, and 20 percent more likely to have high myopia than their siblings (2).

The potential link was reinforced when the study authors adjusted for one of two measures of educational exposure: highest education qualification or age at completion of full-time education. This caused the relationship between birth order and myopia to disappear, strongly suggesting that increased educational investment does account for the higher risk. As the study was carried out in an older cohort than in previous studies (3), it also shows that this environmental factor isn't new, and has been around for at least 30 to 40 years.

There were some limitations though – the study didn't include any information on time spent outdoors as a child. The use of self-reporting to exclude participants with cataracts, and the large age range used, may also have affected the robustness of the results. Nevertheless, the study authors conclude that their analysis "supports a role for reduced parental investment in education of children with later birth orders in their relative protection from myopia." *RM*

References

1. *R Gallagher, "Myopia Dystopia", The Ophthalmologist, 3, 16–21 (2013). https://theophthalmologist.com/issues/0313/301.*
2. *JA Guggenheim, et al., "Role of educational exposure in the association between myopia and birth order", JAMA Ophthalmol, [Epub ahead of print] (2015). PMID: 26448589.*
3. *JA Guggenheim, et al., "Birth order and myopia", Ophthalmic Epidemiol, 20, 375–384 (2013). PMID: 24168726.*

Unlocking CXL's Molecular Mysteries – With Mice

Swiss researchers have developed methods for performing corneal crosslinking with riboflavin and corneal biomechanical testing in mice – opening up the world of transgenics and molecular testing.

Corneal collagen cross-linking (CXL) with UV-A illumination and riboflavin is a useful way of increasing corneal stiffness to halt the progression of corneal ectatic disorders like keratoconus. But there's still much to be learned about the cellular and molecular events that take place during CXL and afterwards – and plugging those gaps in knowledge has been difficult. *Ex vivo* testing fails to provide an accurate picture because hydration and preservation processes after enucleation change the properties of the tissue and affect the accuracy of the testing, and to date, only indirect (and often inaccurate) methods of determining the efficacy of CXL in vivo exist. But change is afoot; a group of Swiss researchers led by Farhad Hafezi have tackled the problem by successfully establishing a CXL procedure, *in vivo*, in mice and then developing tools to accurately measure biomechanical changes in the mouse cornea that are induced by the procedure (1).

They achieved this by performing CXL with riboflavin on two groups of mice: the first group was used to determine appropriate adaptation of human CXL parameters to the mouse cornea (which is about five times thinner than a human

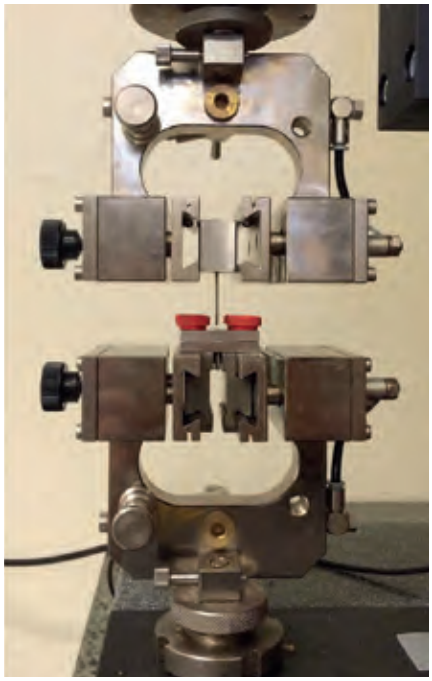

Figure 1. The testing equipment involved a customized mouse corneal holder mounted on an extensometer/indenter.

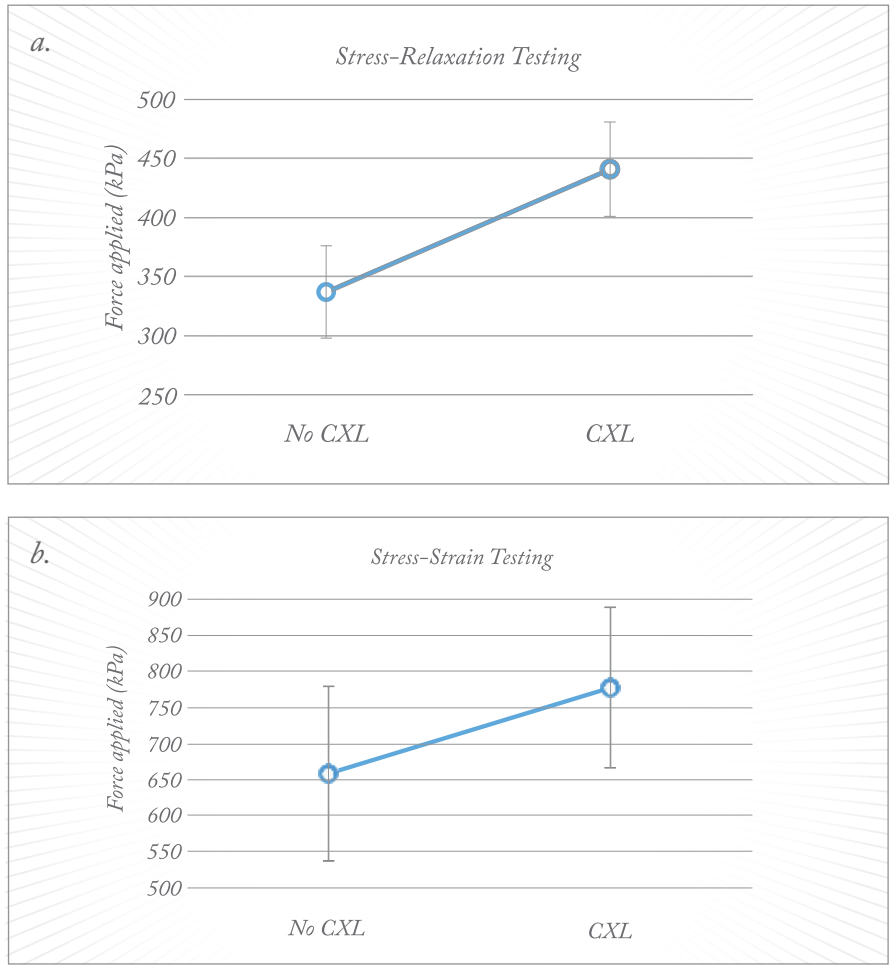

Figure 2. The results of biomechanical testing. a) Stress-relaxation testing showed greater stiffness in corneas treated with CXL than in untreated corneas. b) Stress-strain testing confirmed those results.

cornea); the second group of mice underwent CXL, but the UV-A fluence was reduced consecutively (from 3 mW at 3 mins, to 1 minute, to 30 seconds) in order to determine the threshold fluence level for effective CXL in the mouse cornea. After treatment, the mice were sacrificed and their corneas harvested for two-dimensional biomechanical testing using a customized corneal holder, designed to accommodate the small corneas of mice (see Figure 1).

The biomechanical analysis involved three steps: 1. preconditioning with three stress-strain cycles, 2. two minutes of stress-relaxation testing (in which constant force was applied to the cornea and the decrease in stress recorded), and 3. stress-strain extensometry (in which increasing force was applied until the cornea broke).

In all cases, stress-relaxation analysis showed significant biomechanical differences between the corneas of mice who received CXL with riboflavin, and those who did not. Cross-linked corneas maintained a higher stress (see Figure 2a) after 120 seconds of constant strain – meaning that they possessed greater structural integrity than non-cross-linked corneas. The findings were confirmed by stress-strain analysis (see Figure 2b), though the team found that this test was less sensitive to CXL-induced changes. Overall, they reached two main conclusions: that two-dimensional extensometry testing more closely mimics natural conditions than previous (one-dimensional) tests on pig, rabbit and human corneas, and that stress-relaxation testing provides a clearer measure of differences between groups than the more standard stress-strain testing. Combining these new discoveries with the establishment of mice as a useful model for CXL testing opens up new opportunities to examine the molecular effects of cross-linking in a living organism – particularly with transgenic mice. *FH*

Reference

1. *A Hammer, et al., "Establishing corneal cross-linking with riboflavin and UB-A in the mouse cornea in vivo: biomechanical analysis", Invest Ophthalmol Vis Sci, 56, 6581–6590 (2015). PMID: 26465887.*