

Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

Effects of Dry Eye on Activity and Productivity

June 2021

In a longitudinal analysis within the Dry Eye Assessment and Management (DREAM) trial, Greco et al. assessed the effects of dry eye disease (DED) on general activity and work productivity. They found that severe DED was linked to low levels of activity and productivity.

For this study, 535 participants with moderate or severe DED were asked to complete the Work Productivity and Activity Impairment questionnaire at baseline and at the six- and 12-month marks. They also were evaluated for DED symptoms and signs at these time points. Assessments included conjunctival and corneal staining, tear-film breakup time (TBUT), and the Schirmer test.

Work productivity and activity were assessed in relation to DED signs and symptoms via linear regression models that controlled for demographics and comorbidities. Main outcome measures were impairment of work productivity and general activity.

The mean overall level of activity impairment was 24.5%. Among patients who were employed at baseline ($n = 279$; 52%), the mean scores were 2% for absenteeism, 18% for presenteeism (defined as impaired performance during working hours), and 19.6% for overall work impairment.

Higher ocular surface disease index

(OSDI) scores, correlated with greater absenteeism, presenteeism, and activity impairment. For each 10-unit difference in OSDI score, mean impairments in productivity and activity rose by 4.3% and 4.8%, respectively ($p <$

.001). Although poor corneal staining and TBUT findings were associated with greater impairment in both forms of activity, longitudinal changes in these variables did not further affect either activity.

Although this research did not address differences between people with and without DED, the effects of severe DED on productivity and general activity were well quantified. Results of this study boost the evidence of DED's adverse economic and personal burdens, noted the authors, which may be relieved by better efforts to reduce DED symptoms.

Surgical Practice Types and Cataract Outcomes

June 2021

Do surgeons who focus primarily on cataract surgery experience better patient outcomes when compared to colleagues with more diversified surgical practices? Campbell et al. set out to explore whether the risk of adverse



events related to cataract surgery is affected by a practice's overall case mix. They found that surgeons with moderate levels of diversification performed as well as those who focused solely on cataract surgery. However, surgeons whose practices were devoted mostly to other types of ophthalmic surgery were more likely to experience adverse events during cataract surgery.

This population-based study comprised all patients ≥ 66 years of age who had cataract surgery in Ontario, Canada, from January 2002 through December 2013. Their surgeons were classified by the proportion of cataract surgeries performed: 100% cataract ("exclusive"), 1% to 50% other than cataract ("moderately diversified"), or more than 50% other than cataract ("highly diversified").

Linked health care databases were used for analyses, along with patient-, surgeon-, and institution-level covariates. Surgeon-level covariates included surgical experience and volume. The composite outcome was one of four adverse events: posterior capsule rupture, dropped lens fragment, retinal detachment, and suspected endophthalmitis.

Altogether, 1,101,864 cataract operations were performed during the study period. Demographic and clinical traits of patients treated by the various groups of surgeons were comparable at baseline. Adverse events occurred in 0.73% of operations by exclusive

cataract surgeons, 0.78% of procedures by moderately diversified surgeons, and 2.31% of cases handled by highly diversified surgeons. The difference in risk of surgery-related adverse events with moderately diversified surgeons versus exclusive cataract surgeons was not significant (odds ratio [OR], 1.08). However, the risk of adverse events was higher in the hands of highly diversified surgeons relative to surgeons who focus primarily on cataract surgery (OR, 1.52; $p = .01$). This represents an absolute risk difference of 0.016 and a number-needed-to-harm of 64. Results were similar for the sensitivity analyses based on surgical experience and volume.

The authors recommend further study of the relationship between surgical focus and outcomes, including the potential for more adverse events with higher diversification and the utility of a cutoff point at which outcomes do become affected.

Alcohol Intake and Cataract Development

June 2021

Studies of alcohol's effect on cataract formation have been fraught with design flaws and conflicting conclusions. Chua et al. conducted a large longitudinal study to better understand the possible relationship. They observed a strong correlation between levels of alcohol use currently categorized as "safe" and lower likelihood of cataract, with wine being the most beneficial beverage. Cataract surgery was more common among nondrinkers and those who drank heavily.

The study population was derived from two large registries (UK Biobank and EPIC-Norfolk) of patients who had cataract surgery and agreed to provide detailed lifestyle information. The researchers used Cox proportional hazards models to explore possible links between cataract surgery and the amount and type of alcohol consumed. The categories of alcohol consumption were none, <1-3 times/month, 1-2 times/week, 3-4 times/week, and daily or near-daily. Analyses were adjusted for age, sex, ethnicity, social support,

body mass index, smoking status, and diabetes. The primary outcome was incident cataract surgery.

Altogether, there were 23,584 incident cases of cataract surgery. Mean follow-up time was 95 months and 193 months for the UK Biobank and EPIC-Norfolk cohorts, respectively. Compared with nondrinkers, drinkers in both cohorts were less likely to undergo cataract surgery. After adjustment for covariates, the hazard ratio was 0.89 for the UK Biobank cohort and 0.90 for the EPIC-Norfolk group. Among alcohol users in EPIC-Norfolk, greater consumption correlated with reduced risk of cataract surgery ($p < .001$), whereas the UK Biobank data showed a U-shaped curve, indicating elevated risk for those on either end of the spectrum of alcohol intake. Compared with abstinence from alcohol, moderate drinking (1-4 times/week) was associated with a 6%-7% lower risk of cataract surgery. Relative to moderate drinkers, heavy drinkers had a 5%-6% higher risk of cataract surgery.

Red wine was found to confer the greatest protective benefit, possibly because of the concentration of polyphenol antioxidants in the skin of red grapes. The highest level of safe wine consumption reduced the risk of cataract surgery by 23% (EPIC-Norfolk) and 14% (UK Biobank).

The authors cautioned that their findings signify a correlational rather than a causal connection. Moreover, they noted that alcohol consumption raises the risk of many diseases that are serious and chronic.

—Summaries by Lynda Seminara

Ophthalmology Glaucoma

Selected by Henry D. Jampel, MD, MPH

Obstructive Sleep Apnea and Exfoliation Syndrome

May/June 2021

Shumway et al. set out to investigate the association between obstructive sleep apnea and exfoliation syndrome (XFS). They found that patients with obstructive sleep apnea may be at increased risk of XFS, particularly if

they also have hypertension.

For this case-control, retrospective cohort study, the researchers used the Utah Population Database to identify subjects with obstructive sleep apnea ($n = 81,735$). For comparison, case control subjects ($n = 319,939$), also identified via the database, were matched on sex and birth year.

The patients' mean age at diagnosis of sleep apnea was 64.6 years, and the mean age at time of XFS diagnosis was 74.9 years. Those with sleep apnea were diagnosed between 1999 and 2017; those with XFS were diagnosed between 1996 and 2015.

Odds ratios (ORs) were calculated from multivariable logistic regression models to estimate the risk of XFS in patients with sleep apnea compared with controls. Covariates potentially related to both obstructive sleep apnea and XFS—including obesity, hypertension, tobacco use, atrial fibrillation, and chronic obstructive pulmonary disease—were analyzed. The primary outcome was the risk of having an XFS diagnosis, including exfoliative glaucoma (XFG), in tandem with a diagnosis of obstructive sleep apnea.

Of those with sleep apnea, 248 (0.3%) had XFS, compared to 749 (0.2%) of controls. After accounting for matching variables and with covariate adjustment, the researchers observed a modest increased risk of XFS in patients who had sleep apnea (OR, 1.27; 95% confidence interval [CI], 1.02-1.59; $p = .03$).

With regard to specific covariates, patients with sleep apnea were more likely to be obese (45.9%, vs. 20.3% of controls), to have a history of atrial fibrillation (9.8%, vs. 2.9% of controls), and to have hypertension (26.8%, vs. 9.3% of controls). Patients with both sleep apnea and hypertension had an increased risk of XFS compared with patients who had hypertension without sleep apnea (OR, 2.67; 95% CI, 2.06-3.46; $p < .0001$).

According to the researchers, these findings support the understanding that XFS is a genetically predisposed systemic illness that is affected by and correlated with various systemic comorbidities. —Summary by Jean Shaw

Cost Analysis of Routine PPV

June 2021

Berkowitz et al. set out to calculate the complete cost profiles of routine pars plana vitrectomy (PPV), using electronic health record (EHR) time logs. They found a significant reimbursement gap between true PPV costs and the maximum allowable Medicare reimbursement.

For this analysis, the researchers evaluated financial data on 281 patients treated during 2019 at Vanderbilt University. A process flow map—from initial patient arrival and check-in to post-op clinic—was created based on observation of routine vitrectomy cases. The time needed to perform a PPV was calculated using de-identified time logs. Internal financial management software was used to gauge the costs of materials and overhead, and costs per minute for space, equipment, and personnel also were based on internal figures. This information was used for a time-driven activity-based analysis.

The results showed that the total cost for routine PPV surgery at Vanderbilt was \$7,169.78 per case—with costs of \$1,019.86 for labor, \$1,721.80 for materials, and \$4,428.12 for space and equipment.

In contrast, CMS reimbursement was \$5,115.93. Overall, the authors found, vitrectomy cases will not break even unless the case takes 26.81 minutes or less to perform, overhead is reduced by 53.78%, or reimbursement is increased by 40.15%. Moreover, in the cohort used for this study, 68% of cases were unprofitable, with increasing losses directly proportional to the length of the case.

Of note, one key limitation of this study is that it was conducted in a large academic ophthalmology department. Thus, the analysis includes teaching and other academic needs. The authors suggest that future studies should attempt to validate any cost imbalances for PPV surgeries across diverse institutions and operating settings.

—Summary by Jean Shaw

Should Keratoplasty Be Delayed to Adulthood?

June 2021

Wajnsztajn et al. compared findings for children and adults who underwent penetrating or deep anterior lamellar keratoplasty for keratoconus. They found that the visual outcomes and rates of rejection-free and graft survival were comparable for children and adults, suggesting that the surgery need not be delayed for young patients.

For this retrospective review, the authors gathered information from the U.K. Transplant Registry for children (defined as age 16 years or younger) and adults (defined as age 17 or older) who received their first transplant for keratoconus between 2003 and 2018. Main outcome measures were two-year visual, rejection-free, and graft survival data.

Altogether, 7,361 initial corneal transplantations were performed during the study period; of these, 170 took place in children. Pre-op visual acuity (VA) of 20/200 or worse was more prevalent in children, as were rates of corneal vascularization and ocular surface disease. However, within two years of surgery, visual outcomes were comparable for the age groups: Best-corrected VA of 20/20 or better was achieved in 35% of children and 28% of adults. Rates of rejection and graft failure were marginally lower for children, but confidence intervals were wide. After penetrating keratoplasty, the endothelial rejection rate was slightly higher for children (13% vs. 10% for adults), but no child experienced irreversible rejection with either type of transplant. Despite the similar rejection rates, Cox regression analysis showed a statistically significant relationship between patient age and graft rejection: For each five-year increase in age, the hazard of graft rejection decreased by 6%. Neither surgical procedure was superior to the other for the outcomes explored.

The authors concluded that there is

no clear advantage to delaying keratoplasty until adulthood. They acknowledged that most complications in children occur within a few months of transplantation and that VA is relatively stable from two to five years post-op.

Effect of Anti-VEGF Therapy on RNFL Density of Glaucomatous Eyes

June 2021

Although treatment of neovascular age-related macular degeneration (AMD) with multiple anti-VEGF injections doesn't appear to thin the retinal nerve fiber layer (RNFL) significantly, patients with confirmed or suspected glaucoma have been excluded from such research. It is plausible that glaucoma may worsen from elevations in intraocular pressure (IOP) that occur with intravitreal injections. However, findings of a retrospective study by Swaminathan et al. suggest that most patients with mild or moderate glaucoma can receive a moderate number of injections for AMD without the risk of accelerated RNFL thinning. Even though some patients with glaucoma will require IOP-lowering therapy before anti-VEGF injections, the authors do not endorse widespread use of preinjection procedures.

The study participants had neovascular AMD in one eye and confirmed or suspected glaucoma in both eyes. They had received at least three RNFL OCT scans and at least six intravitreal injections. The primary endpoint was the difference in rates of RNFL thinning between the injected and the fellow uninjected eye, as estimated by linear mixed models. Secondarily, the authors looked at injection frequency, total number of injections, and high postinjection IOP levels in relation to RNFL thinning.

Fifty-three patients (mean age, 79.0 years; 62.3% female; 92.4% White) met the criteria for inclusion. The mean number of intravitreal injections was 26.4 ± 15.9 , at an average rate of 5.4 ± 2.5 injections per year. The average rate of RNFL thinning in untreated eyes was significant: $-0.620 \mu\text{m}/\text{year}$ ($p = .029$). Among injected eyes, there

was an additional (but insignificant) incremental loss of $-0.385 \mu\text{m}/\text{year}$. Over time, no association was observed between injection status and RNFL density data. In the subgroup of 33 patients with confirmed glaucoma, most of whom had mild or moderate disease, the rate of change in RNFL thinning of injected eyes was not significant ($-0.568 \mu\text{m}/\text{year}$). Moreover, there was no meaningful relationship between any secondary endpoint and the rate of RNFL thinning.

Despite the promising findings of this study, the authors cautioned that a small number of patients will have progressive RNFL loss with intravitreal treatments.

—Summaries by Lynda Seminara

JAMA Ophthalmology

Selected and reviewed by Neil M. Bressler, MD, and Deputy Editors

OHTS: 20 Years of Follow-up Data on POAG

May 2021

Kass et al. set out to determine the cumulative incidence and severity of primary open-angle glaucoma (POAG) during 20 years of follow-up among participants of the Ocular Hypertension Treatment Study (OHTS). They found that 25% of the study participants developed visual field loss during follow-up.

OHTS originally ran from February 1994 to December 2008. Follow-up began on Jan. 6, 2016, and it continued until April 15, 2019. During that time, study participants received ophthalmic examinations and visual function assessments.

Initially, 1,636 patients enrolled in OHTS. Their mean age was 55.4 years, 56.9% were women, and most were White (69.6%). Over the course of the study (including follow-up), 515 participants died. After a median follow-up of 20.2 years, 483 participants (29.5%) developed POAG in one or both eyes. The cumulative incidence of POAG at 20 years, adjusted for exposure time, was 45.6% among all participants. The cumulative incidence by ethnicity was 55.2% among Black participants and

42.7% among other ethnic groups. The 20-year cumulative incidence of visual field loss was 25.2%. When the OHTS prediction model—which categorizes patients into low-, medium-, and high-risk groups—was applied, the cumulative incidence of POAG was 31.7% among low-risk patients, versus 47.6% and 59.8% among those at medium and high risk, respectively.

The researchers noted that this information, when used with the OHTS prediction model, may help clinicians and patients make informed, personalized decisions about management of ocular hypertension.

Preventing Conversion to Neovascular AMD

May 2021

Heier et al. evaluated whether intravitreal injections of aflibercept can be used as a prophylactic treatment against conversion to neovascular age-related macular degeneration (AMD) in high-risk eyes. They did not find evidence to support this strategy.

For this randomized study, which was conducted at four U.S. clinical sites, the researchers enrolled 128 patients who had intermediate AMD in one eye (study eye) and neovascular AMD in the other. Intermediate AMD was defined as the presence of more than 10 medium drusen, at least one large druse, and/or retinal pigmentary changes. The patients were randomized to receive either 2-mg injections of aflibercept or sham injections on a quarterly basis in the study eye. The primary endpoint was the proportion of patients who experienced conversion to neovascular AMD at month 24, as characterized by the development of choroidal neovascularization.

For this analysis, data were available on 127 patients (mean age, 76.5 years). Of these, 63 received aflibercept, and 64 had sham injections. The two groups were balanced with regard to demographic and baseline characteristics. By month 24, six patients (9.5%) in the aflibercept group and seven (10.9%) in the sham cohort developed neovascular AMD in the study eye ($p = .98$). Patients who had had neovascular

AMD in their fellow eye for more than two years at baseline were less likely to experience conversion to neovascular AMD in the study eye. In addition, most of the conversions took place during the first year of the study.

Based on these results, the use of intravitreal anti-VEGF injections as prophylaxis against conversion to neovascular AMD is not recommended at this time.

Controlling Costs of Adenoviral Conjunctivitis

May 2021

Kuo and Gower assessed the cost savings of a “red eye policy” designed to prevent conjunctivitis outbreaks at a major academic medical center. They found that, by furthering accurate diagnosis and infection control, the policy reduces the number of unnecessary work furloughs, thus leading to substantial cost savings.

The policy was implemented at Johns Hopkins Medical Center in 2011. Under it, employees can present to the medical center’s occupational health clinic to be immediately evaluated for red eye. Those who have had a red eye for fewer than seven days and have highly suggestive symptoms (e.g., discharge or tearing, contact with a person with adenoviral conjunctivitis, and/or recent cold, cough, or flu-like symptoms) are swabbed by a nurse practitioner. After the employee’s eye is swabbed, the person is temporarily furloughed as the specimen is evaluated with a rapid polymerase chain reaction (PCR) test validated for adenoviral conjunctivitis. Those who test positive remain on furlough, while those with negative test results return to work.

For this quality improvement study, the researchers assessed the results of this triage system from Nov. 1, 2011, through Oct. 21, 2018. All told, 2,142 employees with red eye presented to the occupational health clinic during this time. Of these, 1,520 were suspected to have adenoviral conjunctivitis and underwent swabbing, and PCR test results were positive for 130 employees. Most of those who tested negative were seen by a comprehensive ophthalmol-

ogist within 24 hours; common causes of their red eyes included dry eye and allergic conjunctivitis.

With regard to cost, furloughing 130 employees—versus all 1,520 of those initially suspected to be affected—resulted in an estimated annual savings of \$442,073, for a total of \$3,094,511 during the seven-year period. The policy has also proved effective from a public health perspective, as no adenoviral conjunctivitis outbreaks have occurred since it was implemented.

Of note, the PCR test used at Johns Hopkins was developed and validated there. The researchers expressed hope that these results may provide impetus for the development of a commercially available test that is sensitive and specific for adenoviral conjunctivitis and does not require a specialized laboratory. (*Also see related commentary by Amanda K. Bicket, MD, MSE, and Joshua D. Stein, MD, MS, in the same issue.*) —Summaries by Jean Shaw

OTHER JOURNALS

Selected by Prem S. Subramanian, MD, PhD

Neuro-Ophthalmic Measures for Detecting Concussion in Athletes

JAMA Network Open

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Feller et al. explored the potential role of computerized eye-tracking methods to distinguish concussion among college-age athletes. They found that a specific set of measures denoted slow visual reaction time. In addition, they found that the measures were sensitive and specific for differentiation.

For this study, the researchers included 34 athletes who sustained concussion and a control group of 54 uninjured athletes who were involved in noncontact sports. Those in the control group had not experienced any previous head injuries. Concussion was diagnosed by an experienced clinician and was defined as head trauma with either 1) witnessed or self-reported brief loss of consciousness, amnesia, or confusion or 2) the occurrence of headache, short-term memory concerns, dizziness, or imbalance within 24

hours of injury. The injured athletes' eye movements and cognitive function were measured at a median of 19 days postinjury, and these findings were compared with those observed in the control group.

Among the 42 eye-tracking metrics tested, eight (19%) differed significantly between the study groups. For six of the eight metrics, area under the receiver operator characteristic curve (AUROC) was at least 0.70, the criterion for clinical significance. All six of the metrics pertain to reaction time: simple and discriminate reaction time, discriminate and choice visual reaction speed, and reaction time for two measures of dynamic visual acuity. Data for the six parameters demonstrated slower reactions for participants with concussion. None of the six metrics correlated with visual memory or motor speed, and half of them were unrelated to reaction time on cognitive testing. The combined AUROC of the six metrics was 0.90 (95% confidence interval, 0.80-0.99). Combined sensitivity was 77.8%, and specificity was 92.6%. Further sensitivity testing produced similar results.

This research suggests that a composite of select eye-tracking measures of visual reaction time may be an objective detector of concussion among injured athletes. In turn, this may decrease the disability associated with missing the diagnosis. The highly discriminative metrics identified in this study imply disruption to specific oculomotor pathways, said the authors, who maintain that greater understanding of this possibility could provide unique insight for managing concussion as well as detecting it.

RGC Morphology of Eyes With POAG

Investigative Ophthalmology & Visual Science

2021;62(3):34

Liu et al. set out to describe the morphologic changes in retinal ganglion cells (RGCs) that occur in patients with primary open-angle glaucoma (POAG) associated with hemifield defect. Using adaptive optics (AO) OCT, they found

that these patients had lower ganglion cell layer (GCL) soma density and symmetry, greater soma size, and more variation of GCL soma reflectance compared with healthy controls.

The study included six patients with early or moderate POAG and hemifield defect (mean age, 58 years) and six age-matched healthy controls (mean age, 61 years). All participants received in vivo high-resolution AO-OCT imaging of RGCs at the same primary locations of the macula. GCL somas were counted manually, and the morphologic parameters of GCL soma density, size, and symmetry were calculated. From these data, the relationship between RGC characteristics and functional visual field measurements was explored.

At 3, 6, and 12 degrees, GCL soma density was $12,799 \pm 7,747$ cells/mm², $9,370 \pm 5,572$ cells/mm², and $2,134 \pm 1,494$ cells/mm² (respectively) in the glaucoma group, compared with $25,058 \pm 4,649$ cells/mm², $15,551 \pm 2,301$ cells/mm², and $3,891 \pm 1,105$ cells/mm² (respectively) in the control group ($p < .05$ for all locations). These data represent reductions of 49%, 40%, and 45% for patients with glaucoma relative to controls. Soma diameter was significantly larger in glaucomatous eyes (mean, 14.20 ± 2.30 μ m vs. 12.32 ± 1.94 μ m in controls; $p < .05$ for all locations). Symmetry values were 0.36 ± 0.32 and 0.86 ± 0.13 for the glaucoma and control cohorts, respectively. AO-OCT also was useful for detecting subcellular reflectance changes in GCL somas and for tracking inner retinal changes in some eyes with POAG.

These results indicate that RGCs are equally affected by glaucoma throughout the macula but that loss of these cells affects vision more in the periphery, said the authors. This is likely due to reduced RGC density and decreased cone-to-RGC ratio in that region. The morphologic changes noted in this study are characteristic of hemifield defects, and the cellular-level structural loss in glaucomatous eyes correlated with loss of visual function. Therefore, the authors believe that AO-based morphologic parameters have the potential to be biomarkers for glaucoma.

—Summaries by Lynda Seminara