



City Research Online

City St George's, University of London

Citation: Evans, J. R. & Lawrenson, J. (2014). A review of the evidence for dietary interventions in preventing or slowing the progression of age-related macular degeneration. *Ophthalmic and Physiological Optics*, 34(4), pp. 390-396. doi: 10.1111/opo.12142

This is the accepted version of the paper.

This version of the publication may differ from the final published version. To cite this item please consult the publisher's version.

Permanent repository link: <https://city-ref-test.eprints-hosting.org/id/eprint/4824/>

Link to published version: <https://doi.org/10.1111/opo.12142>

Copyright and Reuse: Copyright and Moral Rights remain with the author(s) and/or copyright holders. Copies of full items can be used for personal research or study, educational, or not-for-profit purposes without prior permission or charge, unless otherwise indicated, provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way. For full details of reuse please refer to [City Research Online policy](#).

Citation

Evans JR, Lawrenson JG. A review of the evidence for dietary interventions in preventing or slowing the progression of age-related macular degeneration. *Ophthalmic Physiol Opt.* 2014 Jul;34(4):390-6. doi: 10.1111/opo.12142. Epub 2014 Jun 5.

A review of the evidence for dietary interventions in preventing or slowing the progression of age-related macular degeneration

Evans, Jennifer R¹, Lawrenson, John G^{2*}

1. International Centre for Eye Health, London School of Hygiene and Tropical Medicine, Keppel St, London WC1E 7HT.
Email: Jennifer.Evans@lshtm.ac.uk
2. Division of Optometry and Visual Science, City University London, Northampton Square, London EC1V 0HB. Email: J.G.Lawrenson@city.ac.uk

* Corresponding author

Running title: Review of dietary interventions for AMD

Keywords: Macular degeneration, vitamins, omega 3 fatty acids

Disclosures: None

Acknowledgements: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. We are grateful to the staff of the Cochrane Eyes and Vision Group for their help in the preparation of the Cochrane Reviews .

Abstract

Purpose: to summarise the results of recent Cochrane systematic reviews that have investigated whether nutritional supplements prevent or slow the progression of AMD.

Recent findings: there is no good evidence from randomised controlled trials (RCTs) that the general population should be taking antioxidant vitamin supplements to reduce their risk of developing AMD later on in life. By contrast, there is moderate quality evidence that people with AMD may experience a delay in progression by taking specific antioxidant vitamin and mineral supplements. This finding is drawn from one large RCT conducted in the USA in a relatively well-nourished population. Although observational studies have shown that the consumption of dietary omega 3 long chain polyunsaturated fatty acids (LCPUFA) may reduce the risk of progression to advanced AMD, two recently published RCTs failed to show any benefit of omega 3 supplements on AMD progression.

Summary: there is no high quality experimental evidence that nutritional supplementation is beneficial for the primary prevention of AMD. However, people with AMD may benefit from supplementation with antioxidant vitamins. 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.

Background

Age-related macular degeneration (AMD) accounts for over 50% of blind and partially sighted registrations in the UK(1), and with an ageing population the prevalence of the disease is predicted to rise exponentially, with an estimated 679,000 cases of late AMD by 2020(2). In addition to the obvious personal impact of AMD, the societal burden is substantial. Economic costs arise from both the direct costs of treatment as well as indirect costs associated with visual impairment, including the provision of social care(3). The cumulative direct and indirect cost for the UK over the decade 2010 to 2020 has been estimated to be more than £16.4 billion(4).

Although effective treatments in the form of vascular endothelial growth factor inhibitors are available that can slow the progression of the neovascular form of the disease, there is still no effective treatment for atrophic AMD, which affects the majority of AMD sufferers. It is likely that the pathogenesis of AMD is multi-factorial, arising from a complex interplay between genetic and environmental factors. Significantly, a number of gene polymorphisms have been identified which appear to increase an individual's susceptibility to environmental risk factors (reviewed in Ding et al(5)). Smoking has been consistently reported as a major risk factor for AMD. Current smoking increases the risk of AMD approximately two-fold(6) and the finding of a dose-response relationship between the number of 'pack years' smoked and a lower risk in past smokers would suggest that smoking cessation may be an effective strategy for AMD prevention and control. The role of diet and nutrition has also attracted significant interest. Observational studies have reported that particular dietary components such as omega-3 fatty acids, carotenoids, antioxidant vitamins or diets with a lower glycaemic index can reduce the risk of developing AMD or slow its progression (see (7) for a recent review). However, these results from non-experimental studies should always be interpreted with caution, since people with a diet rich in particular nutrients may differ in other ways from those who do not. Nonetheless, these data have been used as the basis for promoting nutritional supplements for eye health, which contain high doses of specific micronutrients. These products are targeted at the general population and are also widely recommended by eye healthcare professionals for people who have signs of AMD(8). The aim of this review is to summarise the results of recent Cochrane systematic reviews that have specifically investigated whether nutritional supplements prevent or slow the progression of AMD. The review will also consider the risk of adverse effects associated with these supplements.

Antioxidant vitamin and mineral supplements

The “free radical theory of ageing” proposes that the rate of ageing is, in part, determined by the ability of organisms to deal with the harmful effects of metabolites of molecular oxygen, known as reactive oxygen species or free radicals (reviewed in (9)). AMD is an age-related degenerative condition. The retina is thought to be under oxidative stress due to the action of light on the photoreceptors which generate free radicals. The hypothesis is that AMD develops, in part, because of the cumulative effects of oxidative stress and that antioxidants may be important in its prevention (reviewed in (10)).

There are two key questions: should the general population take antioxidant supplements to reduce the risk of developing AMD later on in life (primary prevention) or should people with AMD take antioxidant supplements to slow down the progression of the disease (secondary prevention).

Primary prevention

The Cochrane review “Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration” was last updated in 2012(11). The review includes four trials that randomised 62,520 people in total. The trials were conducted in Australia, Finland and the USA and investigated vitamin E and beta-carotene supplements. Overall the quality of the evidence was high. People who took these supplements were not at decreased (or increased) risk of developing AMD. The pooled risk ratio for any antioxidant supplement in the prevention of any AMD was 0.98 (95% confidence interval (CI) 0.89 to 1.08) (Figure 1).

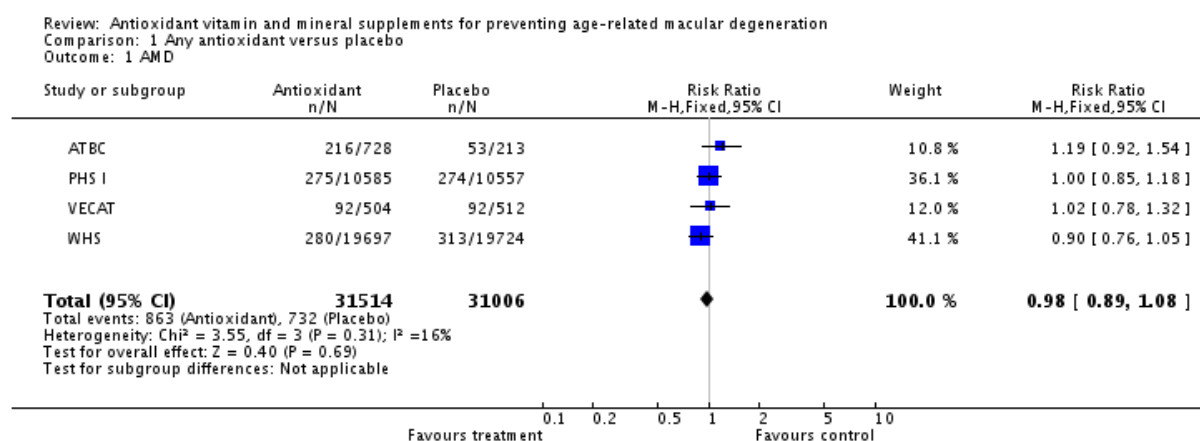


Figure 1. Forest plot of trials comparing the effect of antioxidant vitamins on the development of any AMD. In this meta-analysis a fixed effects approach was used and the weighted risk ratios were calculated using the Mantel-Haenszel (M-H) method.

There were fewer cases of advanced AMD and the estimate of effect was therefore less certain 1.05 (95% CI 0.80 to 1.39) (Figure 2) however there is little support for the hypothesis that these supplements prevent the development of AMD. Similar results were seen when the analyses were done separately for beta-carotene and vitamin E.

Since this review was last updated the results of the Physicians Health Study (PHS) II have been published(12). The PHS II evaluated a daily multivitamin supplement, Centrum Silver, which includes antioxidant vitamins (A, C, E, zinc and lutein) as well as a number of other vitamins and minerals (for a full list of ingredients see (13)). PHS II was set up to evaluate the effects on prevention of cancer and CVD but cataract and AMD were pre-specified secondary end points. AMD was determined by self-report confirmed by medical record review. A total of 14,641 US male physicians took supplements for an average of 11 years and 281 cases of visually significant AMD were identified during that time (152 cases in the multivitamin group and 129 cases in the placebo group). There was no evidence of any protective effect of this multivitamin supplement on development of AMD (hazard ratio\$ 1.19; 95% CI 0.94 to 1.50). This trial will be included in the next update of the Cochrane review.

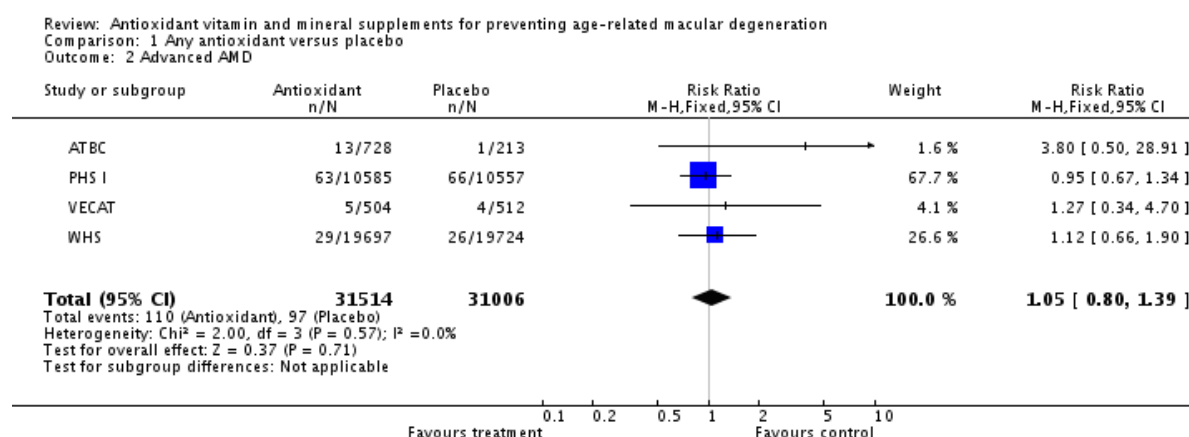


Figure 2. Forest plot of trials comparing the effect of antioxidant vitamins on the development of advanced AMD

In summary, there is good evidence that taking vitamin E or beta-carotene supplements will not prevent or delay the onset of AMD. Furthermore, there is no evidence from randomised controlled trials that other antioxidant supplements, such as vitamin C, lutein and zeaxanthin, or any of the commonly marketed multivitamin combinations will prevent the development of AMD.

Secondary prevention

The Cochrane review “Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration” was also last updated in 2012(14). Compared to the primary prevention review, a larger number of trials were included (n=13) but these were in general smaller with a total of 6,150 participants. Over half the participants (3,640) were randomised in one trial, AREDS in the USA(15), 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% 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 quality of the evidence to be moderate. The main reason for downgrading the assessment of quality was because, for several analyses, only one trial was included and therefore consistency of the findings could not be assessed.

Since the review was last updated, the results of AREDS2 have been published (16). In AREDS2 participants took the AREDS supplement (or a variation of) and were randomly assigned to either omega 3 fatty acids supplements or lutein/zeaxanthin. The study was a factorial design. A total of 4,203 people who had bilateral large drusen or large drusen in one eye and advanced AMD in the fellow eye were followed up for 5 years. The primary analysis found that the addition of lutein and zeaxanthin to the original supplement did not have any detectable effect on progression to advanced AMD (hazard ratio 0.90, 98.7% CI 0.76 to 1.07). However, the authors did some further exploratory analyses on the trial data by comparing those taking and not taking lutein/zeaxanthin (17). These analyses suggested that lutein and zeaxanthin may be a better component of the AREDS formula substituting beta-carotene. AREDS2 will be included in the next update of the Cochrane review.

Adverse effects of antioxidant vitamin supplements

Although generally regarded as safe, vitamin supplements, particularly if high dose, may have harmful effects. Trials, particularly if they are small in size, may not be the best way to assess adverse effects because important adverse effects may occur rarely and trials are usually not large enough to measure rare outcomes.

In the trials of antioxidant vitamins and minerals the best evidence on adverse effects comes from AREDS. The main adverse effect of note was that people taking high-dose zinc were at increased risk of hospital admission due to genitourinary diseases (11.1% versus 7.6% $P = 0.0003$) (18).

The issue of adverse effects has been studied in larger trials for other medical conditions. The ATBC trial found an increased risk of lung cancer associated with beta-carotene supplementation(19), a finding that was repeated in the large CARET trial(25). As a result of the evidence from these trials, people who smoke or have been exposed to asbestos, are advised not to take beta-carotene.

For the last update of the Cochrane reviews on antioxidant vitamins supplements we did a search for reviews of adverse effects. One review did not identify any consistent adverse effects of mineral and vitamin supplements but only included nine RCTs (20). A Cochrane Review investigating antioxidant supplements for preventing all-cause mortality, including 78 trials with 296,707 participants, concluded *"We found no evidence to support antioxidant supplements for primary or secondary prevention. Beta-carotene and vitamin E seem to increase mortality, and so may higher doses of vitamin A"* (21).

Omega 3 fatty acids

Primary and secondary prevention

There is a plausible biological rationale for increasing dietary omega 3 fats in AMD. The omega 3 fatty acid docosahexaenoic acid (DHA) accounts for 50% to 60% of the total fatty acid content of the outer segments of photoreceptors. The constant turnover of outer segment membranes requires a continuous dietary supply of DHA or its precursors and a deficiency may predispose to the development of AMD. Furthermore, omega 3 LCPUFA may also confer protection against the oxidative, inflammatory and vasogenic processes that play a key role in the pathogenesis of AMD(22, 23). Observational studies in humans have reported that the consumption of fish or foods rich in omega 3 long-chain polyunsaturated fatty acids (LCPUFA) could reduce the risk of developing AMD(24-27). Similarly, a nested cohort study within the Age-Related Eye Disease Study (AREDS) found that participants at moderate to high risk of progressing to late AMD, who reported the highest consumption of omega 3 LCPUFA, were 30% less likely to develop geographic atrophy and neovascular AMD when compared to those reporting the lowest consumption(28).

Two randomised controlled trials that specifically investigated whether omega 3 LCPUFA supplementation could decrease the risk of developing advanced AMD were recently published (17, 29). In the Age-related Eye Disease Study 2 (AREDS2), 2080 people aged 50-85, at high risk of progressing to advanced AMD, were randomised to receive a daily dose of DHA (350mg) (N=1068) and eicosapentaenoic acid (EPA) (650mg) or a control supplement (N=1012). The median follow up period was 5 years. In the Nutritional AMD Treatment 2 (NAT-2) study, 263 people aged 55-85 were randomly assigned to receive 840 mg of DHA and 270 mg EPA per day or a placebo for a period of 3 years. In both trials, the main outcome measures were the development of advanced AMD and progression to moderate or worse vision loss (defined as a loss of 15 or more letters on a standard EDTRS chart). The trials, which had a low risk of bias, provided high quality evidence that people taking omega 3 LCPUFA supplements were not at a decreased (or increased) risk of developing advanced AMD. The pooled hazard ratio for progression of AMD (Figure 3) was 0.96 (95% CI 0.84 to 1.10).

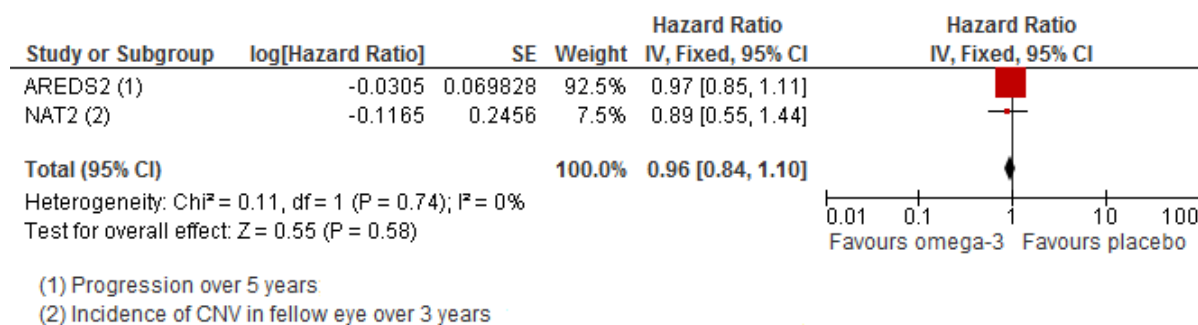


Figure 3. Forest plot of trials comparing the effect of omega 3 fatty acids on progression of AMD. In this meta-analysis the weight assigned to each study is based on the inverse of its variance (IV method).

People taking supplements were similarly no more (or less) likely to lose 15 or more letters of visual acuity (AREDS 2: hazard ratio 0.96 (95% CI, 0.84-1.09); NAT-2 odds ratio 1.15 (95% CI 0.67 to 1.99). No clinically or statistically significant differences in serious adverse outcomes were reported across treatment groups.

Conclusions and future directions

Vitamin supplements, which are widely marketed and consumed by the general population, may have harmful effects. For example, two large trials found an increased risk of lung cancer associated with beta-carotene supplementation. For this reason, it is important to ensure that there is good evidence to support the use of vitamin supplements for either primary or secondary prevention of AMD. Based on the results from RCTs, there is currently no good evidence that the general population should take any of the commonly marketed nutritional supplements to prevent the development of AMD. By contrast, people with AMD may experience a modest delay in progression of the disease with specific antioxidant vitamin and mineral supplementation. This finding is drawn from one large RCT conducted in the USA in a relatively well-nourished population(15). The recently published AREDS2 trial (17) reported that the addition of the carotenoids lutein and zeaxanthin to the original supplement did not provide any further benefit.

A critique of the current literature on whether or not people with AMD should take antioxidant supplements is that recommendations are primarily based on the results of one study – the AREDS study in the USA. Although other trials have been done they have generally been small and of short duration with inconclusive results. Further large scale and simple randomised controlled trials need to be done in this area. Trialists need to report an agreed core set of outcomes to enable the results of studies to be combined in systematic reviews (30). The use of nutritional supplements is an important question and better evidence supporting their use in patients with AMD is needed.

Although observational studies have shown that the consumption of omega 3 LCPUFA may confer protection against AMD and reduce the risk of progression to advanced AMD, this is not supported by published RCTs, which have failed to show any benefit of omega 3 supplements on progression to advanced AMD. Therefore, there is currently no high quality evidence to support increasing levels of omega 3 LCPUFA in the diet for the explicit purpose of preventing or slowing the progression of AMD.

The data presented in this review were based only on RCTs where single micronutrients or particular combinations of antioxidants were compared to placebo. These trials do not address the overall impact of the diet on the development or progression of AMD. The role of diet may be complex, and it is possible that dietary patterns are important (31). Randomised controlled trials may not be a feasible study design for testing the effects of dietary patterns and therefore data from observational (non-randomised) studies will need to be used. The interpretation of observational studies can be problematic since these study designs are more prone to bias and confounding. There is a need for a regularly updated systematic review of the evidence from good quality prospective cohort studies, where researchers have attempted to control for known confounders, to add to the evidence base for the association between diet and AMD.

References

1. Bunce C, Xing W, Wormald R. Causes of blind and partial sight certifications in England and Wales: April 2007-March 2008. *Eye*. 2010;24:1692-9.
2. Owen CG, Jarrar Z, Wormald R, Cook DG, Fletcher AE, Rudnicka AR. The estimated prevalence and incidence of late stage age related macular degeneration in the UK. *Br J Ophthalmol* 2012; 96:752-6.
3. Cruess AF, Zlateva G, Xu X, Soubrane G, Pauleikhoff D, Lotery A, et al. Economic burden of bilateral neovascular age-related macular degeneration: multi-country observational study. *Pharmacoeconomics* 2008;26:57-73.
4. Minassian DR, A. . Epidemiological and economic model for sight loss in the decade 2010-2020. Report prepared for the RNIB. : RNIB 2009. Available from: http://www.rnib.org.uk/aboutus/Research/reports/2009andearlier/FSUK_Summary_2.pdf, accessed 26/2/14.

5. Ding X, Patel M, Chan CC. Molecular pathology of age-related macular degeneration. *Prog Retin Eye Res.* 2009;28(1):1-18.
6. Cong R, Zhou B, Sun Q, Gu H, Tang N, Wang B. Smoking and the risk of age-related macular degeneration: a meta-analysis. *Ann Epidemiol* 2008;18:647-56.
7. Weikel KA, Chiu CJ, Taylor A. Nutritional modulation of age-related macular degeneration. *Mol Aspects Med* 2012;33:318-75.
8. Lawrenson JG, Evans JR. Advice about diet and smoking for people with or at risk of age-related macular degeneration: a cross-sectional survey of eye care professionals in the UK. *BMC Public Health.* 2013;13:564.
9. Finkel T, Holbrook NJ. Oxidants, oxidative stress and the biology of ageing. *Nature* 2000;408:239-47.
10. Gerster H. Review: antioxidant protection of the ageing macula. *Age Ageing* 1991;20:60-9.
11. Evans JR, Lawrenson JG. Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration. *Cochrane Database Syst Rev* 2012;6:CD000253.
12. Christen WG, Glynn RJ, Manson JE, Macfadyen J, Bubes V, Schvartz M, et al. Effects of multivitamin supplement on cataract and age-related macular degeneration in a randomized trial of male physicians. *Ophthalmol* 2014;121:525-34.
13. Centrum. Available from: www.centrum.com/centrum-silver-adults-50-plus#tablets, accessed 26/2/14.
14. Evans JR, Lawrenson JG. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. *Cochrane Database Syst Rev* 2012;11:CD000254.
15. Age-Related Eye Disease Study Research G. 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. *Arch Ophthalmol* 2001;119:1417-36.
16. Age-Related Eye Disease Study 2 Research G. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. *JAMA* 2013;309:2005-15.

17. Age-Related Eye Disease Study 2 Research G, Chew EY, Clemons TE, Sangiovanni JP, Danis RP, Ferris FL, 3rd, et al. Secondary Analyses of the Effects of Lutein/Zeaxanthin on Age-Related Macular Degeneration Progression: AREDS2 Report No. 3. *JAMA Ophthalmol* 2014;132:142-9.
18. Johnson AR, Munoz A, Gottlieb JL, Jarrard DF. High dose zinc increases hospital admissions due to genitourinary complications. *J Urol* 2007;177:639-43.
19. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. *N Engl J Med*. 1994;330:1029-35.
20. Omenn GS. Chemoprevention of lung cancers: lessons from CARET, the beta-carotene and retinol efficacy trial, and prospects for the future. *Eur J Cancer Prev* 2007;16:184-91.
21. Hodge WG, Schachter HM, Barnes D, Pan Y, Lowcock EC, Zhang L, et al. Efficacy of omega-3 fatty acids in preventing age-related macular degeneration: a systematic review. *Ophthalmol* 2006;113:1165-72.
22. Huang HY, Caballero B, Chang S, Alberg AJ, Semba RD, Schneyer CR, et al. The efficacy and safety of multivitamin and mineral supplement use to prevent cancer and chronic disease in adults: a systematic review for a National Institutes of Health state-of-the-science conference. *Ann Int Med* 2006;145:372-85.
23. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. *Cochrane Database Syst Rev* 2012;3:CD007176.
24. Kishan AU, Modjtahedi BS, Martins EN, Modjtahedi SP, Morse LS. Lipids and age-related macular degeneration. *Surv Ophthalmol* 2011;56:195-213.
25. SanGiovanni JP, Chew EY. The role of omega-3 long-chain polyunsaturated fatty acids in health and disease of the retina. *Prog Ret Eye Res* 2005;24:87-138.
26. Chong EW, Robman LD, Simpson JA, Hodge AM, Aung KZ, Dolphin TK, et al. Fat consumption and its association with age-related macular degeneration. *Arch Ophthalmol* 2009;127:674-80.
27. Christen WG, Schaumberg DA, Glynn RJ, Buring JE. Dietary omega-3 fatty acid and fish intake and incident age-related macular degeneration in women. *Arch Ophthalmol* 2011;129:921-9.

28. Tan JS, Wang JJ, Flood V, Mitchell P. Dietary fatty acids and the 10-year incidence of age-related macular degeneration: the Blue Mountains Eye Study. *Arch Ophthalmol* 2009;127:656-65.
29. Souied EH, Delcourt C, Querques G, Bassols A, Merle B, Zourdani A, et al. Oral docosahexaenoic acid in the prevention of exudative age-related macular degeneration: the Nutritional AMD Treatment 2 study. *Ophthalmol* 2013;120:1619-31.
30. Kirkham JJ, Gargon E, Clarke M, Williamson PR. Can a core outcome set improve the quality of systematic reviews?--a survey of the Co-ordinating Editors of Cochrane Review Groups. *Trials*. 2013;14:21.
31. Mares JA, Voland RP, Sondel SA, Millen AE, Larowe T, Moeller SM, et al. Healthy lifestyles related to subsequent prevalence of age-related macular degeneration. *Arch Ophthalmol* 2011;129:470-80.