

Journal Highlights

NEW FINDINGS FROM *OPHTHALMOLOGY*, *AJO*, AND *JAMA OPHTHALMOLOGY*

Ophthalmology

Refractive Error, Glaucoma, and Ethnicity

November *Ophthalmology*

What is the association between refractive error and glaucoma when race and ethnicity are factored in? **Shen et al.** explored this question and found that myopia and hyperopia are associated with particular forms of glaucoma. The investigators looked at primary angle-closure glaucoma (PACG) and 3 types of open-angle glaucoma: primary open-angle glaucoma (POAG), normal-tension glaucoma (NTG), and pseudoexfoliation glaucoma.

For this cross-sectional study, the researchers gathered data (2008-2014) from the electronic health records of members of a Northern California health plan who were aged 35 or older with a documented refractive error. Within this group, 34,040 members had a diagnosis of glaucoma or ocular hypertension (OHTN) and 403,398 had neither. The latter served as controls.

Hyperopia was associated with PACG, while myopia was associated with an increased prevalence of all forms of open-angle glaucoma and OHTN, the researchers found. The

magnitudes of the associations were strongest for those with the greatest refractive error.

In terms of ethnicity, a stronger association was seen between myopia and POAG among non-Hispanic whites, and between myopia and NTG among Asians and non-Hispanic whites. The association between hyperopia and PACG extended across all racial and ethnic groups.

Steroid Injections Raise Risk of Endophthalmitis

November *Ophthalmology*



VanderBeek et al. set out to determine whether the rates of postinjection endophthalmitis differ between injection of intravitreal steroid and anti-VEGF drugs. They found that the risk of endophthalmitis is higher with steroid injections.

For this retrospective cohort study, the researchers evaluated 406,380 intravitreal injections (75,249 patients) administered between 2003 and 2012. Of these, 387,714 were anti-VEGF injections (bevacizumab, ranibizumab, aflibercept, or pegaptanib), and 18,666 were steroid injections (triamcinolone or dexamethasone).

A total of 73 cases of endophthalmitis occurred in the anti-VEGF group,

for a rate of 1 per 5,283 injections (0.019%). In contrast, 24 cases occurred in those who received steroid injections, for a rate of 1 per 778 injections (0.13%).

The authors hypothesized that the larger-gauge needle used for steroid injections may play a role by creating a bigger needle track for easier bacterial penetration into the vitreous. The immunosuppressive nature of the steroids may be an additional risk factor.

This study is the largest collection of data on intravitreal steroid injections and endophthalmitis cases to date. The most significant limitation of this study was lack of access to laboratory culture results, the authors noted, which prevented confirmation of type of endophthalmitis from the charts.

CRAO and Risk of Stroke and Myocardial Infarction

November *Ophthalmology*

Park et al. investigated the risk and timing of stroke and acute myocardial infarction (AMI) in patients with central retinal artery occlusion (CRAO). They found an increased risk of ischemic stroke just after CRAO occurs, particularly in the first week.

For this case series, the researchers used the Korean national claims database of 48 million individuals. They identified 1,655 patients who had CRAO in the time period 2009-

2010. Of these, 139 had an ischemic stroke, 13 had a hemorrhagic stroke, and 15 had an AMI during the year immediately preceding or following the CRAO. After statistical analyses were performed, the study did not find significant associations with hemorrhagic stroke or AMI. The researchers cautioned, however, that this lack of significance could be due in part to the small number of such occurrences during the study period, and they did not discount the possibility of a longer-term risk.

Further analysis showed that the risk of ischemic stroke was particularly high in the first week after CRAO and continued to be elevated throughout the first 30 days. Given these findings, the authors suggest that patients with incident CRAO should receive immediate neurologic evaluation and preventive treatment to reduce morbidity and mortality from stroke.

Anti-VEGF Injections and Cataract Surgery Outcomes

November *Ophthalmology*

Hahn et al. investigated the effect of prior intravitreal anti-VEGF injections on cataract surgery outcomes and complication rates. They found that patients with a history of intravitreal injections may be at greater risk for intraoperative complications and postoperative endophthalmitis.

For this retrospective cohort analysis, the researchers evaluated 203,643 Medicare beneficiaries who underwent cataract surgery from 2009 to 2013, using a 5% sample of claims data. The primary outcome was the risk of subsequent removal of retained lens fragments within 28 days; secondary outcomes included endophthalmitis (both acute and delayed-onset) and a new diagnosis of primary open-angle glaucoma (POAG).

Prior intravitreal anti-VEGF injections were associated with a significantly increased risk of retained lens fragments (hazard ratio [HR], 2.26), acute endophthalmitis (HR, 2.29), and delayed-onset endophthalmitis (HR, 3.65). However, they were not associ-

ated with greater risk of a new POAG diagnosis.

The researchers recommended that cataract surgeons should employ increased preoperative assessment, additional intraoperative caution, and postoperative vigilance in patients who have received anti-VEGF treatment.

American Journal of Ophthalmology

IOP Measurements by Different Devices in Children

November *AJO*

In a study in South Korea, **Feng et al.** compared intraocular pressure (IOP) measurements in children by means of rebound, noncontact, and Goldmann applanation tonometry (GAT) and assessed the relationship of each to central corneal thickness (CCT). They found that all methods can be considered appropriate for routine clinical use in children and that IOP readings of each tonometry positively correlated with CCT.

Measurements were taken in the right eyes of 419 children, who had a mean age of 8.89 ± 3.41 years (range, 3-15 years). Using the 3 types of tonometry, the researchers assessed mean IOP, rates of successful measurement with each type, and the inter-method agreement by Bland-Altman plot. The influences of CCT and of average IOP of the 3 tonometries on IOP differences between methods were also evaluated.

The researchers found significant differences in mean IOP with each tonometry method, with GAT showing the lowest readings. In children younger than 10 years old, IOP was successfully measured by noncontact tonometry in 89%, by rebound tonometry in 75%, and by GAT in 64%. In children older than 10, the rates were 100%, 98%, and 94%, respectively, for those methods. The IOP of each tonometer positively correlated with CCT. Rebound and noncontact tonometry overestimated IOP relative to GAT for thicker CCT. Rebound tonometry overestimated IOP relative to both GAT and noncontact tonometry

at higher average IOPs.

The researchers concluded that IOP readings obtained with the 3 types of tonometry showed a reasonable concordance with each other, and all of them can be considered appropriate for routine clinical use. The noncontact method has the highest rate of success in obtaining an IOP measurement in children. The researchers added that, given the risk of false-positive diagnosis of pediatric glaucoma, attention should be devoted to children whose IOP is in a suspicious high range or who have thicker corneas.

The Association of Race With Childhood Uveitis

November *AJO*

Using a retrospective cohort study design, **Angeles-Han et al.** identified risk factors for a severe disease course among children with non-infectious uveitis. This study reported that non-Hispanic African-American race is a potential predictor of a severe uveitis course; children in this group had an accelerated rate of ocular complications and an increased likelihood of vision loss.

The records of 94 children with uveitis were reviewed at enrollment and every 3 to 6 months thereafter (2011-2015). Severe uveitis was defined as a history of ocular complications or a visual acuity (VA) of 20/200 or worse. Children were compared by disease, VA, complications, and race. When examining race, the researchers focused on non-Hispanic African-American and non-Hispanic white children only.

Of 85 children with uveitis and complete ocular examinations, 27 (32%) had a history of VA of 20/200 or worse. A subanalysis of non-Hispanic African-American and white children showed an increased prevalence of VA of 20/200 or worse in the former group. In addition, non-Hispanic African-Americans were more likely to be diagnosed at an older age and to have intermediate uveitis, bilateral disease, and a higher rate of complications. On multivariable analysis, non-

Hispanic African-American race was a significant predictor of blindness, after controlling for uveitis duration. Non-Hispanic African-Americans developed 2.2 times more unique complications per year of disease than non-Hispanic whites when controlling for uveitis type and duration.

The researchers noted that these findings could be secondary to biological differences or to socioeconomic factors such as health care access. They recommended further study to reduce vision-threatening outcomes among minority patients.

Tear Dysfunction, Corneal Sensitivity, and Correlation With Blink Rate

November *AJO*

In a comparative observational case series, **Rahman et al.** assessed corneal sensitivity in patients with tear dysfunction due to a variety of causes and evaluated correlations between corneal sensitivity, blink rate, and clinical parameters. Outcome measures included corneal and conjunctival staining, corneal sensitivity, blink rate, tear meniscus height, and irritation symptoms.

Ten controls and 33 patients with tear dysfunction were evaluated; in the latter group, 11 had meibomian gland disease, 10 had aqueous tear deficiency, and 12 had conjunctivochalasis. Corneal sensitivity was measured by Cochet-Bonnet and air jet esthesiometers, and blink rate by electromyography. Eye irritation symptoms, tear meniscus height, tear break-up time (TBUT), and corneal and conjunctival dye staining were evaluated.

Compared with the controls, mean sensory thresholds, as measured by either of the esthesiometers, were significantly higher in the aqueous tear deficiency group but were not significantly different in the other groups. Reduced corneal sensitivity correlated significantly with more rapid TBUT and blink rate and with greater irritation and ocular surface dye staining. Mean blink rates were significantly higher in both aqueous tear deficiency and conjunctivochalasis compared

with the controls. Among all subjects, blink rate positively correlated with ocular surface staining and irritation and inversely correlated with TBUT.

The authors concluded that among conditions causing aqueous tear dysfunction, reduced corneal sensitivity was associated with greater irritation, tear instability, ocular surface disease, and blink rate. Rapid blinking is associated with worse ocular surface disease and tear stability.

Impact of Free Glasses and Teacher Incentive on Children's Use of Eyeglasses

November *AJO*

Yi et al. studied the effect of free eyeglasses combined with a teacher incentive on in-school wear of glasses among Chinese urban migrant children. Using a cluster-randomized controlled trial design, the researchers found that free spectacle distribution in combination with education on their use and a teacher incentive maintained high rates of classroom wear over a school year.

Children with visual acuity (VA) of 6/12 or worse in either eye due to refractive error were identified in 94 randomly chosen schools. In 47 schools, the children received free glasses and education on their use, and teachers received an incentive (intervention group); in the 47 control schools, children received glasses prescriptions only. Intervention group teachers received a tablet computer if 80% or more of the children given glasses were wearing them during unannounced visits 6 weeks and 6 months (main outcome) after intervention. Among 4,376 children, 728 met enrollment criteria: 358 were allocated to intervention and 370 to control; 693 completed the study and underwent analysis.

Spectacle wear was significantly higher among intervention children. By direct classroom observation at 6 months, 68.3% of the intervention group and 23.9% of the control group were wearing their eyeglasses. Other predictors of observed wear at 6 months included baseline spectacle

wear, uncorrected VA worse than 6/18, and parental spectacle wear.

In a previous trial by these researchers, the 6-month observed wear rate was only 41% among similar-aged children who were provided free glasses without teacher incentives. Both that earlier study and the current trial demonstrate the need for interventions—and not just free spectacles—in encouraging children to wear their glasses.

JAMA Ophthalmology

Microscope-Integrated OCT During Ophthalmic Surgery

October *JAMA Ophthalmology*

Ehlers et al. assessed the feasibility and effect on surgical decision making of a microscope-integrated intraoperative OCT (iOCT) system. Their report highlights the 1-year results (March 2014-Feb. 2015) from the Rescan 700 (Carl Zeiss Meditec) portion of a single-site, multisurgeon, prospective consecutive case series study known as DISCOVER (Determination of Feasibility of Intraoperative Spectral Domain Microscope Combined/Integrated OCT Visualization During End Face Retinal and Ophthalmic Surgery).

Data on clinical characteristics of patients undergoing ophthalmic surgery were collected, and iOCT was performed at surgical milestones, as directed by the operating surgeon. A questionnaire was issued to each surgeon and completed after each case to evaluate the role of iOCT during surgery. The main outcomes were the percentage of cases with successful image acquisition with iOCT (i.e., its feasibility) and the percentage of cases in which iOCT altered surgical decision making (i.e., its utility).

During year 1 of the DISCOVER study, a total of 227 eyes (91 anterior segment cases and 136 posterior segment cases) underwent imaging with the Rescan 700 system. Successful imaging—that is, the ability to acquire an OCT image of the tissue of interest—was obtained for 224 of 227 eyes (99%). With regard to utility, the

iOCT data altered the surgeon's decision making in 38% of lamellar keratoplasty cases (e.g., showing complete graft apposition when the surgeon believed there was interface fluid). In membrane-peeling procedures, iOCT information was discordant with the surgeon's impression of completeness of peel in 19% of cases (e.g., lack of residual membrane or presence of occult membrane), which affected surgical maneuvers.

The authors concluded that this study demonstrates the feasibility of real-time iOCT with a microscope-integrated system for use in ophthalmic surgery. The information gained from iOCT appears to allow surgeons to assess subtle details in a unique perspective from standard en face visualization. Although the use of this device affected surgical decision making in some cases, the impact of these changed decisions on outcomes remains unknown. A randomized masked trial would be valuable in confirming these results.

Compounded Bevacizumab and Postinjection Endophthalmitis

October *JAMA Ophthalmology*

Current draft guidelines set forth by the U.S. FDA for compounded or repackaged medications could greatly limit the use of bevacizumab by ophthalmologists. However, apart from highly publicized case reports, there is little evidence on the need for additional regulations. VanderBeek et al. sought to determine whether bevacizumab distributed through compounding pharmacies increases the risk for endophthalmitis compared with ranibizumab in single-use vials from the manufacturer.

This retrospective cohort study used medical claims data that were submitted to a large national U.S. insurer from ambulatory care centers across the United States. Information was available from 530,382 intravitreal injections administered from Jan. 1, 2005, through Dec. 31, 2012. Individuals from this data set who received at

least 1 intravitreal injection of bevacizumab or ranibizumab and had at least 6 months of data before and 1 month after the injection were eligible. Patients were excluded for any previous diagnosis of endophthalmitis, multiple injected drugs on the index day, or intraocular surgery within 15 days of the injection or between the injection and a diagnosis of endophthalmitis. The main outcome was the odds of developing endophthalmitis after an intravitreal injection of bevacizumab compared with ranibizumab.

After exclusions, there were 296,565 injections of bevacizumab (51,116 patients) and 87,245 injections of ranibizumab (7,496 patients). The authors found 71 cases of endophthalmitis (49 in the bevacizumab cohort and 22 in the ranibizumab cohort) for an endophthalmitis rate of 0.017% (1 case per 6,061 injections) for bevacizumab and 0.025% (1 case per 3,968 injections) for ranibizumab. After controlling for age, race, sex, injection-related diagnosis, and year of injection, the authors found no significant association with development of endophthalmitis after bevacizumab injection compared with ranibizumab (odds ratio, 0.66; 95% CI, 0.39-1.09; $p = .11$).

The results suggest that bevacizumab, as currently administered via intravitreal injection in the United States, does not increase the risk for endophthalmitis; thus, additional regulations on the use of repackaged bevacizumab with respect to endophthalmitis may be unnecessary.

Body Levels of Trace Metals and Glaucoma Prevalence

October *JAMA Ophthalmology*

Abnormal body levels of essential elements and exposure to toxic trace metals have been postulated to contribute to the pathogenesis of diseases affecting many organ systems. Lin et al. investigated possible associations between trace metals and the prevalence of glaucoma in a cross-sectional population-based study in South Korea.

Blood or urine metallic element levels and information pertaining to ocular disease were available for 2,680 individuals 19 years and older participating in the fourth Korea National Health and Nutrition Examination Survey between Jan. 1, 2008, and Dec. 31, 2009.

Glaucoma diagnosis was based on criteria established by the International Society of Geographic and Epidemiologic Ophthalmology. Demographic, comorbidity, and health-related behavior information was obtained through interviews. Multivariable logistic regression analyses were performed to determine associations between blood and urine trace element levels and the odds of glaucoma diagnosis. The main outcome was the presence or absence of glaucoma.

After adjustment for potential confounders, blood manganese level was negatively associated with the odds of glaucoma diagnosis (odds ratio [OR], 0.44). Blood mercury level was positively associated with glaucoma prevalence (OR, 1.01). No definitive association was identified between blood cadmium or lead levels or urine arsenic level and a diagnosis of glaucoma. Although these findings suggest that a lower blood manganese level and a higher blood mercury level are associated with greater odds of glaucoma, prospective studies are needed to confirm the role of trace minerals in development of glaucoma.

ROUNDUP OF OTHER JOURNALS

Visual Acuity and Reproducibility of Visual Fields

Investigative Ophthalmology & Visual Science

2015;56(9):5630-5635

Matsuura et al. investigated the association between visual acuity (VA) and the reproducibility of test-retest visual field (VF) measurements in glaucoma patients. They found that as VA declines, the reproducibility of VF tests declines as well,

particularly when a patient's logMAR VA is worse than 0.5.

For this retrospective study, the researchers evaluated 627 patients (627 eyes) who had open-angle glaucoma. All underwent Humphrey 24-2 or 30-2 VF tests twice within 3 months; the same mode was used for both tests. Refractive error was measured in -0.25 D steps. VA was calculated in logMAR (range, -0.18 to 1).

Based on their evaluation of the correlation between VF reproducibility and logMAR VA, the researchers noted that although VA is a useful parameter for assessing the reproducibility of VFs, its usefulness declines with greater refractive error. Therefore, they recommended a logMAR cut-off value of worse than 0.5 when using VF outcomes in glaucoma research or in monitoring progression or effects of interventions.

Eye Protection, Eye Injuries, and Field Hockey

Pediatrics

2015;136(3):521-527

Does wearing protective eyewear reduce the risk of injuries in field hockey players? Kriz et al. evaluated this issue in a group of female high school players and found that those who use the eyewear have a lower rate of certain eye injuries. However, the players remain at significant risk of experiencing a concussion.

For this retrospective study, the researchers analyzed data collected from national and regional databases 2 years before and 2 years after a national mandate for protective eyewear at the high school level was put into place in 2011. All told, 206 high schools were involved, accounting for a total of 624,803 athletic exposures (defined as 1 athlete participating in 1 practice or competition).

Within the 4-year time span, eye and orbital injuries dropped from 22 before the mandate to 8 after; these included eyebrow/eyelid lacerations, periorbital contusions, and corneal abrasions. With regard to concussions,

93 occurred before the mandate, and 116 occurred after it. Other head and facial injuries (excluding eye injuries and concussions) dropped from 97 to 79 in the study period. The authors noted that greater concussion awareness in recent years might have played a role in the higher number of concussions reported during the later study period.

The authors stated that their findings with regard to eye injuries support the mandatory use of protective equipment in field hockey at all amateur levels.

Tasimelteon for Sleep-Wake Disorder in the Blind

The Lancet

Published online Aug. 5, 2015

Lockley et al. evaluated whether once-daily oral tasimelteon could reset the circadian pacemaker in totally blind people with non-24-hour sleep-wake disorder. They found that the drug can synchronize, or entrain, totally blind people to a 24-hour circadian cycle, but it must be taken on an ongoing basis to sustain the benefits.

The researchers conducted 2 phase 3 trials. Sixty-two patients completed the first study (known as SET), and 20 completed the second (known as RESET). Patients were randomized to receive either 20 mg of tasimelteon or placebo daily 1 hour before bedtime. Compared with the placebo group, a significantly higher percentage of patients taking tasimelteon had clinically meaningful improvements in the duration of nighttime sleep and reduced undesired daytime sleep. It also improved patients' sleep stability and physicians' ratings of patient functioning. However, results of the RESET trial indicated that continuing treatment with tasimelteon is necessary for circadian entrainment to be maintained.

Tasimelteon is a dual-melatonin receptor agonist, and it is the first drug to be approved by both the U.S. Food and Drug Administration and the European Medicines Agency for non-24-hour sleep-wake disorder.

Supplements and Cognitive Function in AREDS2 Participants

JAMA

2015;314(8):791-801

Chew et al. tested whether oral supplementation with omega-3 fatty acids and lutein plus zeaxanthin had any impact on cognitive functioning in patients with age-related macular degeneration (AMD). They found that it did not.

This study involved 3,741 of the 4,203 participants in the Age-Related Eye Disease Study 2 (AREDS2). Patients were randomized to receive either 1) placebo, 2) the omega-3 fatty acids docosahexaenoic acid and eicosapentaenoic acid, 3) lutein/zeaxanthin, or 4) a combination of the fatty acids and lutein/zeaxanthin. They also received 1 of 4 AREDS supplements: 1) the original formulation, 2) a version without beta carotene, 3) a low-zinc version, or 4) a low-zinc, no-beta carotene formulation.

Validated cognitive function tests were administered at baseline and every 2 years during the 5-year study. No statistically significant effects were noted with regard to cognitive function when supplementation was compared with placebo.

However, the researchers noted several factors that limited the generalizability of the findings: The study population consisted of well-nourished, highly educated people; participants had at least intermediate or advanced AMD, which is a type of neurodegenerative disease; and supplementation might have been started too late in the aging process in this study population, which had a mean age at baseline of 72.7 years.

Ophthalmology summaries are written by Jean Shaw and edited by Susan M. MacDonal, MD. American Journal of Ophthalmology summaries are edited by Thomas J. Liesegang, MD. JAMA Ophthalmology summaries are based on authors' abstracts, as edited by senior editor(s). Roundup of Other Journals is written by Jean Shaw and edited by Deepak P. Edward, MD.