

Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Russell N. Van Gelder, MD, PhD

Routine Coffee Drinking Raises POAG Risk

September 2022

Li et al. looked at the relationship between coffee consumption and the risk of primary open-angle glaucoma (POAG). Using several sets of instrumental genetic variables to assess possible causal links, they found that habitual coffee drinking significantly raises the risk of POAG.

In their two-sample Mendelian randomized (MR) study, single-nucleotide polymorphisms (SNPs) related to coffee consumption were selected from a previous genome-wide association study (GWAS) of 121,824 people of mainly European descent. Phenotype 1 represented six SNPs and the number of cups of coffee consumed per day. Phenotype 2 involved three SNPs reflecting the level of daily coffee intake. In addition, the biobank of the Medical Research Council (MRC) Integrative Epidemiology Unit at the University of Bristol (MRC-IEU UK), which represents nearly 429,000 European individuals, was searched for relevant content. Summary-level POAG data were obtained from publicly available meta-analyses involving 16,677 patients with POAG

and 199,580 controls. The inverse variance-weighted (IVW) method was used for the primary MR analysis, and POAG diagnosis was the main outcome measure. Sensitivity analyses included weighted median, mode-based estimate (MBE), the MR Pleiotropy Residual Sum and Outlier (PRESSO) test, and MR-Egger regression.

According to the IVW analyses, POAG risk was elevated with pheno-

type 1 (odds ratio [OR], 1.241) and phenotype 2 (OR, 1.155). When the same methodology was applied to GWAS data from the MRC-IEU UK biobank, the association was even stronger (OR, 1.727). For both phenotypes, results of sensitivity analyses for

weighted median, weighted MBE, and MR-Egger were similar. Causality was confirmed by the Steiger directionality test. The intercepts derived from MR-Egger regression analysis and the global MR-PRESSO test were not statistically significant. An investigation of SNP-associated secondary phenotypes using online databases showed no evidence of traditional POAG risk factors, suggesting the lack of alternate causal pathways.

This research indicates that POAG risk is elevated for people with genetic SNPs for high coffee consumption. The

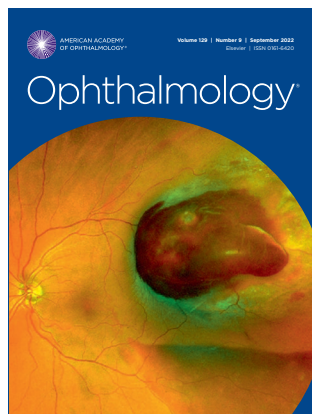
authors hope their findings will lead to better strategies to prevent and manage POAG in at-risk individuals. They recommend MR studies of individual-level data to explore dose-response relationships between coffee intake and POAG risk and to confirm their findings in larger GWAS samples as they become available.

Medicare Reimbursements Are Higher for Male Ophthalmologists

September 2022

Medicare reimbursement by sex has not been studied widely for ophthalmologists. The few studies that exist have not fully addressed the differences in reimbursement or billing patterns by service category or procedure type, and none has accounted for procedural services or socioeconomic factors by practice location. To fill these gaps, Halawa et al. analyzed billing patterns for a longer period than in previous studies, while accounting for potential confounding variables. They found that female ophthalmologists billed for fewer services and received less reimbursement than their male counterparts, even when controlling for confounders.

In this review, the authors looked at Medicare reimbursements to ophthalmologists from 2013 to 2019. They used “physician and other supplier” data from CMS to determine total reimbursements and the number of services submitted by ophthalmologists. The payouts were standardized to account for geographic differences in Medicare reimbursement by service.



Data from the American Community Survey (ACS) were used to determine socioeconomic characteristics by the zip code of each physician's practice. These included employment status and levels of poverty, income, and education. Multivariate linear regression was applied to assess differences in annual reimbursement by sex, accounting for calendar year, years of experience, number of services, ACS zip code data, and proportions of procedural services. The main outcome measures were total annual reimbursements and specific reimbursements by billing code.

During the study period, 20,281 ophthalmologists were reimbursed by Medicare, 76% of whom were men. The most common billing codes assigned were for outpatient visits and eye exams (13.8 million charges/year), retinal diagnostic imaging (5.6 million charges/year), intravitreal injections (2.9 million charges/year), and cataract removal plus IOL insertion (2.4 million charges/year). In the primary analysis, the median annual Medicare reimbursement was approximately \$94,734 for females, versus \$194,177 for males ($p < .001$). The median annual number of billed services also was lower for females (1,228 vs. 2,259 for males; $p < .001$). After adjustment for covariates, annual Medicare reimbursement was \$20,209 higher for male ophthalmologists, and men billed for 1,015 more services per year (both $p < .001$).

Medicare does not discriminate by sex when reimbursing for services, so other sources of the disparities should be explored, said the authors. They hope that further research in larger datasets will lead to policies that reduce the reimbursement gender gap.

Three-Piece IOLs Reduce VAO Risk After Pediatric Cataract Surgery

September 2022

Küchlin et al. looked at the time course of secondary visual axis opacification (VAO) leading to surgery after primary IOL implantation in children, as well as the type of lenses associated with the recurrence. In their study of 135 eyes, VAO occurred in 13, and the median time

to recurrence was 10 months following the primary surgery. Ten of the 13 eyes had received a one-piece in-bag IOL.

This was a single-center study of children (1-14 years old) who had undergone cataract surgery with implantation of an IOL. The same surgeon performed all procedures. The surgical technique was either bag-in-lens placement or in-bag placement with primary posterior capsulotomy and anterior vitrectomy. Eyes with major visual ocular comorbidities were excluded. Main outcome measures were surgical complications and the proportion of eyes without VAO recurrence that required clearing of the visual axis after the initial procedure. VAO-free survival by type of lens/technique was assessed using Kaplan-Meier methodology and a Cox proportional hazards model with predefined adjustments for age at surgery, year of surgery, and the German Index of Socioeconomic Deprivation (score by postal code). To lengthen the follow-up time, patients were invited to attend a clinical visit.

Ninety-five children (135 eyes) met the inclusion criteria. Of these eyes, 64 received an acrylic three-piece IOL, 51 had an acrylic single-piece IOL, and 20 had an acrylic single-piece bag-in-lens IOL. The respective mean ages at surgery were 53 months, 52 months, and 60 months. The median follow-up period was 19 months. There were 13 cases of VAO, which occurred at a median of 10 months post-op (interquartile range, 10-12 months). Ten of these eyes had a one-piece in-bag IOL, two had a bag-in-lens IOL, and one had a three-piece in-bag IOL. Compared with three-piece in-bag IOLs, the adjusted hazard ratios were 32.8 for one-piece acrylic IOLs ($p = .003$) and 19.6 for bag-in-lens IOLs ($p = .036$). Two eyes with bag-in-lens surgery (10%) had an iris capture. There was one case of endophthalmitis and no cases of post-operative retinal detachment or new glaucoma.

In this study, VAO that required a clearance procedure usually occurred within 15 months of the original surgery. Opacification rates were lowest with three-piece acrylic bag-in-lens IOLs. The lack of retinal detachment or

new glaucoma in this study may be due partly to follow-up loss or the small, restricted study sample, said the authors. Regardless, their data corroborate many findings of earlier studies, including the age-dependent nature of VAO, the timeline to VAO recurrence, and the influence of lens type. The authors emphasized paying special attention to lens selection in young patients with cataract, especially given their vulnerability to VAO and amblyopia.

—Summaries by Lynda Seminara

Ophthalmology Retina

Selected by Andrew P. Schachar, MD

Mediterranean Diet Slows GA

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Can diet have an effect on the speed at which the area of geographic atrophy (GA) enlarges? Agrón et al. set out to determine whether close adherence to a Mediterranean diet could help answer this question. They found that the diet was associated with slower GA enlargement, particularly in those who had a higher intake of whole fruits and monounsaturated fats and a lower intake of red meat and alcohol.

For this post hoc analysis of the Age-Related Eye Disease Study 2 (AREDS2), the researchers evaluated 1,155 eyes (850 participants) with GA at two or more visits. The area of GA was measured from color fundus photographs taken at each annual visit. An alternative Mediterranean diet index (aMedi) was calculated for each participant, using a food frequency questionnaire. The intake of nine dietary components was assessed (whole fruits, vegetables, whole grains, nuts, legumes, fish, red meat, alcohol, and the ratio of monounsaturated fatty acid to saturated fatty acid [MUFA:SFA]). For each component, sex-specific intake quartiles (1-4) were calculated, with quartile 4 representing the lowest intake of red meat, moderate intake of alcohol, and the highest intake of MUFAs and the other components. Mixed-model regression was performed for the square root of the GA area. The main outcome measure was the change in square root of the GA area over time.

Over a mean follow-up of 3.1 years, the mean rate in GA enlargement was .282 mm/year (95% confidence interval [CI], .270-.293). For those in groups 1, 2, and 3, the mean rates of enlargement were .298 (.280-.317), .290 (.268-.311), and .256 (.236-.276) mm/year, respectively, suggesting a dose-response to the diet. With regard to individual dietary components, GA enlargement occurred more slowly in those who ate more whole fruits and more quickly in those who ate greater amounts of red meat. No statistically significant interaction was observed for fish intake, in contrast to earlier AREDS2 dietary evaluations.

In their discussion, the authors note that the difference in enlargement rates “could be clinically important over the long time periods taken for GA to enlarge.” Given the paucity of current treatments for GA, they add that dietary modification “might represent an important strategy to delay disease progression in patients affected by GA.”

—Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Lyme Disease and Scleritis

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Lyme disease is a multisystem disorder, and ocular involvement can occur at any stage, but reports of scleritis caused by Lyme disease are sparse. Berkenstock et al. looked at the incidence of scleritis in the Baltimore metropolitan area of the United States, a region where Lyme disease is endemic. During the nine-year study timeline, only nine cases of scleritis were ascribed to Lyme disease, representing a prevalence of .052%. The authors concluded that Lyme disease is not a common cause of scleritis, even in areas where the disease is relatively common.

For this study, the authors gathered data from electronic health records of patients who visited the Wilmer Eye Institute from 2012 through 2020 and had a diagnosis of Lyme disease according to 2020 joint criteria of the Infectious Diseases Society of America, American Academy of Neurology, and

American College of Rheumatology. After identifying all new-onset cases of scleritis from the database, they calculated the proportion of new-onset scleritis concurrent with Lyme disease using data from the Baltimore area that had been reported to the CDC. They queried other major academic eye centers in the area to capture any other cases of scleritis related to Lyme disease, then calculated the incidence of this condition using U.S. Census data. In addition, they looked at the clinical features of Lyme-related scleritis.

Among 980 cases of scleritis reported during the study period, only six (.6%) were caused by Lyme disease. One additional case was identified in 2021. The query of other eye facilities did not yield any other cases. The estimated annual incidence of scleritis caused by Lyme disease was .2 per 1,000,000 population in the Baltimore area, and the incidence of Lyme disease in the area was three per 10,000 population per year. All cases of Lyme-related scleritis were anterior, unilateral, and resolved with antibiotic use (without relapse) in a median of 39.5 days (range, 29-57 days). No case was necrotic. Scleritis occurred in only .052% of patients with Lyme disease. Other features of Lyme disease were documented for four patients: a history of erythema migrans in two, cardiovascular disease in one, and arthritis in another. Other than residing in an endemic area, no demographic factors were consistent among the affected individuals.

Even though scleritis is a rare manifestation of Lyme disease, physicians should be aware of the possible connection, said the authors, particularly as the prevalence of Lyme disease grows. Of note, scleritis may be the sole clinical sign of the disease in some patients.

Management of Low-Risk Small Choroidal Melanoma

September 2022

The approach to managing small choroidal melanoma (SCM) remains a highly debated topic. Diagnostic uncertainty is common, and many tumors labeled SCMs have turned out to be

choroidal nevi that wouldn't need vision-threatening intervention. Despite the trend toward immediate treatment of tumors deemed to be SCMs, the risk of metastasis in patients with these tumors is reportedly very low ($\leq 3\%$). Using a diagnostic predictive model, Singh et al. applied probabilistic selection to discern SCMs that could be observed rather than treated immediately. They also quantified the potential loss of vision and the potential avoidance of metastasis for patients treated immediately who may have benefited from a surveillance period to monitor growth before proceeding to treatment.

The authors identified 167 patients who appeared to have an SCM (5-16 mm in largest basal diameter and 1-2.5 mm in height). Forty-two were treated after documentation of tumor growth during surveillance, and 125 were treated immediately. A model was applied to each patient in the immediate-treatment group to obtain the predicted risk of melanoma (high vs. low) and to compare gain (freedom from metastasis) and loss (vision loss) between the low-risk immediate treatment group and the group treated after surveillance. Kaplan-Meier methodology was used to estimate the rates of metastasis-free and overall survival.

Using the optimal cutoff point (.60; 95% confidence interval, .37-.61) of predicted risk for SCM (sensitivity, .74; specificity, .95), 75% of cases were classified as high risk (score $\geq .6$) and 25% as low risk (score $< .6$). During the median follow-up period of 34.6 months, metastasis occurred in five patients in the immediate-treatment group (four high risk, one low risk) and one in the initial-surveillance group. By 36 months, the proportion of patients whose VA declined by less than 15 letters did not differ significantly between low-risk patients treated immediately or after surveillance (81% vs. 83%, respectively). Among patients with documented tumor growth before treatment, none died, and one experienced metastasis. Among the low-risk group treated immediately (no surveillance), two died, and one had metastasis. The Kaplan-Meier estimate of three-year metastasis-free survival was 100%

for those who initially were observed and 96% for low-risk patients treated immediately.

“Low-risk choroidal melanoma identified by the prediction model can be labeled as an indeterminate melanocytic tumor,” said the authors. For such cases, they recommend an observation period to monitor tumor growth before initiating treatment, which does not appear to increase the risk of metastasis-related death, they said.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

Preventing Ocular Changes During Spaceflight

August 2022

Can the changes to the optic nerve head and retina that occur during spaceflight be mitigated by brief in-flight application of 25-mm lower-body negative pressure? Pardon et al. addressed this question during a prospective cohort study. They found that long-duration spaceflight was associated with peripapillary tissue thickening, decreased cup volume, and mild central macular thinning—and that exposure to lower-body negative pressure did not alter optic nerve head or retinal morphology.

For this study, the researchers evaluated OCT scans of the optic nerve head and macula of 14 U.S. and international crew members who completed six- to 12-month missions on the International Space Station. The OCTs were taken before, during, and after the missions. In-flight scans were obtained under normal weightless conditions as well as during exposure to lower-body negative pressure in 10- to 20-minute sessions. Pre- and postflight data were collected while crew members were in three postures (seated, supine, and head-down tilt). Main outcome measures were changes in minimum rim width, optic cup volume, Bruch membrane opening height, peripapillary total retinal thickness, and macular thickness.

Mean flight duration was 214 days. Ocular changes on flight day 150, as compared with preflight seated posture,

included an increase in minimum rim width (33.8 μ m; 95% confidence interval [CI], 27.9–39.7 μ m; $p < .001$), decrease in cup volume (.038 mm³; 95% CI, .03–.046 mm³; $p < .001$), posterior displacement of Bruch membrane opening (−9 μ m; 95% CI, −15.7 to −2.2 μ m; $p = .009$), and decrease in macular thickness (fovea to 500 μ m, 5.1 μ m; 95% CI, 3.5–6.8 μ m; $p < .001$). The exposure to lower-body negative pressure did not affect these parameters.

These findings suggest that a longer duration of exposure to lower-body negative pressure may be needed to counteract the fluid shift and resulting ocular changes that occur during missions to space, the authors said. They noted that other mechanisms may be involved in spaceflight-induced changes.

Using AI to Screen for ROP in Low- and Middle-Income Countries

August 2022

Blindness from retinopathy of prematurity (ROP) can be prevented with timely screening; however, such screening presents a challenge in many parts of the world. Coyner et al. aimed to determine whether an artificial intelligence (AI)–based risk model, incorporated into existing telemedicine infrastructure, could reduce the screening burden and identify infants who need treatment in low- and middle-income countries (LMICs). They found that their risk model could identify all at-risk infants up to 11 weeks before clinical diagnosis of treatment-requiring (TR)–ROP in three separate screening cohorts in Asia.

In a previous study, the researchers used their model to identify at-risk infants in the United States. For this diagnostic study, they tailored it to the LMIC setting using a dataset acquired by an ROP telemedicine screening program in India. Using fivefold cross-validation, logistic regression models were trained on two variables (gestational age and vascular severity score) for prediction of TR-ROP.

The researchers validated the model on datasets from India, Nepal, and Mongolia. Primary outcome measures

included 1) sensitivity, specificity, and positive predictive value and negative predictive value for predictions of future occurrences of TR-ROP; 2) the number of weeks before clinical diagnosis when a prediction of TR-ROP was made; and 3) the potential reduction in number of examinations required.

A total of 3,760 infants were included in the study. The infants' median postmenstrual age was 37 weeks, and 1,950 (51.9%) were male. The diagnostic model had a sensitivity and specificity, respectively, as follows: India, 100% and 63%; Nepal, 100% and 77.8%; and Mongolia, 100% and 45.8%. Infants with TR-ROP were identified a median of 2 (0–11) weeks before diagnosis in India, .5 (0–2) weeks in Nepal, and 0 (0–5) weeks in Mongolia. Implementing this model with a single examination for infants found to be at low risk of TR-ROP would reduce the overall number of examinations by 38.4% in Nepal, 45% in India, and 51.3% in Mongolia.

The authors noted that “by focusing resources on those who screen positive [with the risk model], it is less likely TR-ROP will be missed or treated late.” They added that this is especially true for aggressive ROP (A-ROP), which is more common in LMICs. (*Also see related commentary by Isdin Oke, MD, in the same issue.*)

County by County: Prevalence of VA Loss or Blindness

August 2022

Lundeen et al. set out to produce county-level assessments of the prevalence of VA loss or blindness in the United States. They found considerable geographic variation and a positive correlation with the poverty level of individual counties.

For this study, the researchers used data from five population-based studies to calculate the combined prevalence of VA loss (defined as BCVA of 20/40 or worse in the better-seeing eye) or blindness (BCVA of 20/200 or worse in the better-seeing eye). They used integrative systems modeling to generate composite county-level prevalence estimates and calculated the linear trend

between these estimates and the level of poverty in each county.

Crude prevalence rates of VA loss or blindness ranged from .75% in Douglas County, Colorado, to 13.16% in Kalawao County, Hawaii. Standardized prevalence rates ranged from .99% in Cumberland County, Maine, to 10.88% in Clay County, Kentucky. County-level standardized prevalence rates were positively correlated with the percentage of the county's population living below the federal poverty level (r , .40).

The authors note that these data can be used to guide interventions to improve care in underserved areas, as counties with a higher level of VA loss and blindness may have less access to and use of eye care services.

—Summaries by Jean Shaw

OTHER JOURNALS

Selected by Prem S. Subramanian, MD, PhD

Visual Disturbances With EDOF Lenses

Journal of Cataract and Refractive Surgery

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Although monofocal IOLs are widely used and produce good distance vision, they now have competition from an array of multifocal lenses that may improve near and/or mid-range vision as well. With the newer lenses, the risk of visual disturbances such as glare and halos is relatively high, leading to dissatisfaction for some patients. Extended depth-of-focus (EDOF) lenses are designed to improve the full range of vision, but near vision may be inferior to that with bifocal IOLs because of overlapping images on the retina. To learn more about visual disturbances by lens type, Guarro et al. compared post-op results and patient perspectives after implantation of one of three EDOFs or a monofocal lens (control). They found that recipients of diffractive EDOFs had the most visual disturbances.

For this prospective, randomized, double-masked study, the researchers evaluated the AcrySof IQ Vivity, AT Lara 829MO, Tecnis Symfony ZXR00,

and the monofocal AcrySof IQ SN-60WF. There were 22 patients in each lens group. The variables assessed for each patient at three months postoperatively included light distortion index (LDI), best-fit circle radius, and self-reported quality of vision according to the McAlinden questionnaire.

For LDI and best-fit circle radius, there were no differences under monocular conditions between the study groups. However, in the binocular setting, significant differences were noted. Patients who received the monofocal lens had better values than those who received the Tecnis Symfony (p = .025 and p = .024, respectively) or the AT Lara (p = .002 for both variables). The results were better with Vivity than with Symfony (p = .015 and p = .014, respectively) or AT Lara (p = 0.001 for both variables). Halos were least common with monofocal lenses: they were absent in 20 of the 22 patients in the monofocal group, 18 in the Vivity group, 13 in the Symfony cohort, and 11 in the AT Lara cohort.

The two diffractive EDOF lenses in this study (Symfony, AT Lara) induced comparable visual disturbances. Of note, for all parameters, the disturbances were worse than those produced by the nondiffractive EDOF model (Vivity) or the monofocal lens.

Asymptomatic NAION Is Common in Fellow Eyes

Journal of Neuro-Ophthalmology

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Although sequential nonarteritic anterior ischemic optic neuropathy (NAION) occurs in about 15% of patients within five years of the initial episode, the prevalence of presumed previous asymptomatic NAION in fellow eyes is not known. Barbosa et al. reviewed the medical records of patients with acute NAION to determine the frequency of a visual field (VF) defect in fellow eyes that had appeared asymptomatic. They found that 10% of fellow eyes exhibited a VF abnormality suggestive of NAION, which had not been detected previously. All defects occurred in a hemifield.

The study included 139 patients

with a diagnosis of acute NAION who were seen at the authors' neuro-ophthalmology facility during a period of nearly six years, ending in September 2021. Data collected from the medical charts included NAION risk factors (e.g., diabetes, hypertension, dyslipidemia, obstructive sleep apnea, smoking history), VA data for both eyes, ocular exam results, mean deviation and shape of VF defect on automated 24-2 perimetry in both eyes, and OCT-measured thickness of the peripapillary retinal nerve fiber layer (RNFL) and ganglion cell complex-inner plexiform layer (GCC-IP). VF defects were classified as diffuse, altitudinal (superior or inferior), or nerve fiber bundle (superior or inferior). A VF was presumed to indicate previous NAION if there was corresponding pallor of the optic nerve head and OCT evidence of RNFL or GCC-IP thinning, after all other possible causes of the defect were ruled out. Any VF with more than 33% of fixation losses or more than 15% false positives were considered unreliable and excluded from analysis, as were patients who lacked VF or OCT data, did not return for follow-up, or had an ocular comorbidity that may have impeded analysis (e.g., prior stroke or retinal detachment).

Each patient who qualified for the analysis had reliable VF data. VF defects were present in the fellow eyes of 63 patients (45.3%), and 54 defects (38.8%) were deemed to represent previous NAION. In 14 (10.1%) of the patients, a presumed prior episode of fellow-eye NAION was asymptomatic. All VF defects in asymptomatic eyes occurred in a hemifield, accompanied by new VF loss in the symptomatic eye. The most common defect in asymptomatic eyes was inferior altitudinal defect-sparing fixation (50%). In five patients, the type of defect was similar in both eyes.

This study demonstrates that a "previous presumed asymptomatic episode of NAION in the fellow eye of patients presenting with acute NAION is not uncommon," said the authors. They noted that clinicians may wish to reassure appropriate patients of the low risk of subsequent NAION events.

—Summaries by Lynda Seminara