Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

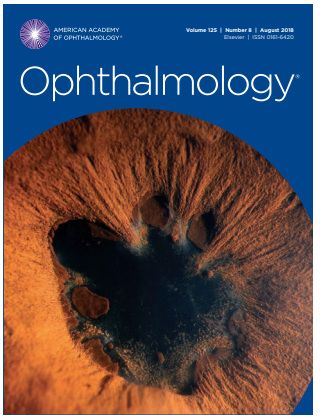
Ophthalmology

Selected by Stephen D. McLeod, MD

Outdoor Activity and Myopia Progression in Children

August 2018

Building on evidence of the benefit of outdoor activity for prevention and control of myopia, **Wu et al.** implemented a program to encourage young Taiwanese schoolchildren to spend more time outside. After 1 year, those students who had been encouraged to spend at least 11 hours per week outdoors, with exposure to light intensity of at least 1,000 lux, had significantly less myopic shift and axial elongation than did those in the control group.



The study included 693 first graders at 16 schools. The intervention group (n = 267) participated in school-oriented outdoor activities, including fresh-air recess and summer learning assignments, and they were encouraged to spend at least 11 hours per week outside. The control group (n = 426) did not receive these interventions but spent some time outside. Both groups had outdoor exercise initiatives. All participants wore a light meter recorder and, with help from their parents, completed weekly activity diaries and questionnaires. Time outdoors was defined as the period during which light intensity was at least 1,000 lux according to the light meter. Outcomes of interest were changes in spherical equivalent and axial length from baseline to 1 year, as well as intensity and duration of exposure to outdoor light.

The researchers found that more students in the intervention group (50% vs. 23% of controls) spent more than 11 hours per week outdoors. Students who spent at least 200 minutes per week outside during school hours were found to have significantly less myopic shift with lux readings as follows: ≥1,000 lux, 0.14 D; ≥3,000 lux, 0.16 D. The intervention group had significantly less myopic shift than the control group (0.35 D vs. 0.47 D) and axial elongation (0.28 mm vs. 0.33 mm). The risk of rapid myopia progression was 54% lower in the intervention group (odds ratio, 0.46; p = .003). The protective effects against myopia were seen among myopic and nonmyopic children in the intervention group.

The authors concluded that exposure to strong sunlight may not be required for prevention of myopia. Longer periods of relatively low outdoor light intensity, as in the shade of trees, may be sufficient for the protective effect. Larger studies of longer duration are warranted. *(Also see related commentary by Ian G. Morgan, BSc, PhD, in the same issue.)*

Cataract Surgery: Comparing Outcomes of MCS and FLACS

August 2018

Berk et al. compared visual and refractive outcomes of femtosecond laser-assisted cataract surgery (FLACS) and manual cataract surgery (MCS) and found no significant differences between the 2 approaches.

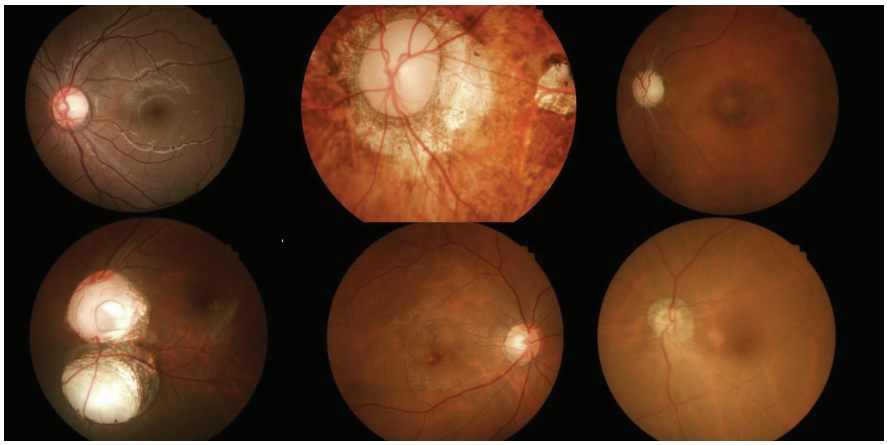
For this single-center, comparative, retrospective analysis, the authors looked at outcomes for eyes that received FLACS or MCS during a 37-month period. All told, 883 eyes underwent MCS and 955 received FLACS. Collected data included demographics, ocular history, preoperative measurements/biometry, and postoperative results. A generalized linear mixed model was used to analyze data, and adjustments were made for differences in baseline characteristics and for within-patient correlations. Two-tailed p values of <.05 were deemed significant.

The main outcome measure was the percentage of eyes for which the absolute error (AE) was ≤0.5 D. Secondary outcomes were the percentages of eyes with AE ≤0.25 D and AE ≤1.0 D, and the proportions of distance-targeted eyes for which uncorrected distance visual acuity (UDVA) was 20/20 or better, 20/25 or better, and 20/30 or better.

Three weeks after surgery, approximately 83% of FLACS eyes and 79% of MCS eyes had AE ≤0.5 D, representing an adjusted odds ratio (OR) of 1.28 for FLACS relative to MCS (within this target range). Approximately 97% of eyes in both groups had AE ≤1.0 D

at this time point (OR, 0.96); 49% of FLACS eyes and 46% of MCS eyes had AE ≤0.25 D (OR, 1.13).

Factors that predicted favorable refractive outcomes were axial length of 22 to 24.8 mm, use of a toric intraocular lens, lower cylinder preoperatively, and higher average keratometry preoperatively. There were no significant differences in the percentages of distance-targeted eyes with postoperative UDVA of 20/20 or better, 20/25 or better, or 20/30 or better.



FALSE POSITIVES. *Typical false-positive cases detected by the deep learning algorithm developed by Li et al. included physiologic large cupping (top left) and macular hole (bottom center).*

Detecting Glaucomatous Optic Neuropathy via Deep Learning

August 2018

Li et al. devised an automated algorithm for classifying glaucomatous optic neuropathy (GON), based on color fundus photographs, and tested its disease-detection ability. They found the system to be highly sensitive and specific for detecting referable GON.

For this study, the authors used 48,116 fundus photographs to create and evaluate a new deep learning algorithm. Twenty-one trained ophthalmologists graded the photographs as unlikely, suspect, or certain GON. First, each image was assigned randomly to a single ophthalmologist and subsequently to additional graders until 3 consistent grades were obtained. The consensus grade was considered the conclusive grade for the image.

Referable GON was defined as suspect or certain GON having a vertical cup-to-disc ratio of ≥0.7 and other typical traits of GON. A separate validation dataset of 8,000 fully gradable fundus photographs was used to test the algorithm's performance. Main outcome measures were area under the receiver operator characteristic curve (AUC), sensitivity, and specificity.

In the validation dataset, the deep learning system achieved AUC of 0.986, sensitivity of 95.6%, and specificity of 92.0%. False-negative grading (n = 87) of GON was most likely to occur with coexisting eye conditions (n = 44, 50.6%), particularly pathologic or high myopia (n = 37, 42.6%). The most common reason for false-positive grading (n = 480) was the presence of other eye conditions (n = 458, 95.4%). False-positive misclassification occurred in 22 eyes (4.6%) with a normal-appearing fundus.

Nearly all of the false-positives in this study resulted from abnormalities not related to GON—and more than half of the false-positive eyes had large cupping that required further investigation. The algorithm's accuracy could be improved by augmenting the real-world patient data that accompany images so that the classification system mirrors the ground truth as closely as possible. Further research is needed to explore the utility of the algorithm for different populations and ophthalmic conditions. *(Also see related commentary by Donald C. Hood, PhD, in the same issue.)*

—Summaries by Lynda Seminara

Ophthalmology Glaucoma

Selected by Henry D. Jampel, MD

Artificial Intelligence and Glaucoma Detection

July/August 2018

Using monoscopic fundus photos, **Liu et al.** developed a deep learning–based algorithm to detect glaucomatous optic discs. They found that their artificial intelligence (AI) algorithm was highly accurate in identifying glaucomatous discs. In addition, they concluded that, as it is relatively easy to obtain monoscopic images, the algorithm has potential for use in screening large populations and in telemedicine.

For this database study, the researchers obtained fundus photos (n = 3,768) from several previous clinical studies and images from publically available online databases (n = 626), including the High-Resolution Fundus (HRF) database. They then merged the databases, with the exception of the HRF database, and divided the images into a training set that comprised 80% of all cases and a testing set that comprised 20% of all cases. The HRF images were used as an additional testing set. Both healthy and glaucomatous eyes were represented in all datasets.

The researchers tested their AI model and found that its accuracy was 92.7% and that it achieved 89.3% sensitivity and 97.1% specificity. When the HRF dataset was used for additional testing, the AI model again was highly accurate and achieved 86.7% in both sensitivity and specificity.

In order to compare the AI model's accuracy with the diagnostic skill of experienced clinicians, the researchers randomly selected a series of monoscopic images and submitted them to a panel of 18 ophthalmologists, which included 11 glaucoma specialists from several countries. They also submitted the HRF images to 3 of the 18 ophthalmologists for evaluation. The clinicians' overall accuracy rate was 65%; those who evaluated the HRF images achieved a higher level of accuracy (77%).

In previous studies, clinician accu-

racy has been found to be higher when stereoscopic fundus images are used, and the authors noted that stereoscopic images tend to provide better inter- and intraobserver reproducibility. The monoscopic images used in this study varied in terms of quality and resolution, and the testing set included a considerable number of images of anomalous optic discs and photos representing different disease stages.

—Summary by Jean Shaw

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Medicare Part B Spending and Anti-VEGF Drugs

August 2018

Patel set out to tally the annual Medicare Part B costs associated with anti–vascular endothelial growth factor (VEGF) medications used by ophthalmologists. He found that aflibercept and ranibizumab account for 12% of the Medicare Part B budget. In addition, he estimated that switching to bevacizumab might save more than $2 billion each year.

For this observational cohort study, the author analyzed data from 2011-2015 for intravitreal injections of aflibercept and ranibizumab. Comparable data on ophthalmology-specific injections of bevacizumab were not available, and this analysis excluded beneficiaries in the Medicare Advantage program, non-Medicare beneficiaries, and privately insured patients.

Annual Medicare Part B spending for ranibizumab was $1.43 billion for 671,869 injections in 2011; this dropped to $1.15 billion for 573,796 injections in 2015. For aflibercept, annual Medicare spending was $1.08 billion for 518,836 injections in 2013 (the first year that data were available for the drug); the cost grew to $1.81 billion for 866,749 injections in 2015. For each drug, beneficiaries received an average of 4.8 injections per year.

Although the author was unable to extract ophthalmology-specific data on bevacizumab spending, he noted that the numbers in his analysis could be used to estimate savings associated with switching to the less expensive medication. For instance, for 2015 alone, he determined that switching from aflibercept and ranibizumab to bevacizumab would have totaled $2.87 billion in Medicare savings.

Despite this cost differential, the author noted that the choice of anti-VEGF agent is a complex one—and that switching to bevacizumab raises a number of issues, including concerns about the drug's efficacy for certain patients and the need to rely on compounding pharmacies.

—Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Risk of Glaucoma Surgery After Corneal Transplantation

August 2018

The reported incidence of glaucoma after corneal transplantation varies greatly, as does the definition of post-transplant glaucoma. In a retrospective study, **Zheng et al.** used the endpoint of glaucoma surgery to represent severe cases and tallied rates for this surgery in the year following corneal transplant procedures. Although some research suggests that greater angle alteration during a corneal transplant confers higher risk for glaucoma surgery, the authors found no significant differences in risk among transplant groups. As expected, the patients with preexisting glaucoma were more likely to require surgical intervention for it.

For their study, the authors looked at a random sample of Medicare beneficiaries, identified by Current Procedural Terminology codes for penetrating keratoplasty (PK), endothelial keratoplasty (EK), anterior lamellar keratoplasty (ALK), and keratoprosthesis (KPro). They performed a separate analysis on the group of patients who had preexisting glaucoma. The primary endpoint was glaucoma surgery within the year following a corneal transplant.

This 4-year study period (2010-2013) included 3,098 patients. EK was performed in 1,919, PK in 1,012, ALK in 46, and KPro in 32; while 89 patients received both PK and EK. Rates of glaucoma surgery in the first year ranged from 6.1% to 9.4%, with no significant differences between transplant groups. Surgical intervention for glaucoma was needed in 10% of patients with preexisting glaucoma, as opposed to 5.3% of those without it. The rate was highest for PK recipients with preexisting glaucoma (12.4%), a finding that surgeons should consider when selecting a cornea transplant procedure for patients with glaucoma.

The authors emphasized the importance of close monitoring for glaucoma after corneal transplants, even if angle anatomy has been preserved. Longer-term, studies are needed to determine whether the rates will change over time or will differ substantially for certain types of corneal transplants.

Chloral Hydrate Sedation in Children Is Safe and Effective

August 2018

Cooperation of young children is a concern when diagnostic or therapeutic procedures are required. **Karaoui et al.** assessed the safety and efficacy of chloral hydrate (CH) in facilitating ophthalmic procedures in pediatric outpatients. Overall, the sedative-hypnotic was effective and safe when administered by a dedicated sedation service according to strict protocols.

This prospective interventional study was conducted at an eye care hospital in Saudi Arabia and included 324 children aged 1 month to 5 years (mean, 2.2 years); mean weight was 10.9 kg. Before undergoing ocular imaging or evaluation, the patients received CH administered by a dedicated sedation service. Documented data included the dosage, level of sedation, vital signs, and adverse events. The primary outcome was the percentage of patients with a sedation level ≥4 within 45 minutes of receiving CH. Secondary outcomes were adverse events and the time until discharge.

For 306 patients (94.4%), adequate sedation was achieved with a mean initial CH dose of 77.4 mg/kg (standard deviation [SD], 14.7 mg/kg). Nine others (1.9%) received a second dose (50% of the initial dose); of these patients, 6 ob-

tained adequate sedation. Patients who needed the second dose tended to be older and heavier. Overall, 312 patients (96.3%) had adequate sedation from either 1 or 2 doses. From the time just before CH administration to 25 minutes after sedation, mean reductions in oxygen (O^2) saturation, heart rate, and respiratory rate were 0.81% (SD, 1.2%), 11.7 (SD, 14.3) beats/minute, and 1.2 (SD, 2.4) breaths/minute, respectively.

The odds of sedation continuing until 45 minutes after CH administration were 2.53 times higher for American Society of Anesthesiologists (ASA) class II or III patients than for class I patients, 1.03 times higher per milligram increase in the initial sedation dose, and 2.70 times higher per unit increase in the number of planned procedures. Adverse events were minor and occurred in only 3 patients (O^2 desaturation occurred in 2, and 1 patient experienced paradoxical reaction). The median time from sedation administration to discharge was 90 minutes.

All planned procedures were completed in 300 children (92.9%). Of the remaining 24, 6 did not achieve adequate sedation to begin the procedure, and 15 did not maintain adequate sedation to allow completion of the procedure. (Data are missing on procedure completion for 3 children.) After sedation, all patients could move their extremities, breathe deeply, and cough freely. *—Summaries by Lynda Seminara*

JAMA Ophthalmology

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

Glaucoma Risk Stratification and 24-Hour IOP Monitoring

July 2018

Although 24-hour wireless monitoring of intraocular pressure (IOP) is practical and effective, it is currently unknown whether the information it yields is useful for glaucoma risk stratification. **De Moraes et al.** compared findings from recording sessions with data from visual field (VF) exams and noted that the recording patterns provided a signature that was associated with previous VF progression.

For this study, 445 patients (445 eyes) with open-angle glaucoma underwent a 24-hour recording session with a contact lens sensor (CLS) system. The researchers used the Triggerfish (Sensimed AG) device, which captures 300 data points over a 30-second period every 5 minutes. Participants were required to have undergone at least 3 reliable VF tests before this study began. The primary outcome measure was the association between CLS-generated variables and the rates of VF change.

At the time of CLS recording, mean deviation (MD) was −9.0 dB. The mean rate of MD change was −0.46 dB/year in 5.2 years of follow-up. After adjustment for baseline MD severity, age, and treatment, the following CLS variables were associated with rapid VF progression: mean peak ratio while awake ($\beta = -0.021$), number of long peaks during sleep ($\beta = 0.036$), night bursts ocular pulse frequency standard deviation ($\beta = 0.027$), and night bursts ocular pulse amplitude standard deviation ($\beta = 19.739$). For correlation with progression, CLS data were superior to the Goldmann measurements obtained during follow-up visits.

Findings from this multicenter study corroborate those of a smaller single-site study and demonstrate that a 24-hour CLS recording session may assist in risk stratification. According to the authors, information generated by the CLS system may help to predict the risk of future functional loss, even for patients whose historical VF information is insufficient.

Using OCT-A to Evaluate Diabetic Macular Ischemia

July 2018

Dupas et al. used optical coherence tomography angiography (OCT-A) to examine the relationship between visual acuity (VA) and macular vessel density in patients with diabetic retinopathy (DR) and poorly controlled type 1 diabetes. They found that decreased VA in patients with severe DR may coincide with greater loss of vessel density in the deep capillary plexus.

This study included a retrospective cohort of 22 patients (22 eyes) with type 1 diabetes who did not have macular edema (mean age, 30 years). All patients had bilateral DR that progressed rapidly and required panretinal photocoagulation (PRP), and all were required to have undergone imaging with OCT-A at least once in the 12 months following PRP. The control group consisted of 12 eyes from age-matched healthy participants with normal vision.

Eyes were classified into 2 groups based on their VA (normal and decreased). Primary outcome measures were VA and the mean vessel density in the deep capillary complex and the 3 retinal capillary plexuses (superficial, intermediate, and deep).

The mean hemoglobin A_{1c} level for the 22 patients with DR was 8.9%. Thirteen eyes with DR had normal VA, and 9 had decreased VA. In all 4 regions examined, mean vessel density was lower for DR eyes with normal VA than for control eyes (deep capillary complex, 44.3% vs. 50.6%; superficial vascular plexus, 44.1% vs. 49.1%; intermediate capillary plexus, 43.8% vs. 49.3%; and deep capillary plexus, 24.5% vs. 30.5%).

Among the DR group, mean vessel density was lower in the eyes with decreased VA. The loss was more pronounced in the deep capillary complex (34.6% vs. 44.3% for DR with normal VA), especially in the deep capillary plexus (15.2% vs. 24.5%), as opposed to the superficial vascular plexus (39.6% vs. 44.1%).

Despite the small sample size, the results suggest that in severe DR without macular edema, decreased VA has strong association with low vessel density in the deep capillary complex. *(Also see related commentary by Chui Ming Gemmy Cheung, FRCOphth, and Tien Yin Wong, MBBS, PhD, FRCS, in the same issue.)*

Medicare Patients More Likely to Undergo Cataract Surgery

July 2018

In a study of patients with cataract enrolled in Medicare or the Veterans Health Administration (VHA), **Wu et al.** discerned and compared the factors associated with receiving cataract sur-

gery. Although patient characteristics were found to be similar in these health systems, substantially more Medicare patients underwent the surgery.

The study involved more than 3 million patients with cataract, diagnosed during a 10-year period. Patients were identified from Medicare Part B files (5% sample) and the VHA National Patient Care Database. Collected data included demographics, Charlson Comorbidity Index (CCI) scores, and comorbidities. The association of these variables with attaining cataract surgery was assessed. The authors tallied the number of patients in each health system who received cataract surgery within 1 and 5 years of cataract diagnosis.

Roughly 1.2 million patients were Medicare members (mean age, 73.7 years) and 1.9 million were VHA members (mean age, 66.8 years). Among the Medicare group, more than a third were 65 to 69 years of age, 59% were female, and 88% were white. VHA members tended to be younger (47% were younger than 65) and male (97%) and were less likely to be white (28%). Within 1 year of cataract diagnosis, a larger percentage of Medicare patients had undergone the surgery (18.5% vs. 6.3% of VHA patients); the disparity was similar at the 5-year mark (35.9% vs. 12.6%).

Factors associated with attaining surgery within 5 years of diagnosis were older age per 5-year increase (Medicare odds ratio [OR], 1.24; VHA OR, 1.18), residence in the southern vs. eastern United States (Medicare OR, 1.38; VHA OR, 1.40), and coexisting chronic pulmonary disease (Medicare OR, 1.26; VHA OR, 1.40). In the Medicare group, female sex was associated with greater likelihood of surgery within 5 years (OR, 1.14). Higher CCI scores (≥3 vs. 0-2) correlated with better odds of surgery within 5 years among VHA members but not Medicare members (Medicare OR, 0.94; VHA OR, 1.24). Black (vs. white) race was linked to lower likelihood of cataract surgery within 5 years of diagnosis (Medicare OR, 0.79; VHA OR, 0.75). *(Also see related commentary by Kristina B. Lindsley, MS, in the same issue.)*

—Summaries by Lynda Seminara

Other Journals

Selected by Deepak P. Edward, MD

Small-Aperture Intracorneal Inlay: 3-Year Results

Journal of Cataract and Refractive Surgery
2018;44(5):541-556

Good results have been achieved with the small-aperture corneal inlay in presbyopic adults, but sample sizes and follow-up time have been limited. **Vukich et al.** reported 36-month findings of the prospective U.S. investigational device exemption (IDE) clinical trial. The data confirmed the safety and effectiveness of the inlay procedure.

The trial involved 507 patients (45-60 years of age) with emmetropic presbyopia. In all patients, distance visual acuity (VA) had been corrected to 20/20 in both eyes. The Kamra small-aperture inlay (AcuFocus) was placed in the nondominant eye, which had uncorrected near visual acuity (UNVA) of 20/40 to 20/100 and cycloplegic refractive spherical equivalent of +0.50 D to –0.75 D, with ≤0.75 D of refractive cylinder, and required near correction of +1.00 D to +2.50 D (reading addition). Other criteria for recipient eyes were minimum central corneal thickness ≥500 µm, corneal power ≥41.00 D, all meridians ≤47.00 D, and endothelial cell count >2,000/mm^2.

Thirty-six months after implantation, eyes in the effectiveness cohort (n = 417) exhibited 3.5 D of defocus range above 20/40. Monocular UNVA was 20/40 or better in 363 patients (87.1%), and binocular UNVA was 20/40 or better in 391 patients (93.8%). Patients who received the inlay via a femtosecond laser pocket procedure with a spot/line setting of 6 µm × 6 µm or tighter had the most improvement in near vision: 131 (90.3%) and 137 (94.5%) of these 145 patients had 20/40 or better monocular and binocular UNVA, respectively. Uncorrected distance VA of 20/25 or better was maintained in nearly all of these eyes.

Following the surgery, less than 1.5% of eyes lost 2 or more lines of corrected distance VA for 3 months or longer. Forty-four inlays (8.7%) were removed during the 3-year period, and 6 were repositioned. Deeper placement correlated with lower removal rates. Less than 1% of patients reported severe glare or halos. Overall, corneal health was maintained through 36 months postoperatively.

Timolol Eyedrops for Acute Migraine Attacks

JAMA Neurology
Published online May 14, 2018

The oral beta-blockers approved for migraine prophylaxis may not be effective for acute attacks because of slow absorption and modification by first-pass metabolism, which delays effective plasma levels for hours or even days. With timolol eyedrops, maximum plasma concentration is achieved within 15 minutes of administration. In a pilot study, **Cossack et al.** tested the effectiveness of the eyedrops as an abortive migraine treatment and found it helpful for some patients.

This placebo-controlled crossover study was conducted among 10 adults with recurrent migraine, with or without aura, who were recruited from the authors' neurology and ophthalmology clinics. Patients were assigned randomly to receive timolol maleate 0.5% or artificial tears (placebo) and were instructed to insert 1 drop in each eye at migraine onset and 30 minutes later. The participants were seen monthly for 4 months (5 visits per patient). After a 3-day washout at the 2-month mark, they were switched to the opposite treatment arm. Patients ranked the severity of each migraine attack on a scale of 0 (least) to 3 (greatest) and rated the effectiveness of each treatment on a scale of 1 (least) to 4 (greatest).

Among the 10 patients, 198 migraine attacks occurred during the study period. Four patients reported that timolol was highly effective in comparison to placebo; another patient noted the opposite. Thirty-seven (67%) of 55 migraines that occurred during timolol use had severity of none to mild at 2 hours, versus 58 (75%) of the 77 migraines during placebo use. No adverse events were observed during the study.

—Summaries by Lynda Seminara