

Macular Re-pigmentation Enhances Driving Vision in Elderly Adult Males with Macular Degeneration

Stuart Richer^{1,2*}, Dong-Wouk Park³, Rachel Epstein⁴, James S. Wrobel⁵ and Carla Thomas⁶

¹Associate Professor, Family and Preventive Medicine, Rosalind Franklin University of Science and Medicine, North Chicago, IL, USA

²Assistant Professor Ophthalmology, UIC, Chicago, Illinois, USA

³Medical Student, year 3, Rosalind Franklin University of Science and Medicine, North Chicago, IL, USA

⁴Medical Student, year 2, Rosalind Franklin University of Science and Medicine, North Chicago, IL, USA

⁵Associate Professor, Internal Medicine, University of Michigan, Ann Arbor, MI, USA

⁶Research coordinator, Rosalind Franklin University of Science and Medicine, North Chicago, IL, USA

Abstract

Background: The risk of injury or fatality (driver, passenger or pedestrian) associated with motor vehicle accidents has been determined to increase with age, as a result of age-related declines in vision, motor and cognitive functioning. Elderly drivers with age related macular degeneration are particularly vulnerable to sensory visual impairment when driving at night, as they suffer declines in both Contrast sensitivity (CS) and Glare recovery (GR).

Objective: This study evaluates the relationship between carotenoid supplementation, CS and GR and the relationship between driving ability and retinal macular pigmentation.

Methods: Self-described driving performance is the basis of this report, with data derived from the Zeaxanthin and Vision Function (ZVF) Study (FDA IND #78,973), a 1 year, n=60, 4 visit, prospective randomized controlled clinical trial (RCT) of predominantly elderly male veterans (74.9 SD 10 y) with mild / moderate Age related Macular Degeneration (AMD). The twenty five question - National Eye Institute Visual Functioning Questionnaire (VFQ-25) v. January 2000, Rand Corporation® includes 3 questions assessing driving performance and were completed at baseline and 1 year after nutritional supplementation with approximately equal daily doses of the retinal macular carotenoids: lutein (9 mg) or zeaxanthin (8 mg). Replicate measures of foveal 1 degree estimated retinal macular pigment optical density were evaluated with the QuantifEye® (ZeaVision, Chesterfield, MO) heterochromic flicker photometer.

Results: VFQ25 self-described driving ability was notably associated with baseline pre-supplementation macular pigmentation. Linear regression modeling suggests that self-described ability to safely drive a car was strongly associated with final macular re-pigmentation post supplementation (P=0.02). Moreover, the greatest effect was found with zeaxanthin (ns but P = 0.057 for trend) even though lutein had greater effects than zeaxanthin with respect to CS and GR, suggesting that unique zeaxanthin post-receptorial processes may be at play.

Discussion: Carotenoid supplementation and subsequent macular repigmentation improved the self-described driving ability of patients with macular degeneration. Older male drivers with AMD should be encouraged to have their foveal macular MP measured at yearly eye examinations. If low macular pigment is found, these patients should attempt macular re-pigmentation via diet and/or supplementation to improve the sensory aspect of driving.

Keywords: Driving vision; Age related macular degeneration; Macular pigment; Carotenoids

Introduction

As of 2009, there were almost 39 million drivers aged 65 and older in the United States [1]. While driving enables an aging population to remain active and autonomous, motor vehicle accident is one of the leading causes of death for the elderly [2]. The risk of injury or fatality associated with motor vehicle accidents has been determined to increase with age as a result of age-related decline in vision [3,4], motor and cognitive functioning [5,6]. Elderly drivers with Age related Macular Degeneration (AMD), a leading cause of vision loss in patients of European ancestry in the Western world, are particularly vulnerable to sensory visual impairment when driving at night, as they suffer declines in both CS [7,8], and GR [9,10].

It is clear that the pathogenesis of AMD is amenable to environmental nutritional modification [11-14]. The yellow pigment of the human fovea is largely composed of the dietary carotenoids, specifically lutein and zeaxanthin, collectively termed Macular Pigment (MP). They are selectively accumulated in the retina at a concentration between 1000x and 10,000x greater than that in the blood serum [15]. Dietary carotenoids have been determined to protect the human lens

against cataract through their antioxidant function and play a crucial pre-photoreceptor protective role through absorption of short-wavelength light (400-500nm) [16]. More recently, MP has been found to be intimately involved in pre-receptorial receptor (rods / cones) and post-receptor-neural-cognitive function [17].

MP naturally declines with age and increasingly so in patients with AMD [18]. Denser MP improves dark and light sensitivity, which is especially useful for drivers driving in and out of tunnels. Accordingly, an increase in MP has been associated with an increase in CS [19].

***Corresponding author:** Stuart Richer, OD, PhD, Director, Ocular Preventive Medicine, Optometry/Ophthalmology 112e, Captain James, Lovell Federal Health Care Facility, 3001 Green Bay Rd, North Chicago, IL 60064-3095, USA, Tel: 224-610-7145; E-mail: Stuart.Richer1@VA.Gov

Received February 15, 2012; Accepted April 21, 2012; Published April 23, 2012

Citation: Richer S, Park DW, Epstein R, Wrobel JS, Thomas C (2012) Macular Re-pigmentation Enhances Driving Vision in Elderly Adult Males with Macular Degeneration. J Clin Exp Ophthalmol 3:217. doi:10.4172/2155-9570.1000217

Copyright: © 2012 Richer S, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Enhanced MP translates to lessened glare disability and better GR as well [20]. The clinical importance of MP in retinal health and disease is summarized in a recent consensus paper [21]. In the present paper, we examine the role of MP in elderly (primarily male) drivers, with retinal degeneration.

Methods

The Zeaxanthin and Vision Function Study was a 1 year, n = 60, 4 visit, prospective randomized controlled clinical trial of patients (74.9 SD 10 y) with mild / moderate AMD (FDA IND #78,973). 22 Patients were randomly assigned to one of 2 dietary supplement carotenoid pigment intervention groups: 8mg zeaxanthin (n=25) & 8 mg zeaxanthin + 9 mg lutein (n=25) or to a 9 mg lutein (faux - placebo - control group, n=10). The National Eye Institute Visual Functioning Questionnaire score (NEI VFQ-25) is a validated instrument employed to assess the patient's vision-related quality of life and was used as an additional secondary outcome measure in ZVF [22]. The 25 question version 2000, self-administered format, January 2000, Rand Corporation® was utilized, specifically the 3 questions that address driving performance (Appendix 1) [23].

Statistics

Baseline within treatment group differences was assessed with one-way ANOVA assessing the equal variance assumption using Bartlett's test. Post-Hoc differences were assessed using Scheffe's test. Within group differences were assessed using a two-sample t test with equal variances. Multivariate linear regression models were built with candidate variables selected ($P < 0.05$). All calculations were made using STATA 10.1 (College Station, TX, USA) software.

Macular Pigment (MP)

Replicate measures of foveal 1 degree estimated MP were evaluated with the Quantify® MPS 9000 macular pigment screener, a modified Heterochromic Flicker Photometer (HFP). Estimated foveal MP (without an eccentric reference) was chosen for the ZVF study population because a substantial number of elderly subjects had concurrent cataracts (more so than in our first RCT study of lutein, called LAST), introducing additional variability, in addition to fatigue and uncertainty. Central only foveal readings have been found to be statistically representative of the degree of macular pigmentation of the retina [22].

Contrast Sensitivity (CS)

The area under the curve of the resulting CS function at 5 spatial frequencies was measured with The Vision Function Analyzer® (Stereo Optical, Chicago, IL) with best refraction. The CS function is a measure of how an eye sees large objects (low spatial frequencies @ 1.5 and 3 cycles / degree) as well as small objects such as Snellen letters (higher spatial frequencies i.e. 18 cycles / degree) - x axis, at differing contrasts - y axis [24].

Glare Recovery (GR)

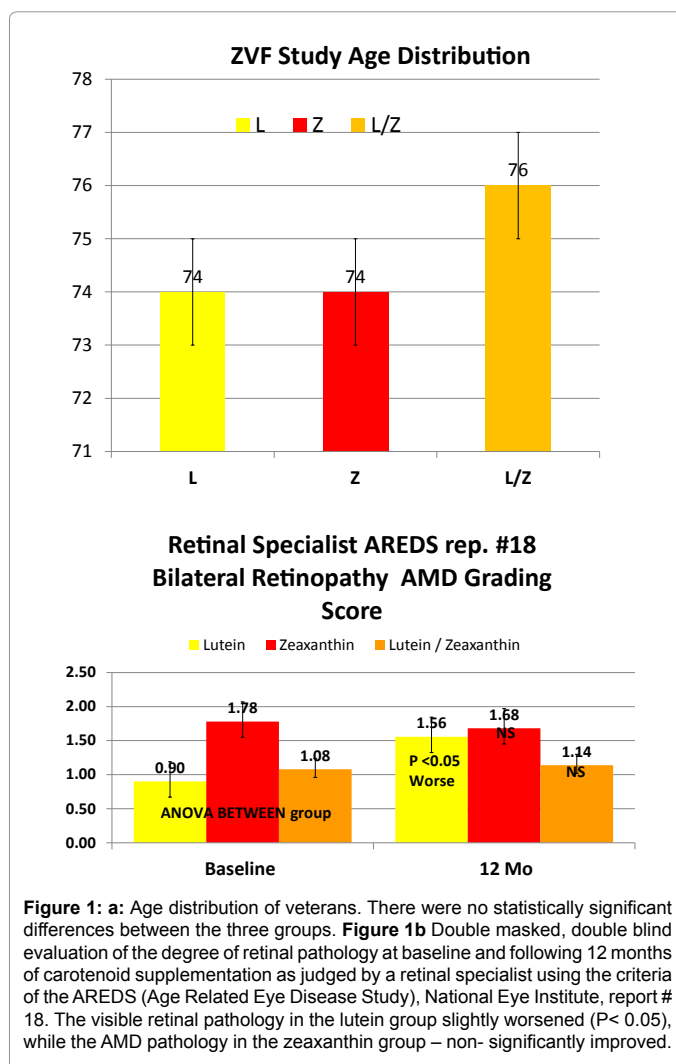
Glare photo-stress recovery (in seconds) following 30 seconds of continuous retinal bleach, was assessed using 2 line supra-threshold low contrast randomly presented Landolt Cs using the KOWA AS14B Night Vision Tester (KOWA Optimed, Tokyo, Japan).

Results

ZVF (FDA IND #78, 973) did not evaluate carotenoid serum values,

only the more important biologic end-tissue response of macular pigment. Compliance was assessed independently through pill count and serial telephone query. There was 96% pill intake compliance. The age distribution and retinal specialist AMD severity grading score of the n= 60 patients is shown in (Figures 1a, b).

Measures of low contrast vision comprise greater contributions of rod-based parafoveal vision and are shown in (Figures 2a-d). Baseline (pre-supplementation) low contrast near visual acuity, important in driving, was inferior to that of high contrast letters by at least 2 to 5 visual acuity lines (data not shown), consistent with the presence of retinal degeneration in these elderly patients. Lutein supplementation proved superior to zeaxanthin with respect to multiple measures of rod-based vision. (Figure 1a) illustrates that following 12 months of supplementation, the low contrast letters were better visualized with either lutein (+ 7.2 letters, $P= 0.04$) or lutein and zeaxanthin supplementation (+ 8.8 letters, $P= 0.02$) but not significantly improved with zeaxanthin alone (+ 4.3 letters, $P= ns$). An overall increase in average CS was demonstrated, with the lutein group most effective (Figure 2b). Baseline and final AUC CS function (integrated Area-under-the-curve, CS @ 5 spatial frequencies) for lutein (% difference improvement =+ 48%; $P= 0.05$) and zeaxanthin (+ 24%; ns but $P= 0.09$ for trend) but surprisingly not for equally weighted lutein and



zeaxanthin supplementation (+ 20%; ns). For blue cone parafoveal thresholds, lutein proved best (ns but $P=0.09$ for trend) ANOVA @ 8 months and ($P=0.05$) ANOVA @ 12 months consistent with its known anatomical distribution. (Figure 2c) GR (seconds) improvement was significant for lutein ($P=0.02$) and particularly for the combined lutein and zeaxanthin group ($P=0.002$) with only a trend for improvement with the zeaxanthin subgroup (ns but $P=0.09$), paired t-Test, baseline to 12 months (Figure 2d).

A greater self-reported vision function score on the NEI VFQ-25 self-evaluation driving subscale was associated with greater MP (average eye macular pigment at 12 months post supplementation), demonstrated as increasing self-reported composite driving subscale scores associated with increased average eye macular pigment at 12 months post supplementation (Figure 3). Accordingly, MP12 had the highest correlation with driving by the end of the study, post supplementation ($p=0.02$) as determined via linear regression model of ($n=60$) subjects enrolled in ZVF, using the parameters MPB (average eye macular pigment baseline), MP12, VFQB (NEI VFQ25 composite driving score baseline) and VFQ12 (NEI VFQ25 composite driving score at 12 months post supplementation) (Figure 4).

Discussion

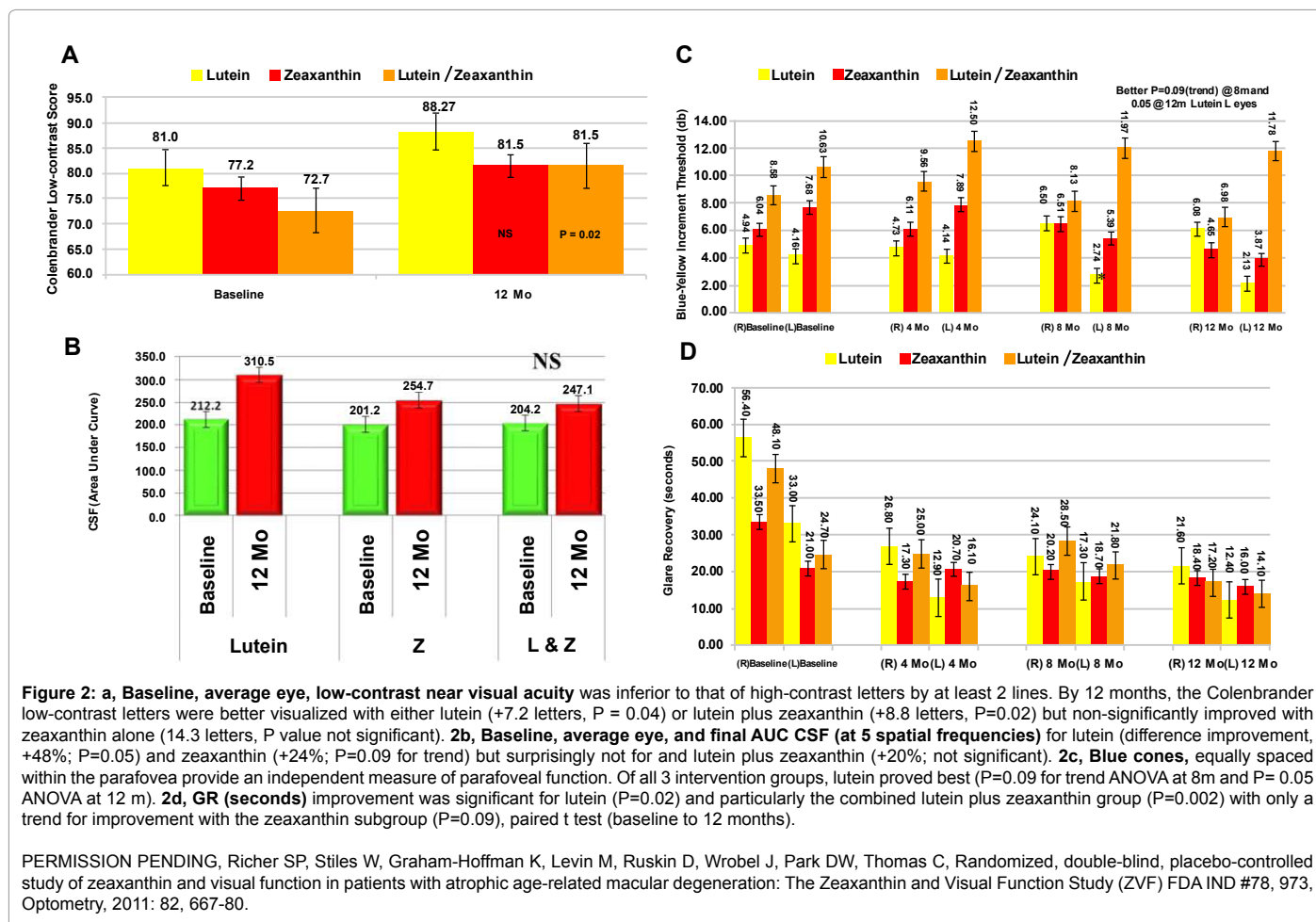
There is benefit in determining MP in the retina as it can be nutritionally modified in most seniors. Both the LAST (Lutein Antioxidant Supplementation Trial) RCT emphasizing the carotenoid

lutein, and the ZVF study, emphasizing the carotenoid zeaxanthin, demonstrate MP enhancement through supplementation, with attendant improvement in CS and photo stress GR. Both parameters are related to the sensory aspects of vision involved in twilight and night driving. Both visual parameters diminish with aging.

The importance of CS in driving has been shown [7]. Owsley et al. studied state motor vehicle crash record and found that crash involved drivers were 8 times more likely to have a severe CS reduction in the worse eye and 6 times more likely to have severe CS reduction in both eyes compared to crash-free drivers [3]. Specifically, CS is associated with decreased highway sign discrimination [7], decreased performance on braking [25], poorer driving maneuvers/skills [26], patient-reported driving difficulty [27], and slower reaction times [28]. Turano et al. have described that in glaucoma, CS was associated even with the walking speed [29].

The importance of GR in driving has been shown before, as decreased GR restricts driving [30]. Rubins et al. showed that glare sensitivity is a significant predictor of crash involvement [9], and Gray and Regan demonstrated that increase in glare is significantly associated with decrease in safety margin [10]. Detailed analysis of how high intensity discharge lamps impair driving of older adults, was evaluated by Mainster and Timberlake [31].

In this paper, a small but significant aspect of driving ability that can be beneficially modified in elderly male patients with AMD was



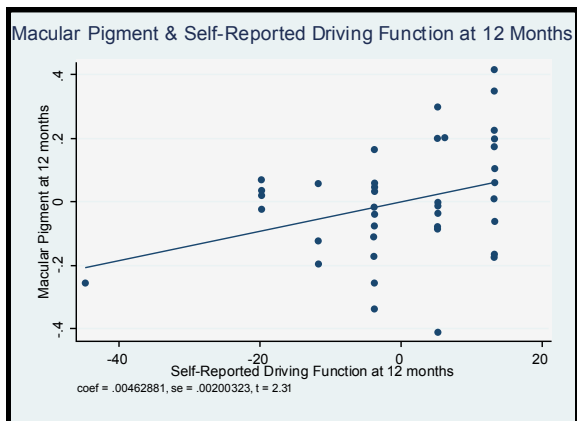


Figure 3: Macular pigment and self-reported driving function at 12 months are linearly related, post supplementation (p=0.02).

Regression (Linear Modeling n=60)

pwcorr mpb mp12 vfdriveb vfdrive12 vfqb vfq12, sig

"MP12 has the highest correlation with driving at end of study, although there is a higher correlation with baseline functioning and driving..."

	mpb	mp12	vfqdriveb	vfqdrive12	vfqb	vfq12
mpb	1.00					
mp12	0.62 0.0000	1.00				
vfqdriveb	0.12 NS	0.18 NS	1.00			
vfqdrive12	0.26 P=0.08	0.33 P=0.02	0.68 0.0000	1.00		
vfqb	0.14 NS	-0.01 NS	0.73 0.0000	0.55 0.0001	1.00	
vfq12	0.25 0.09	0.10 0.49	0.56 0.0000	0.68 0.0000	0.90 0.0000	1.00

Figure 4: Regression and (Linear Modeling n = 60 patients) of NEI VFQ data Key: mpb = average eye macular pigment at baseline; mp12 = average eye macular pigment at 12 months; vfqb = total NEI VFQ score at baseline; vfq12 = total NEI VFQ score at final visit; vfdriveb = NEI VFQ driving subscale composite 3 – question driving score at baseline pre- supplementation n; vfdrive12 = NEI VFQ driving subscale composite 3 – question driving score at the final visit post supplementation.

identified. Specifically, lutein supplementation, and to a lesser extent zeaxanthin supplementation, was associated with better low contrast vision and visual recovery from blinding glare. Self-described driving ability was associated with baseline pre-supplementation macular pigmentation (non- significantly). However, when subjected to linear regression modeling, the self-described ability to drive a car was associated with increased pigmentation (P=0.02) by the end of 12 months of supplementation with nutritional carotenoids. Moreover, the greatest effect was surprisingly reserved for zeaxanthin (ns but P=0.057). In the ZVF Study, zeaxanthin improved foveal visual acuity, shape discrimination and scotoma resolution and appears to beneficially impact cognitive function as well. Such post-receptorial attributes of this carotenoid might trump any differences in visual function compared with lutein.

Several groups are studying brain and / or post-receptorial visual function effects of the macular pigments. One group has shown that MP is positively related to cognition in the elderly in a battery of tests

[17]. The Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA, has also shown that lutein / zeaxanthin levels in centenarians' brains (upon autopsy) are related to cognitive function. Temporal CS function (TCSF) is related to MP [32]. This same group has shown that MP is related to heterochromatic luminance contrast thresholds. Both of these visual functions are post-receptorial and suggest MP assists the brain and retina function, so they work efficiently together. Future research focusing on Useful Field of View (UFOV) might also be a promising area of investigation as it involves both sensory (visual) input and cognition [33-36].

Older drivers with AMD, in particular, should be encouraged to request a foveal macular MP reading at least once during their yearly eye examination. Currently, no CPT 9 (Procedural Terminology version 9) code for MP, CR or GR testing exists, and may present a barrier to utilization. Nonetheless, two simplified and widely available commercial heterochromatic flicker photometry devices are now available: the QuantifEye® (ZeaVision, Chesterfield, MO) and the MacuScope (Marco Instrument, Jacksonville, FL). Clinicians should invest in measuring retinal pigmentation as well as CS and GR evaluation technology. A normal 1862 Snellen acuity measurement provides a false sense of security with respect to twilight and night driving even in elderly patients maintaining "20/20" high contrast visual acuity. Relatively low doses of dietary over the counter carotenoids were used in the ZVF study. No evidence of toxicity and no adverse events related to this intervention were found by the ZVF Data Safety Monitoring Protocol. Both dietary carotenoids (lutein and zeaxanthin) and macular re-pigmentation should be considered in elderly male patients having night driving difficulty.

Acknowledgements

We thank the veterans who participated in this research study. This material is based on original work supported by the Captain James Lovell Federal Health Care Center (FHCC) and the Department of Veterans Affairs Research Service / CARES, Hines, IL. Chrysantis / Ball Horticulture Inc (West Chicago, IL) is the primary ZVF granting sponsor. Kowa Optimed Inc (Torrance, CA and Tokyo, Japan), Stereo Optical Inc (Chicago, IL), Rush Ophthalmics Inc (Gold Beach, OR), Pharnanex, Inc (Provo, UT), ZeaVision, Inc (Chesterfield, MO), Heidelberg Instruments Inc (Heidelberg, Germany) and RTVue (Fremont, CA) all provided instrumentation as secondary sponsors in support of both ZVF and our Ocular – Nutrition Laboratory.

References

1. National Household Travel Survey.
2. Center for Disease Control.
3. Owsley C, Stalvey BT, Wells J, Sloane ME, McGwin G Jr (2001) Visual risk factors for crash involvement in older drivers with cataract. Arch Ophthalmol 119: 881-887.
4. Owsley C, McGwin G Jr, Sloane M, Wells J, Stalvey BT, et al. (2002) Impact of cataract surgery on motor vehicle crash involvement by older adults. JAMA 288: 841-849.
5. Uc EY, Rizzo M (2008) Driving and neurodegenerative diseases. Curr Neurol Neurosci Rep 8: 377-383.
6. Wagner JT, Müri RM, Nef T, Mosimann UP (2011) Cognition and driving in older persons. Swiss Med Wkly 140: w13136.
7. Evans DW, Ginsburg AP (1985) Contrast sensitivity predicts age-related differences in highway-sign discriminability. Hum Factors 27: 637-642.
8. Ginsburg AP (2003) Contrast sensitivity and functional vision. Int Ophthalmol Clin 43: 5-15.
9. Rubin GS, Ng ES, Bandeen-Roche K, Keyl PM, Freeman EE, et al. (2007) A prospective, population-based study of the role of visual impairment in motor vehicle crashes among older drivers: the SEE study. Invest Ophthalmol Vis Sci 48: 1483-1491.
10. Gray R, Regan D (2007) Glare susceptibility test results correlate with temporal

- safety margin when executing turns across approaching vehicles in simulated low-sun conditions. *Ophthalmic Physiol Opt* 27: 440-450.
11. Age-Related Eye Disease Study Research Group (2001) A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8.
 12. Chakravarthy U, Wong TY, Fletcher A, Piau E, Evans C, et al. (2010) Clinical risk factors for age-related macular degeneration: a systematic review and meta-analysis. *BMC Ophthalmol* 10: 31.
 13. Chen Y, Bedell M, Zhang K (2010) Age-related macular degeneration: genetic and environmental factors of disease. *Mol Interv* 10: 271-281.
 14. Kokotas H, Grigoriadou M, Petersen MB (2011) Age-related macular degeneration: genetic and clinical findings. *Clin Chem Lab Med* 49: 601-616.
 15. Bone RA, Landrum JT (2010) Dose-dependent response of serum lutein and macular pigment optical density to supplementation with lutein esters. *Arch Biochem Biophys* 504: 50-55.
 16. Chiu CJ, Taylor A (2007) Nutritional antioxidants and age-related cataract and maculopathy. *Exp Eye Res* 84: 229-245.
 17. Johnson EJ (2011) The role of Lutein, Zeaxanthin and Omega-3 Fatty Acids in Age-Related Visual and Cognitive Function. 16th International Carotenoid Symposium, Krakow, Poland, 17-22 July.
 18. Whitehead AJ, Mares JA, Danis RP (2006) Macular pigment: a review of current knowledge. *Arch Ophthalmol* 124: 1038-1045.
 19. Wooten BR, Hammond BR (2002) Macular pigment: influences on visual acuity and visibility. *Prog Retin Eye Res* 21: 225-240.
 20. Stringham JM, Hammond BR (2008) Macular pigment and visual performance under glare conditions. *Optom Vis Sci* 85: 82-88.
 21. Bernstein PS, Delori FC, Richer S, van Kuijk FJ, Wenzel AJ (2010) The value of measurement of macular carotenoid pigment optical densities and distributions in age-related macular degeneration and other retinal disorders. *Vision Res* 50: 716-728.
 22. Richer SP, Stiles W, Graham-Hoffman K, Levin M, Ruskin D, et al. (2011) Randomized, double-blind, placebo-controlled study of zeaxanthin and visual function in patients with atrophic age-related macular degeneration: the zeaxanthin and Visual Function Study (ZVF) FDA IND #78, 973. *Optometry* 82: 667-680.
 23. Orr P, Rentz AM, Margolis MK, Revicki DA, Dolan CM, et al. (2011) Validation of the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) in Age-Related Macular Degeneration. *Invest Ophthalmol Vis Sci* 52: 3354-3359.
 24. Loshin DS, White J (1984) Contrast sensitivity: The visual Rehabilitation of the Patient with Macular Degeneration. *Arch Ophthalmol* 102: 1303-1306.
 25. Zhang L, Baldwin K, Munoz B, Munro C, Turano K, Hassan S, et al. (2007) Visual and cognitive predictors of performance on brake reaction test: Salisbury eye evaluation driving study. *Ophthalmic Epidemiol* 14: 216-222.
 26. Haymes SA, LeBlanc RP, Nicoleta MT, Chiasson LA, Chauhan BC (2008) Glaucoma and on-road driving performance. *Invest Ophthalmol Vis Sci* 49: 3035-3041.
 27. Rubin GS, Roche KB, Prasada-Rao P, Fried LP (1994) Visual impairment and disability in older adults. *Optom Vis Sci* 71: 750-760.
 28. Plainis S, Murray IJ (2002) Reaction times as an index of visual conspicuity when driving at night. *Ophthalmic Physiol Opt* 22: 409-415.
 29. Turano KA, Rubin GS, Quigley HA (1999) Mobility performance in glaucoma. *Invest Ophthalmol Vis Sci* 40: 2803-2809.
 30. West CG, Gildengorin G, Haegerstrom-Portnoy G, Lott LA, Schneck ME, et al. (2003) Vision and driving self-restriction in older adults. *J Am Geriatr Soc* 51: 1348-1355.
 31. Mainster MA, Timberlake GT (2003) Why HID headlights bother older drivers. *Br J Ophthalmol* 87: 113-117.
 32. Renzi LM, Hammond BR Jr (2010) The relation between the macular carotenoids, lutein and zeaxanthin, and temporal vision. *Ophthalmic Physiol Opt* 30: 351-357.
 33. Ball K (2009) The Effects of Training on Driving Competence – Crash Risk, in Transportation Research Board Annual Meeting. Washington DC, USA.
 34. Edwards JD, Delahunt PB, Mahncke HW (2009) Cognitive Speed of Processing Training Delays Driving Cessation. *J Gerontol A Biol Sci Med Sci* 64: 1262-1267.
 35. Edwards JD, Myers C, Ross LA, Roenker DL, Cissell GM, et al. (2009) The longitudinal impact of cognitive speed of processing training on driving mobility. *Gerontologist* 49: 485-494.
 36. Owsley C (2010) The Vision and Driving Challenge. *J Neuroophthalmol* 30: 115-116.