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Drug treatment

Ophthalmology. 2012 Nov 10. pii: S0161-6420(12)00977-3. doi: 10.1016/j.ophtha.2012.10.006. [Epub ahead of print]

Variants in the VEGFA Gene and Treatment Outcome after Anti-VEGF Treatment for Neovascular Age-related Macular Degeneration.

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PURPOSE: To determine the association of genetic variants of the VEGFA gene with outcome of anti-vascular endothelial growth factor (VEGF) treatment in neovascular age-related macular degeneration (AMD).

DESIGN: A prospective cohort study.

PARTICIPANTS: We included 201 consecutive patients receiving anti-VEGF injections for neovascular AMD.

METHODS: Patients were followed over 12 months. They were treated with 3 initial monthly ranibizumab or bevacizumab injections. Thereafter, the decision to retreat was made by clinicians at each follow-up visit on the basis of retreatment criteria. Seven tagged single nucleotide polymorphisms (tSNPs) in the VEGFA gene were selected and examined. Multivariate data analysis was used to determine the role of each tSNP in treatment outcome.

MAIN OUTCOME MEASURES: The influence of selected VEGFA tSNPs on visual acuity (VA) outcome at 6 months.

RESULTS: Mean baseline VA was 51±17 Early Treatment Diabetic Retinopathy Study (ETDRS) letter scores. Overall, the mean change in VA from baseline was +6.5±12, +4.4±13.4, and +2.3±14.6 letters at 3, 6, and 12 months, respectively. The tSNP rs3025000 was the only SNP significantly associated ($P < 1 \times 10^{-4}$) with visual outcome at 6 months with multiple correction. The presence of the T allele (TC or TT genotypes) at this tSNP predicted a better outcome of +7 letters at 6 months compared with the CC genotype. In a subgroup analysis, presence of the T allele predicted a significantly higher chance of the patients belonging to the responder group (gain of ≥5 letters from baseline) after 3, 6, and 12 months treatment (odds ratio, 2.7, 3.5, and 2.4; 95% confidence interval, 1.46-5.07, 1.82-6.71, and 1.27-4.57, respectively) than any other outcome group.

CONCLUSIONS: Pharmacogenetic association with anti-VEGF treatments may influence the visual outcomes in neovascular AMD. In patients with the T allele in tSNP rs3025000, there was a significantly better visual outcome at 6 months and a greater chance of the patients belonging to the responder group with anti-VEGF treatment at 3, 6, and 12 months. The VA outcomes of patients harboring the T allele at SNP rs3025000 were comparable with those of the pivotal clinical trials but with fewer injections, making the treatment perhaps more cost effective in certain subgroups of patients.

PMID: 23149126 [PubMed - as supplied by publisher]

Arch Ophthalmol. 2012 Nov 1;130(11):1466-70. doi: 10.1001/archophthalmol.2012.1542.

Response to ranibizumab following tachyphylaxis to bevacizumab in a patient with radiation maculopathy following stereotactic fractionated radiotherapy for optic nerve meningioma.

Jutley G, Shona OA, Leen RC, Lee N, Olver JM, George SM.

PMID: 23143450 [PubMed - in process]

Other treatment & diagnosis

J Ocul Pharmacol Ther. 2012 Nov 12. [Epub ahead of print]

Nanoparticles in the Treatment of Angiogenesis-Related Blindness.

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Abstract: Nanoparticles can be used for the treatment of various retinal diseases. Due to small sizes, they can improve bioavailability of therapeutic agents and pass through biological barriers of the eye, such as the cornea, conjunctiva, sclera, and even more, blood-retinal barriers. Another important characteristic of nanoparticles is the ability to be fabricated based on the researchers' design through chemical processes. In this regard, they can act as a novel drug delivery system, enabling targeted therapies for angiogenesis-related blindness (ARB). With these possibilities, many researchers have utilized nanoparticles as novel therapeutic options for the treatment of exudative age-related macular degeneration and diabetic retinopathy, both of which are characterized by pathologic neovascularization. In this review, we summarize various attempts and rationales in using nanoparticles to treat ARB. After that, we discuss the toxicity of nanoparticles on the retina. We expect this review to be a stepping stone for novel therapeutics for ARB, resulting in improvement in visual outcomes.

PMID: 23145865 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2012 Nov 13. pii: iovs.12-10582v1. doi: 10.1167/iov.12-10582. [Epub ahead of print]

Accuracy and Reproducibility of Automated Drusen Segmentation in Eyes with Non-neovascular Age-Related Macular Degeneration.

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PURPOSE: To evaluate the accuracy and reproducibility of drusen quantification by an automated drusen segmentation algorithm in spectral domain optical coherence tomography (SD-OCT) images of eyes with non-neovascular age-related macular degeneration (AMD).

METHODS: Drusen segmentation was performed using both a commercial automated algorithm (Cirrus OCT RPE analysis tool) and manual segmentation in 44 eyes of 30 subjects with dry AMD who underwent volume OCT scanning. The drusen (space between outer RPE layer and Bruch's membrane) was segmented automatically using an automated RPE tool and manually by 3D-OCTOR. Drusen area and volume were calculated in all eyes. Age and visual acuity data was also collected. Reproducibility of manual and automated measurements was assessed by intraclass correlation (ICC).

RESULTS: The mean age of subjects was 78.24 ($\pm$ 9.4, range; 56 - 97 years). Mean Log MAR visual acuity was 0.4 (Snellen equivalent $\sim$ 20/50) (SD: 0.40; range: 0 - 1.3). The mean (SD) drusen area was 5.05 (3.67) mm² with manual segmentation and 4.66 (3.51) mm² with the automated RPE tool; the absolute difference was 2.63 (2.5) mm². Mean drusen volume was 1.49 (0.42) mm³ with manual segmentation and 1.42 (0.43) mm³ with the automated RPE tool; the absolute difference was 1.42 (0.43) mm³. Agreement between manual and automated measurements of drusen volume (highest ICC=0.95) was better than the agreement for drusen area (ICC=0.65).

CONCLUSION: The quantification of drusen area and volume using an automated RPE yielded better agreement for volume than for area when compared with human expert manual segmentation. Using this software, drusen volume measurements may be a useful tool for quantifying drusen burden in clinical trials and clinical practice.

PMID: 23150629 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2012 Nov 13. pii: iovs.12-9576v1. doi: 10.1167/iov.12-9576. [Epub ahead of print]

Automated "Disease / No Disease" Grading of Age-Related Macular Degeneration by an Image Mining Approach.

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PURPOSE: To describe and evaluate an automated grading system for age-related macular degeneration (AMD) by color fundus photography.

METHODS: An automated "disease / no disease" grading system for AMD was developed based on image mining techniques. First, image pre-processing was performed to normalize color and non-uniform illumination of the fundus images, to define a region of interest, and to identify and remove pixels belonging to retinal vessels. To represent images for the prediction task, a graph based image representation using quadrees was then adopted. Next, a graph mining technique was applied to the generated graphs to extract relevant features (in the form of frequent sub-graphs) from images of both AMD and healthy volunteers. Features of the training data were then fed into a classifier generator (Naïve Bayes and Support Vector Machines were used with respect to the evaluation presented later in this paper) for training purposes before employing the trained classifiers to classify new "unseen images".

RESULTS: The algorithm was evaluated on two publically available fundus image datasets (ARIA and STARE) comprising 258 images (160 AMD and 98 normal). Ten-fold cross validation was used. The experiments produced a best specificity of 100% and a best sensitivity of 99.4% with an overall accuracy of 99.6%. Our approach outperformed previous approaches reported in the literature.

CONCLUSIONS: The proposed technique has demonstrated a proof of concept for an automated AMD

grading technique. It has the potential to be further developed as an automated grading tool for future whole scale AMD screening programs.

PMID: 23150624 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2012 Nov 13. pii: iovs.12-10732v1. doi: 10.1167/iovs.12-10732. [Epub ahead of print]

In vivo confocal intrinsic optical signal identification of localized retinal dysfunction.

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PURPOSE: The purposes of this study are to investigate the physiological mechanism of stimulus-evoked fast intrinsic optical signals (IOSs) recorded in dynamic confocal imaging of the retina, and to demonstrate the feasibility of in vivo confocal-IOS mapping of localized retinal dysfunctions.

METHODS: A rapid line-scan confocal ophthalmoscope was constructed to achieve in vivo confocal-IOS imaging of frog (*Rana Pipiens*) retinas at cellular resolution. In order to investigate the physiological mechanism of confocal-IOS, comparative IOS and electroretinography (ERG) measurements were conducted using normal frog eyes activated by variable intensity stimuli. A dynamic spatiotemporal filtering algorithm was developed to reject the contamination of hemodynamic changes on fast IOS recording. Laser-injured frog eyes were employed to test the potential of confocal-IOS mapping of localized retinal dysfunctions.

RESULTS: Comparative IOS and ERG experiments revealed a close correlation between the confocal-IOS and retinal ERG, particularly the ERG a-wave which has been widely used to evaluate photoreceptor function. IOS imaging of laser-injured frog eyes indicates that the confocal-IOS can unambiguously detect localized (30 μ m) functional lesions in the retina before a morphological abnormality is detectable.

CONCLUSIONS: The confocal-IOS predominantly results from retinal photoreceptors, and can be used to map localized photoreceptor lesion in laser-injured frog eyes. We anticipate that confocal-IOS imaging can provide applications in early detection of age-related macular degeneration, retinitis pigmentosa and other retinal diseases that can cause pathological changes in the photoreceptors.

PMID: 23150616 [PubMed - as supplied by publisher]

Eur J Pharm Sci. 2012 Nov 7. pii: S0928-0987(12)00414-9. doi: 10.1016/j.ejps.2012.10.014. [Epub ahead of print]

Therapeutic RNA Aptamers in Clinical Trials.

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Abstract: RNA aptamers can fold into complex structures and bind with high affinity and selectivity to various macromolecules, viruses, and cells. They are isolated from a large pool of nucleic acids by a conceptually straightforward iterative selection process called SELEX. Aptamers have enormous potential as therapeutics due to their ability to bind to proteins and specifically inhibit their functions with minimal or no harmful side-effects. The first aptamer therapeutic was FDA approved in 2005 and a number of novel

aptamer-based therapeutics are currently undergoing clinical trials for treating diseases such as macular degeneration, choroidal neovascularization, intravascular thrombus, acute coronary syndrome, von Willebrand factor related disorders, von Hippel-Lindau syndrome (VHL), angiomas, acute myeloid leukemia, renal cell carcinoma, non-small cell lung cancer, thrombotic thrombocytopenic purpura, and several others. In this review, we present aptamers in on-going, completed, and terminated clinical studies highlighting their mechanism of action as well as the inherent challenges of aptamer production and use.

PMID: 23142634 [PubMed - as supplied by publisher]

Pathogenesis

PLoS One. 2012;7(11):e48501. doi: 10.1371/journal.pone.0048501. Epub 2012 Nov 14.

Biological effects of cigarette smoke in cultured human retinal pigment epithelial cells.

Yu AL, Birke K, Burger J, Welge-Lussen U.

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Abstract: The goal of the present study was to determine whether treatment with cigarette smoke extract (CSE) induces cell loss, cellular senescence, and extracellular matrix (ECM) synthesis in primary human retinal pigment epithelial (RPE) cells. Primary cultured human RPE cells were exposed to 2, 4, 8, and 12% of CSE concentration for 24 hours. Cell loss was detected by cell viability assay. Lipid peroxidation was assessed by loss of cis-parinaric acid (PNA) fluorescence. Senescence-associated β -galactosidase (SA- β -Gal) activity was detected by histochemical staining. Expression of apolipoprotein J (Apo J), connective tissue growth factor (CTGF), fibronectin, and laminin were examined by real-time PCR, western blot, or ELISA experiments. The results showed that exposure of cells to 12% of CSE concentration induced cell death, while treatment of cells with 2, 4, and 8% CSE increased lipid peroxidation. Exposure to 8% of CSE markedly increased the number of SA- β -Gal positive cells to up to 82%, and the mRNA expression of Apo J, CTGF, and fibronectin by approximately 3-4 fold. Treatment with 8% of CSE also increased the protein expression of Apo J and CTGF and the secretion of fibronectin and laminin. Thus, treatment with CSE can induce cell loss, senescent changes, and ECM synthesis in primary human RPE cells. It may be speculated that cigarette smoke could be involved in cellular events in RPE cells as seen in age-related macular degeneration.

PMID: 23155386 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2012 Nov 13. pii: iovs.12-9963v1. doi: 10.1167/iov.12-9963. [Epub ahead of print]

Chemokine Expression in Retinal Pigment Epithelial ARPE-19 Cells in Response to Co-culture with Activated T Cells.

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PURPOSE: To investigate the effects of T cell-derived cytokines on gene and protein expression of chemokines in a human RPE cell line (ARPE-19).

METHODS: We used an in vitro co-culture system in which the RPE and CD3/CD28-activated T cells were separated by a membrane. RPE cell expression of chemokine genes was quantified using three different types of microarrays. Protein expression was determined by single- and multiplex ELISA and

immunoblotting.

RESULTS: Co-culture with activated T cells increased RPE mRNA and protein expression of chemokines CCL2 (MCP-1), CCL5 (RANTES), CCL7 (MCP-3), CCL8 (MCP-2), CXCL1 (GRO- α), IL8 (CXCL8), CXCL9 (MIG), CXCL10 (IP10), CXCL11 (ITAC), and CX3CL1 (fractalkine). CCL7, CXCL9, CXCL10, and CXCL11 were secreted significantly more in the apical direction. Using recombinant human cytokines and neutralizing antibodies we identified IFN γ and TNF α as the two major T cell-derived cytokines responsible for the RPE response. For CCL5, CXCL9, CXCL10, CXCL11, CXCL16, and CX3CL1 we observed a synergistic effect of IFN γ and TNF α in combination. CCL20, CXCL1, CXCL6, and IL8 were negatively regulated by IFN γ .

CONCLUSIONS: RPE cells responded to exposure to T cell-derived cytokines by upregulating expression of multiple chemokines related to microglial, T cell, and monocyte chemotaxis and activation. This inflammatory stress response may have implications for immune homeostasis in the retina, and for the further understanding of inflammatory ocular diseases such as uveitis and age-related macular degeneration.

PMID: 23150618 [PubMed - as supplied by publisher]

Clin Chem Lab Med. 2012 Nov 12;1-7. doi: 10.1515/cclm-2012-0402. [Epub ahead of print]

Aqueous humor glycation marker and plasma homocysteine in macular degeneration.

Obeid R, Ninios K, Loew U, Gatzoufas Z, Hoffmann S, Seitz B, Geisel J, Herrmann W.

Abstract Background: We investigated concentrations of total homocysteine (tHcy) in elderly people without and those with age-related macular degeneration (AMD). In addition, we tested the association between plasma tHcy and one glycation marker in aqueous humor. **Methods:** People with cataract only (n=48), patients with dry AMD (n=38) and those with wet AMD (n=31) were studied. Blood concentrations of tHcy, and methylation and vitamin markers were measured in 116 blood samples. The concentrations of the extracellular soluble receptor for advanced glycated end products (esRAGE) were measured in 77 aqueous humor samples. **Results:** Mean aqueous humor concentration of esRAGE and that of plasma tHcy did not differ significantly between the groups. Arterial hypertension but not eye disease explained the tHcy elevation in plasma in this study. In the cataract group, a significant negative correlation was found between plasma tHcy and that of esRAGE in aqueous humor ($r=-0.483$, $p=0.006$). In patients with dry AMD, the concentration of esRAGE in aqueous humor correlated negatively to tHcy and positively to serum folate. **Conclusions:** Plasma tHcy levels were positively associated with hypertension, but not with AMD in this study. Higher esRAGE in aqueous humor was related to higher folate and lower tHcy in blood. Following studies may assess whether B-vitamins can protect against age-related ocular diseases by reducing glycation.

PMID: 23152422 [PubMed - as supplied by publisher]

Methods Mol Biol. 2013;935:227-43. doi: 10.1007/978-1-62703-080-9_16.

Assessment of mitochondrial damage in retinal cells and tissues using quantitative polymerase chain reaction for mitochondrial DNA damage and extracellular flux assay for mitochondrial respiration activity.

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Abstract: Mitochondrial dysfunction and genomic instability are associated with a number of retinal pathologies including age-related macular degeneration, diabetic retinopathy, and glaucoma. Consequences of mitochondrial dysfunction within cells include elevation of the rate of ROS production due to damage of electron transport chain proteins, mitochondrial DNA (mtDNA) damage, and loss of metabolic capacity. Here we introduce the quantitative polymerase chain reaction assay (QPCR) and extracellular flux assay (XF) as powerful techniques to study mitochondrial behavior. The QPCR technique is a gene-specific assay developed to analyze the DNA damage repair response in mitochondrial and nuclear genomes. QPCR has proved particularly valuable for the measurement of oxidative-induced mtDNA damage and kinetics of mtDNA repair. To assess the functional consequence of mitochondrial oxidative damage, real-time changes in cellular bioenergetics of cell monolayers can be measured with a Seahorse Biosciences XF24 analyzer. The advantages and limitations of these procedures will be discussed and detailed methodologies provided with particular emphasis on retinal oxidative stress.

PMID: 23150372 [PubMed - in process]

Genetics

PLoS Genet. 2012 Nov;8(11):e1003032. doi: 10.1371/journal.pgen.1003032. Epub 2012 Nov 8.

Informed conditioning on clinical covariates increases power in case-control association studies.

Zaitlen N, Lindström S, Pasaniuc B, Cornelis M, Genovese G, Pollack S, Barton A, Bickeböller H, Bowden DW, Eyre S, Freedman BI, Friedman DJ, Field JK, Groop L, Haugen A, Heinrich J, Henderson BE, Hicks PJ, Hocking LJ, Kolonel LN, Landi MT, Langefeld CD, Le Marchand L, Meister M, Morgan AW, Raji OY, Risch A, Rosenberger A, Scherf D, Steer S, Walshaw M, Waters KM, Wilson AG, Wordsworth P, Zienolddiny S, Tchetgen ET, Haiman C, Hunter DJ, Plenge RM, Worthington J, Christiani DC, Schaumborg DA, Chasman DI, Altshuler D, Voight B, Kraft P, Patterson N, Price AL.

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Abstract: Genetic case-control association studies often include data on clinical covariates, such as body mass index (BMI), smoking status, or age, that may modify the underlying genetic risk of case or control samples. For example, in type 2 diabetes, odds ratios for established variants estimated from low-BMI cases are larger than those estimated from high-BMI cases. An unanswered question is how to use this information to maximize statistical power in case-control studies that ascertain individuals on the basis of phenotype (case-control ascertainment) or phenotype and clinical covariates (case-control-covariate ascertainment). While current approaches improve power in studies with random ascertainment, they often lose power under case-control ascertainment and fail to capture available power increases under case-control-covariate ascertainment.

We show that an informed conditioning approach, based on the liability threshold model with parameters informed by external epidemiological information, fully accounts for disease prevalence and non-random ascertainment of phenotype as well as covariates and provides a substantial increase in power while maintaining a properly controlled false-positive rate. Our method outperforms standard case-control association tests with or without covariates, tests of gene x covariate interaction, and previously proposed tests for dealing with covariates in ascertained data, with especially large improvements in the case of case-control-covariate ascertainment. We investigate empirical case-control studies of type 2 diabetes, prostate cancer, lung cancer, breast cancer, rheumatoid arthritis, age-related macular degeneration, and end-stage kidney disease over a total of 89,726 samples. In these datasets, informed conditioning outperforms logistic regression for 115 of the 157 known associated variants investigated ($P\text{-value} = 1 \times 10^{-9}$). The

improvement varied across diseases with a 16% median increase in χ^2 test statistics and a commensurate increase in power. This suggests that applying our method to existing and future association studies of these diseases may identify novel disease loci.

PMID: 23144628 [PubMed - in process] PMCID: PMC3493452

Epidemiology

Br J Ophthalmol. 2012 Nov 10. [Epub ahead of print]

Is sunlight exposure a risk factor for age-related macular degeneration? A systematic review and meta-analysis.

Sui GY, Liu GC, Liu GY, Gao YY, Deng Y, Wang WY, Tong SH, Wang L.

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BACKGROUND: Epidemiologists have recently investigated sunlight exposure as a risk factor for age-related macular degeneration (AMD), but there remains an ongoing dispute over this association due to insufficient evidence and unreliable data.

OBJECTIVES: To analyse comprehensively the epidemiological literature concerning the association between AMD and sunlight exposure.

METHODS: We systematically reviewed the epidemiological literature concerning the association between AMD and sunlight exposure. An electronic search was performed of PubMed, Web of Science and CNKI, which was supplemented by hand searching. The selection of studies, data abstraction and quality assessment were performed independently by three reviewers. After these steps, we performed a random-effects meta-analysis, followed by subgroup analysis and sensitivity analysis, including a random-effects meta-regression for study-specific covariates.

RESULTS: Fourteen studies were identified. Twelve studies identified an increasing risk of AMD with greater sunlight exposure, six of which reported significant risks. The pooled OR was 1.379 (95% CI 1.091 to 1.745). The subgroup of non-population-based studies revealed a significant risk (OR 2.018, 1.248 to 3.265, $p=0.004$). We identified the gross domestic product (GDP) per capita ($p=0.048$), but not the latitude ($p=0.21$), as a factor that led to heterogeneity according to the meta-regression.

CONCLUSIONS: The epidemiological literature published to date indicates that individuals with more sunlight exposure are at a significantly increased risk of AMD. The OR significantly decreased with increasing GDP per capita.

PMID: 23143904 [PubMed - as supplied by publisher]

Ophthalmology. 2012 Nov 10. pii: S0161-6420(12)00740-3. doi: 10.1016/j.ophtha.2012.07.077. [Epub ahead of print]

Vision Impairment and Major Causes of Vision Loss Impacts on Vision-Specific Functioning Independent of Socioeconomic Factors.

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PURPOSE: To quantify the eye disease-specific impact of unilateral and bilateral vision impairment (VI) on

vision-specific functioning (VF).

DESIGN: The Singapore Indian Eye population-based study.

PARTICIPANTS: Ethnic Indians older than 40 years of age living in Singapore.

METHODS: Participants underwent standardized ophthalmic assessments for VI and blindness, defined using presenting visual acuity (United States definition). Sociodemographic data were recorded using a standardized questionnaire. Rasch analysis was used to validate the Visual Function Index 11 and to determine its psychometric properties. The major causes of VI (i.e., cataract, refractive error, age-related macular degeneration, diabetic retinopathy [DR], and glaucoma) were determined by ophthalmologists on examination. Multivariate linear regression analysis was performed to assess the impact of VI on the overall VF Rasch score.

MAIN OUTCOME MEASURES: Vision-specific functioning.

RESULTS: Three thousand three hundred ninety-six persons were analyzed. Participants with VI had a systematic reduction in VF score compared with those with normal vision in both eyes, ranging from -11.2% normal vision in one eye and low vision in the other eye (95% confidence interval [CI], -12.2% to -10.3%; $P < 0.001$), to -12.7% blindness in one eye and normal vision in the other eye (CI, -15.1% to -10.4%; $P < 0.001$), to -19.4% low vision in both eyes (CI, -20.8% to -18.1%; $P < 0.001$), to -52.9% blindness in one eye and low vision in other eye (CI, -55.3% to -50.4%; $P < 0.001$), to -77.2% blindness in both eyes (CI, -82.4% to -72.0%; $P < 0.001$). The impact of VI on VF score varied across different major causes of vision loss, regardless of socioeconomic factors. Vision impairment attributed to cataract in one or both eyes had a significant decrease in VF score by 17.7% and 22.3%, respectively, compared with those with normal vision in both eyes ($P < 0.001$). The impact of unilateral and bilateral VI on VF score was greater in participants with glaucoma (32.2% in unilateral cases and 35.9% in bilateral cases; $P < 0.001$) and DR (29.4% in unilateral cases and 33.3% in bilateral cases; $P < 0.001$).

CONCLUSIONS: Vision impairment and major age-related eye diseases such as cataract, DR, and glaucoma are associated significantly with worse deterioration in VF, regardless of education level, literacy adequacy, or immigration pattern. Glaucoma and DR seemed to have a greater negative impact on VF score compared with cataract. This study highlights the importance of disease-specific interventions in reducing the adverse impact of VI on daily activities.

PMID: 23149127 [PubMed - as supplied by publisher]

Diet

Cochrane Database Syst Rev. 2012 Nov 14;11:CD010015. doi: 10.1002/14651858.CD010015.pub2.

Omega 3 fatty acids for preventing or slowing the progression of age-related macular degeneration.

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BACKGROUND: Evidence from animal models and observational studies in humans has suggested that there is an inverse relationship between dietary intake of omega 3 long-chain polyunsaturated fatty acids (LCPUFA) and risk of developing age-related macular degeneration (AMD) or progressing to advanced AMD.

OBJECTIVES: To review the evidence that increasing the levels of omega 3 LCPUFA in the diet (either by eating more foods rich in omega 3 or by taking nutritional supplements) prevents AMD or slows the progression of AMD.

SEARCH METHODS: We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (The Cochrane Library 2012, Issue 4), MEDLINE (January 1950 to April 2012), EMBASE (January 1980 to April 2012), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to April 2012), the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictip/search/en). We did not use any date or language restrictions in the electronic searches for trials. The electronic databases were last searched on 26 April 2012.

SELECTION CRITERIA: We planned to include randomised controlled trials (RCTs) where increased dietary intake of omega 3 fatty acids was compared to placebo or no intervention with the aim of preventing the development of AMD, or slowing its progression.

DATA COLLECTION AND ANALYSIS: Both authors independently screened titles, abstracts and full-texts of articles to identify studies for inclusion and analysis.

MAIN RESULTS: No trials met the selection criteria. The results of a large, multi-centre, randomised trial (AREDS2) that will assess the effects of oral supplementation with omega 3 LCPUFA on progression to advanced AMD are expected in 2013. Two further trials are also ongoing.

AUTHORS' CONCLUSIONS: Until data from RCTs become available for analysis, there is currently no evidence to support increasing levels of omega 3 LCPUFA in the diet for the explicit purpose of preventing or slowing the progression of AMD.

PMID: 23152282 [PubMed - in process]

Cochrane Database Syst Rev. 2012 Nov 14;11:CD000254. doi: 10.1002/14651858.CD000254.pub3.

Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration.

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BACKGROUND: It has been proposed that antioxidants may prevent cellular damage in the retina by reacting with free radicals that are produced in the process of light absorption. Higher dietary levels of antioxidant vitamins and minerals may reduce the risk of progression of age-related macular degeneration (AMD).

OBJECTIVES: The objective of this review was to assess the effects of antioxidant vitamin or mineral supplementation on the progression of AMD in people with AMD.

SEARCH METHODS: We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (The Cochrane Library 2012, Issue 8), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to August 2012), EMBASE (January 1980 to August 2012), Allied and Complementary Medicine Database (AMED) (January 1985 to August 2012), OpenGrey (System for Information on Grey Literature in Europe) (www.opengrey.eu/), the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictip/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 20 August 2012. We searched the reference lists of identified reports and the Science Citation Index. We contacted investigators and experts in the field for details of unpublished studies. We also searched for systematic reviews of harms of vitamin supplements.

SELECTION CRITERIA: We included randomised trials comparing antioxidant vitamin or mineral

supplementation (alone or in combination) to placebo or no intervention in people with AMD.

DATA COLLECTION AND ANALYSIS: Two authors assessed risk of bias and extracted data from the included trials. Where appropriate, we pooled data using a random-effects model unless three or fewer trials were available in which case we used a fixed-effect model.

MAIN RESULTS: Thirteen trials (6150 participants) were included in this review. Over half the participants (3640) were randomised in one trial (AREDS in the USA), which found a beneficial effect of antioxidant (beta-carotene, vitamin C and vitamin E) and zinc supplementation on progression to advanced AMD (adjusted odds ratio (OR) 0.68, 95% confidence interval (CI) 0.53 to 0.87) over an average of 6.3 years. People taking supplements were less likely to lose 15 or more letters of visual acuity (adjusted OR 0.77, 95% CI 0.62 to 0.96). The other trials, in general, had shorter follow-up (less than two years). No evidence for an effect of supplementation was seen in these smaller trials of shorter duration. Overall we considered the strength of the evidence to be moderate. We did not consider included trials, in general, to be at risk of bias, although we found it difficult to assess reporting biases. The main reason for downgrading the strength of the evidence was because, for several analyses, only one trial was included and therefore consistency of the findings could not be assessed. The included trials reported the following adverse effects: hospitalisation for genito-urinary problems was more common in people taking zinc and yellowing of skin was more common in people taking antioxidants. Systematic searching of the literature identified other potential harms of vitamin supplementation, in particular an increased risk of lung cancer in smokers associated with beta-carotene supplements, but we were unable to identify a good systematic review of the evidence for harms of nutritional supplementation.

AUTHORS' CONCLUSIONS: People with AMD may experience delay in progression of the disease with antioxidant vitamin and mineral supplementation. This finding is drawn from one large trial conducted in a relatively well-nourished American population. The generalisability of these findings to other populations is not known. Although generally regarded as safe, vitamin supplements may have harmful effects. A systematic review of the evidence on harms of vitamin supplements is needed.

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