Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD, and reviewed by Russell N. Van Gelder, MD, PhD

Vision Loss Is a Costly National Burden

April 2022

Rein et al. set out to estimate incremental direct and indirect costs related to vision loss (VL) in the United States in 2017. They found a nationwide VL burden estimate of $134.2 billion for that year.

Participants were those who indicated that they were blind or had a problem seeing even with glasses or contact lenses in three large surveys (American Community Survey, Medical Expenditure Panel Survey, and National Health Interview Survey). Direct costs included medical, nursing home, and supportive services. Indirect costs included absenteeism, lost household-related production, reduced labor-force participation, and informal care.

The estimated total of $134.2 billion included $98.7 billion in direct costs and $35.5 billion in indirect costs. The largest expenditures were attributed to nursing home services ($41.8 billion), other medical care services ($30.9 billion), and reduced labor-force participation ($16.2 billion). Combined, these three components accounted for 66% of the entire cost burden. Sensitivity analyses indicated that the total burden could be even higher, possibly exceeding $215 billion.

The incremental annual burden for a person with VL was $16,838. For young people (≤18 years), informal care was the costliest component. For those aged 19 to 64 years, reduced labor-force participation had the greatest impact. The bulk of VL costs for people 65 and older pertained to nursing home care. The youngest age group accounted for just 7% of the total burden, and women accounted for 58%.

Connecticut, Massachusetts, and New York had the highest average per-person cost, while Arizona, Nevada, and New Mexico had the lowest. The variation by state may help local decision-makers target the best resources to address their state's unique VL burden, said the authors.

AMD Progression Unaffected by Cataract Surgery

April 2022

Although cataract surgery improves vision in patients with age-related macular degeneration (AMD), previous large studies have differed as to whether cataract surgery accelerates AMD progression. In the Beaver Dam Eye Study, two decades of follow-up indicated a link between cataract surgery and late AMD, but this was not true of the Age-Related Eye Disease Study 2 cohort (AREDS2). **Bhandari et al.** further explored this question in a prospective AREDS2 cohort of patients who eventually had bilateral large drusen or unilateral late AMD. In their study, eyes that had cataract surgery before evidence of late AMD were compared with eyes that remained phakic (controls). During follow-up of two to 10 years, the authors found no correlation between cataract surgery and elevated risk of late AMD.

Eligible for cohort inclusion were AREDS2 participants aged 50 to 85 years who received oral supplementation or placebo in AREDS2 and had at least two years of follow-up after cataract surgery.

The main outcome was development of late AMD, determined primarily by fundus photography. Late AMD was defined as any of the following: two or more common signs of neovascularization, a history of treatment for neovascular AMD, or an area of geographic atrophy ≥433 μm in diameter. Cox regression analysis, matched-pair analysis, and logistic regression models were adjusted for age, sex, smoking status, education, treatment group, and AMD severity.

Of the 8,406 eyes in AREDS2, those with a history of cataract surgery (n = 2,370) or late AMD (n = 970) at baseline were not entered into the cohort study. After eyes with insufficient follow-up for AMD were excluded,

4,553 eyes remained for Cox proportional hazard analysis. Altogether, 1,767 eligible eyes underwent cataract surgery. Late AMD occurred in 1,981 eyes during the mean follow-up period of nine years. Cox regression analysis did not show a higher risk of late AMD after cataract surgery for right eyes (hazard ratio, .96; p = .60) or left eyes (hazard ratio, 1.05; p = .56). Among matched pairs, late AMD was detected in 408 eyes that had cataract surgery and in 429 phakic control eyes (odds ratio, .92; p = .34). In the logistic regression model, the risk of late AMD after cataract surgery was not significant (risk ratio, .92; p = .73).

Major differences between population-based studies and AREDS2 include available techniques and IOLs, said the authors, who cautioned that their findings may not be generalizable because AREDS2 participants were healthy volunteers. Even so, the data may be helpful when counseling patients with AMD who are considering cataract surgery.

Long-Term Effectiveness of Teprotumumab

April 2022

Douglas et al. evaluated the long-term effect of teprotumumab for thyroid eye disease (TED) in an open-label study (OPTIC-X) that lasted 48 weeks beyond the OPTIC 72-week study. They found that 90% of week-72 responders did not require additional treatment in the extension period. In addition, 89% of the OPTIC placebo group became teprotumumab responders in OPTIC-X.

For this study, participants with a 72-week response to teprotumumab in OPTIC were contacted at 96 and 120 weeks to determine if they required treatment for TED since their initial involvement in OPTIC. Treatment nonresponders, patients with a flare, and the placebo group of OPTIC were enrolled in OPTIC-X. Flare was defined as proptosis increase of at least 2 mm, elevation of 2 or more points in clinical activity score (CAS), or both. Main outcome measures were proptosis response and safety findings. Patient-reported quality of life (QoL) was a secondary outcome.

Overall, 33 (89.2%) of the 37 OPTIC placebo recipients became proptosis responders to teprotumumab in OPTIC-X (–3.5 ± 1.7 mm). The degree of response matched that in OPTIC. Among these responders, the CAS, proptosis, and diplopia responses were maintained through week 48 in 95.2%, 90.6%, and 85.7%, respectively. Of the five initial nonresponders who were re-treated in OPTIC-X, two had a successful proptosis response, one had a 1.5-mm proptosis reduction from OPTIC baseline, and two discontinued treatment early. Re-treatment was successful in five of eight OPTIC responders who experienced flare (mean proptosis reduction, 1.9 mm from OPTIC-X baseline and 3.3 mm from OPTIC baseline). No new safety signals were observed in the extension study, but pharmacovigilance continues. Mild hearing impairment was reported by four patients.

Results indicate that patients with delayed TED treatment respond similarly to those with early treatment and that initial nonresponders to teprotumumab may benefit from further treatment. The findings require validation in larger studies, said the authors.

—Summaries by Lynda Seminara

Ophthalmology Glaucoma

Selected by Henry D. Jampel, MD, MHS

Preserflo Safety and Effectiveness in POAG

March/April 2022

Beckers et al. assessed the safety and effectiveness of the Preserflo microshunt in patients with primary open-angle glaucoma (POAG). They found that patients' mean IOP and need for glaucoma medications dropped following surgery; these reductions were significant and sustained over the two years of the study. In addition, no long-term, sight-threatening adverse events (AEs) were reported.

For this prospective single-arm study, the researchers evaluated 81 patients (81 eyes) with a mean age of 64.4 years (range, 28-85). All had mild to severe POAG that was inadequately controlled on maximal tolerated medical therapy.

The Preserflo shunt was implanted with adjunctive use of topical mitomycin C (MMC) in two concentrations (0.2 and 0.4 mg/mL). The main outcome measure was IOP and overall success of the procedure at years 1 and 2. Secondary outcomes included need for glaucoma medications and incidence of adverse events at year 2.

Mean IOP decreased from 21.7 ± 3.4 mm Hg at baseline to 14.5 ± 4.6 mm Hg at year 1 and to 14.1 ± 3.2 mm Hg at year 2. Overall success rates at years 1 and 2 (defined as no reoperations or pressure failures) were 74.1%. The mean number of medications decreased from 2.1 ± 1.3 at baseline to 0.5 ± 0.9 at year 2, and 73.8% of patients were medication-free at this point. In a subgroup analysis based on MMC concentrations, those in the 0.4 mg/mL group experienced greater reduction in IOP and need for medication.

In the safety assessment, 55 of the 81 eyes were affected by AEs. All AEs resolved within 46 days, except for one that required surgical treatment. Eight patients underwent a bleb revision during the study, and five received needling or postsurgical injection of the bleb with 5-fluorouracil.

The researchers noted that at the time of the study, the Preserflo shunt had been newly approved in Europe; thus, participating surgeons had limited experience with the device. As a result, they said, further studies may be needed to confirm the results or to study the effects of different MMC concentrations.

—Summary by Megan Mulholland

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Laser Prophylaxis in Patients With Stickler Syndrome

April 2022

Stickler syndrome is a collagenopathy that causes pediatric retinal tears and detachments. Some evidence suggests that prophylactic treatment can reduce retinal detachments (RDs) in patients, but study findings are inconsistent.

Moreover, after reattachment, only 33% to 64% of patients experience improvement in visual acuity (VA). **Khanna et al.** set out to evaluate the impact of laser prophylaxis on RD and VA. They found that extended vitreous base laser (EVBL) appeared to reduce the rate of subsequent RD and was associated with better VA.

For this retrospective study, the researchers evaluated 115 patients (230 eyes) who were treated with EVBL (n = 129 eyes), nonprotocol laser (NPL; n = nine eyes), or no laser (n = 92 eyes). Patients' median age at time of treatment was 9.5 years (range, 6-13). For those who developed an RD after treatment, the median age at time of RD occurrence was 11 years (range, 7-18).

RDs occurred in four (3%) of the EVBL eyes, in all nine NPL eyes (100%), and in 65 (70.6%) of the eyes that did not undergo laser treatment. With regard to visual outcomes, patients who underwent EVBL had better final VA and lower rates of low vision than did those who had NPL or no laser. Overall, EVBL eyes averaged 8 lines better vision—and only one eye treated with EVBL had low vision, versus 33% of the eyes that received NPL or no laser.

The authors noted that their study has several limitations, including the lack of a confirmed genetic mutation for the majority of the patients. Nonetheless, given the number of patients in the study, the findings constitute "at least preliminary evidence" that prophylactic treatment with EVBL may prevent RD and is associated with better VA in patients with Stickler syndrome, they said.

—Summary by Megan Mulholland

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Strabismus Surgery Lowers Injury Risk in Children

April 2022

In a previous claims database study, **Pineles et al.** found that the prevalence of injury among children with strabismus was 30%. Subsequently, they aimed to determine if surgery for strabismus could reduce this risk. Using data from the same source, they found that strabismus surgery lowered the risk of physical injury.

For this study, the authors searched the OptumLabs Data Warehouse for records of patients under 19 years of age who had strabismus during the queried coverage period (2007-2018). Strabismus diagnosis was determined by ICD-9-CM codes, and surgery for strabismus was established by CPT codes. The comparative risk of injury was explored for the surgical and nonsurgical cohorts. The types of physical injuries included fractures, musculoskeletal damage, and head trauma.

Altogether, 344,794 patients with strabismus were identified in the database. Of these, 26,459 (7.7%) underwent surgery to address it. The most common diagnoses were esotropia and exotropia. Hypertropia was less common, and those patients were much more likely to have surgery (24.2%) than were those with esotropia (10.2%) or exotropia (9.6%).

After the first strabismus claim, 29.8% of the nonsurgical cohort experienced a documented injury, versus 21.9% of the surgical cohort postoperatively ($p < .001$) during the mean follow-up periods of 4.3 and 3.8 years, respectively. The adjusted hazard ratio (HR) for the risk of any injury after strabismus surgery was 0.85. The HR was significantly lower after each type of strabismus surgery (esotropia, 0.91; exotropia, 0.82; hypertropia, 0.89). The fact that patients with exotropia were least likely to be injured postoperatively may relate to the superior binocular outcomes achieved for these patients relative to those with esotropia or hypertropia.

"Surgery may be a factor in decreasing injury risk in strabismic patients, particularly in exotropia," the authors concluded. They acknowledged that the results of this study may not necessarily apply to noninsured patients. Regardless, given the large number of children with strabismus in the United States, the authors recommend further assessment of potential strategies to reduce injury in this patient population.

High Levels of Physical Activity Protect Against AMD

April 2022

Mauschitz et al. performed a meta-analysis of large studies to explore the relationship of physical activity and age-related macular degeneration (AMD). They found that high levels of activity exerted a protective effect on AMD development but did not appear to affect disease progression.

The meta-analysis included data on 14,000 patients from seven large longitudinal studies of AMD. Activity levels were determined from standardized surveys. AMD incidence and progression were assessed by Markov multistate models and random-effects meta-analysis. The effect of age was determined by meta-regression, and heterogeneity among the studies was assessed by several statistical tests. The main outcome measure was the hazard ratio (HR) for incident early AMD and for progression to late AMD.

Most patients were White, and their mean age at baseline ranged from 60.7 to 81.4 years among the seven studies. The overall prevalence of early AMD at baseline was 7.7% (range, 3.6%-16.9%). During the follow-up period, which averaged seven years, there were 1,461 events of early AMD and 189 of late AMD. Compared with high-level (vigorous) physical activity, no activity and low-to-moderate activity posed a higher risk for early AMD (HR, 1.19; $p = .04$) but not for progression to late AMD.

The favorable effect of high-level activity was greatest for younger patients. However, meta-regression analysis showed no link between age and the effect of physical activity on incident AMD. Self-reported physical activity was not captured uniformly for all patients, so it was not possible to determine a relationship between accrued activity and the risk of AMD.

In light of these results, the authors recommend incorporating physical activity into AMD prevention strategies and encouraging at-risk patients to achieve and maintain a high level of activity.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

Abusive Head Trauma in Young Children

March 2022

Shah et al. set out to assess the prevalence of abusive head trauma (AHT) in young children and to identify factors associated with mortality. They found that the incidence of AHT decreased by 6.7% each year during the 13-year period of their study, while mortality rates remained constant. In addition, they found that health care disparities may play a role in treatment of AHT.

For this retrospective cross-sectional study, the researchers used the Nationwide Emergency Department Sample database to identify all emergency department (ED) visits in the United States for patients younger than age 5 years with a primary diagnosis of AHT. The study period ran from Jan. 1, 2006, to Dec. 31, 2018. Main outcome measures included prevalence, demographic characteristics, clinical characteristics, mortality, and economic burden associated with AHT.

During the years covered in this study, an estimated 12,287 ED visits took place for AHT in young children. All told, 57.3% (n = 7,046) of the children were younger than 1 year of age, 59.2% (n = 7,268) were male, and 70% (n = 8.585) were covered by Medicaid.

The estimated number of AHT cases decreased by 672 overall during the study period, with a yearly decrease of 6.7%. With regard to mortality, 25 (.2%) of the children died in the ED, and 646 (5.3%) died during the course of their hospitalization. Children who were older than 1 year of age, from lower-income zip codes, and from Midwestern states had higher mortality rates. Clinical findings associated with higher mortality included orbital and skull fractures; retinal, intracranial, subarachnoid, and subdural hemorrhages; cerebral edema; and hypoxic ischemic brain injury. Of the ophthalmic findings, retinal hemorrhages and orbital fracture were associated with higher mortality.

The mean ED charge per patient throughout the study period was $2,758, increasing from a mean of $2,081 in 2006 to a mean of $4,706 in 2018. The total ED charge for all patients was $26.5 million.

Given these findings, the researchers suggested that public health efforts designed to prevent AHT should be targeted toward low-income areas and the Midwest.

Reconsidering Oral and Topical Carbonic Anhydrase Inhibitors

March 2022

Popovic et al. evaluated the safety of oral and topical carbonic anhydrase inhibitors (CAIs) in clinical care. They found a low risk of severe adverse reactions.

This population-based matched cohort study took place in Ontario, Canada. The researchers identified 128,942 patients older than 65 years of age (mean, 75 years) who were prescribed an oral or topical CAI between Jan. 1, 1995, and Jan.1, 2020. The primary endpoint was the occurrence of Stevens-Johnson syndrome, toxic epidermal necrolysis, or aplastic anemia. All told, 71,958 of the patients (55.8%) were women, and 25,057 (19.4%) had a diagnosis of diabetes. The patients were not required to be under the care of an ophthalmologist or to have a diagnosis of glaucoma.

For this analysis, the category of oral CAIs comprised acetazolamide or methazolamide, while that of topical CAIs comprised dorzolamide, brinzolamide, or a combination agent. Zonisamide and topiramate were excluded. Acetazolamide was the most commonly prescribed oral CAI, for a mean initial duration of 8.4 days. Dorzolamide—in a single-agent or combination formula—was the most common topical CAI and was prescribed for a mean initial duration of 23 days.

The researchers identified 321 serious adverse events. Of these, 187 occurred in patients on an oral CAI (absolute risk, 2.90/1,000 patients; number needed to harm, 1/345 patients). The remaining 134 serious adverse events occurred in patients on a topical CAI (absolute risk, 2.08/1,000 patients; number needed to harm, 1/481 patients). These findings were replicated across a diverse set of patient subgroups. The researchers also observed a directly proportional association in the risk of serious adverse events over time, contrary to the standard hypothesis that these events tend to occur soon after therapy is initiated.

In their discussion, the researchers reminded clinicians that appropriate informed consent discussions must take place if CAIs are under consideration. At the same time, they said, the results of this study support taking a second look at the general reluctance to prescribe oral CAIs, in particular, given the low risk of serious adverse events.

Pediatric Cataract Surgery: Five-Year Results

March 2022

Repka et al. assessed outcomes following pediatric lensectomy among children younger than 13 years of age. They found that five years after surgery, age-normal visual acuity (VA) was uncommon and that the risk for glaucoma development had increased.

For this prospective cohort study, the researchers used data from the Pediatric Eye Disease Investigator Group (PEDIG) clinical research registry. BCVA and refractive error were measured from four to six years after the initial lensectomy. Cox proportional hazards regression was used to assess the five-year incidence of glaucoma or glaucoma suspect and additional eye operations. Factors were evaluated for four subgroups: unilateral aphakia (n = 202), bilateral aphakia (n = 316), unilateral pseudophakia (n = 364), and bilateral pseudophakia (n = 386).

A total of 994 children (1,268 eyes) with a mean age of 3.6 years (range, 2 weeks to 12.9 years) were included in this analysis. Slightly more than half (504; 51%) were male. At five years, results were as follows:

VA. Data on VA outcomes were available for 701 of the 1,268 eyes. The median VA was 20/64 (range, 20/40 to 20/100) in 182 bilateral aphakic eyes; 20/32 (range, 20/25 to 20/50) in 209 bilateral pseudophakic eyes; 20/200

(range, 20/50 to 20/618) in 124 unilateral aphakic eyes; and 20/65 (range, 20/32 to 20/230) in 186 unilateral pseudophakic eyes.

Glaucoma or glaucoma suspect. The five-year cumulative incidence of glaucoma or glaucoma suspect ranged from 7% for those with bilateral pseudophakia to 46% for those with bilateral aphakia.

Additional eye surgery. The most common additional eye surgery was clearing the visual axis, with a five-year cumulative incidence ranging from 7% of those with bilateral pseudophakia to 34% of those with unilateral pseudophakia.

Refractive error. The median five-year change in spherical equivalent refractive error was –8.38 D among 89 bilateral aphakic eyes, –1.63 D among 130 bilateral pseudophakic eyes, –10.75 D among 43 unilateral aphakic eyes, and –1.94 D among 112 unilateral pseudophakic eyes.

These results support frequent monitoring after pediatric cataract surgery, the researchers said. *(Also see related commentary by Jeff Yunglam Hui, MB, ChB, MPH, in the same issue.)*

—Summaries by Jean Shaw

OTHER JOURNALS

Selected by Prem S. Subramanian, MD, PhD

Visual Decline Linked to Photoreceptor Loss After RRD Repair

Graefe's Archive for Clinical and Experimental Ophthalmology
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After retinal reattachment surgery, retinal function is impeded by synaptic connectivity changes in the outer plexiform layer, imperfect photoreceptor regeneration, retinal scarring, and other alterations. In a prospective study to better understand the relationship between photoreceptor function and vision, **Rasool et al.** found that photoreceptor degeneration correlated with poorer visual outcomes.

The study consisted of 21 patients who underwent reattachment surgery (13 macula-off, eight macula-on) for rhegmatogenous retinal detachment (RRD). Each patient was examined before surgery and six months postoperatively. Assessments included OCT measurements of the outer nuclear layer (ONL), outer retinal segment (ORS), retinal pigment epithelium-to-ellipsoid zone (RPE-EZ), and external limiting membrane to EZ (ELM-EZ). Findings were compared with those for BCVA and retinal sensitivity.

Six months after reattachment surgery, the ONL was thicker in macula-on cases (97.70 ± 3.62 µm) than in macula-off cases (73.10 ± 4.98 µm). Overall, each 1-µm decrease in ONL and ORS thickness coincided with 0.052-dB and 0.062-dB decreases, respectively, in retinal sensitivity. ORS, ELM-EZ, and RPE-EZ measurements were unrelated to post-op BCVA. The duration of retinal detachment before reattachment surgery did not affect BCVA, ONL thickness, or retinal sensitivity six months after the surgery.

The association of ONL thickness with retinal sensitivity and visual acuity supports the notion that photoreceptor apoptosis after macula-off RRD contributes to reduced visual function. The link between ORS thickness and retinal sensitivity emphasizes the importance of recovering inner and outer photoreceptor function after reattachment surgery, said the authors. They added that "correlations between ONL and ORS thinning with decreased retinal sensitivity may be explained by RRD-induced photoreceptor death."

SARS-CoV-2 Is Uncommon in Conjunctivitis Cases

Clinical Ophthalmology
2022;16:127-133

Karakus et al. looked at the prevalence of conjunctival SARS-CoV-2 among patients with suspected viral conjunctivitis but no respiratory symptoms of COVID-19. They also questioned whether conjunctivitis could be an early sign of COVID infection. Among 36 adults with conjunctivitis treated at their tertiary care center during the pandemic, SARS-CoV-2 RNA was not detected in any specimen collected during the initial visit, and no patient received a COVID-19 diagnosis within the ensuing two weeks.

Participants of this prospective study were ≥18 years of age and presented to the Wilmer Eye Institute with acute conjunctivitis between May 2020 and May 2021. For each patient, the authors recorded demographics and ocular and systemic symptoms. All patients underwent a slit-lamp exam and collection of tissue specimens. Although the protocol was to obtain five specimens per patient (nasopharyngeal, conjunctival from each eye, and nasal from each nostril), three patients did not consent to nasal or nasopharyngeal sampling. The specimens were placed in separate tubes and tested for SARS-CoV-2 by reverse transcription-polymerase chain reaction. Subsequently, each patient was contacted by phone for follow-up regarding their symptoms and any results of adenovirus and COVID testing, if performed elsewhere.

Among the 36 patients enrolled, the most common ocular symptom at presentation was redness, noted in 35 (97%) of the patients. Fourteen patients (39%) had symptoms in both eyes. Thirty-two patients (89%) presented with acute follicular conjunctivitis. SARS-CoV-2 RNA was not found in any sample collected at the study visit (95% confidence interval, 0-0.08), and no participant contracted COVID-19 in the two-week follow-up period. The authors learned that 25 patients were tested for conjunctival adenovirus and that the result was positive for nine. Relatively late testing could play a role in the low positivity rate, said the authors. Cases that were further along may not have been detectable.

Ruling out common viral causes and testing ocular samples for SARS-CoV-2 had been recommended to detect subclinical COVID-19. However, this work suggests that the precautionary measures for suspected viral conjunctivitis need not differ from prepandemic norms. The authors believe that testing for SARS-CoV-2 may not be crucial unless the conjunctivitis is accompanied by COVID symptoms. They acknowledged that larger studies are needed to better estimate the prevalence of conjunctivitis related to SARS-CoV-2.

—Summaries by Lynda Seminara