

Review Article

Food components and ocular pathophysiology: a critical appraisal of the role of oxidative mechanisms

Reinlesh Raman MND¹, Ehsan Vaghefi PhD², Andrea J Braakhuis PhD¹

¹*Discipline of Nutrition, Faculty of Medical and Health Sciences, the University of Auckland, New Zealand*

²*Department of Optometry and Vision Science, Faculty of Medical and Health Science, the University of Auckland, New Zealand*

Background and Objectives: Three of the major ocular diseases, namely cataracts, age-related macular degeneration and glaucoma are associated with oxidative damage. Disease risk and progression may be reduced through consumption of dietary components. To critically examine the literature on dietary and supplemental intakes of fruit and vegetables, meat, antioxidants (vitamins C, E and A), calcium, folate, iron, and their association with ocular disease. **Methods and Study Design:** Google Scholar and key references from texts and publications were searched using search terms (eye disease, antioxidants), (vision, nutrition), no date restriction, only articles in English were included. **Results:** We found probable evidence that dietary intake of fruits and vegetables, and vitamin C lowered incidence of cataracts and age-related macular degeneration. In high supplemental doses, vitamin C increases macular degeneration risk. Vitamin A from food was protective for cataracts and glaucoma, but not in supplemental form. Vitamin A was associated with lower incidence of macular degeneration. We also found probable evidence that higher intakes of meat increased the risk of cataracts and macular degeneration. Dietary calcium and iron appeared protective against glaucoma, but not in supplemental form. **Conclusions:** While a nutrient rich diet high in fruit and vegetables, and associated antioxidants appeared to be protective, we would caution intake of supplementary antioxidants for those with ocular disease.

Key Words: antioxidants, ocular pathology, diet, nutrition, vision

INTRODUCTION

Cataracts (CAT) are the leading cause of visual impairment and blindness worldwide.¹ The total prevalence of visual impairment globally is estimated to be approximately 285 million, of which 39 million are blind. Of this approximately 51% of individuals suffering from blindness are the result of untreated age-related cataract.¹

Age-related macular degeneration (AMD) is the third leading cause of blindness worldwide, however it is the leading cause of blindness in New Zealand and other major countries within the western world.^{2,3} In New Zealand alone, AMD accounts for approximately 48% of blindness registrations among those aged 50 or over.³ The incidence of macular degeneration increases rapidly with age; with around 1 in 4 people over 80 suffering from AMD related visual loss. It is estimated that the number of individuals affected by AMD will rise by 70% by 2030.⁴

Glaucoma (GLA) is the second leading cause of irreversible blindness worldwide, current figures indicate the number of people affected by glaucoma is greater than 70 million.⁵ These figures however may underrepresent the true prevalence of GLA as associated symptoms can remain absent until later stages of pathogenesis. This is supported by population-level surveys indicating only 10 to 50% of participants with GLA are aware they have the disease.⁶

These three ocular diseases induce damage to the eye

through mechanisms of oxidative stress.⁷ Antioxidants are often the body's first line of defence against oxidative stress and are produced both internally and through the diet.⁷ Earlier research by Cao et al⁸ suggested that plasma antioxidant capacity could be increased with consumption of a diet rich in sources of antioxidants, such as fruit and vegetables. The Age-Related Eye Disease Study (AREDS) 1 and 2 showed antioxidant therapy to reduce progression to late AMD by 25%.⁹

Although diets rich in antioxidants have been identified in several studies to reduce the incidence of oxidative stress related eye diseases, various antioxidant supplement studies tend to provide conflicting findings.¹⁰⁻¹³ Conversely, the dietary intake of meat and related micro-nutrients such as cholesterol has been identified in various studies to increase the risk of oxidative stress related eye conditions.¹⁴⁻¹⁷ The impact of diet on the risk of oxidative-stress related eye diseases has been examined previously,¹⁷ but typically address the effect of antioxidant

Corresponding Author: Dr Andrea Braakhuis, The University of Auckland, Faculty of Medical and Health Science, Level 2, Room 504-202, 85 Park Road, Auckland 1023, Grafton, New Zealand.

Tel: +64 9 923 6251; Fax: +64 9 923 1023

Email: a.braakhuis@auckland.ac.nz

Manuscript received 21 January 2016. Initial review completed 29 January 2016. Revision accepted 28 March 2016.

doi: 10.6133/apjcn.082016.01

supplements or fruit and vegetables in isolation, rather than total dietary intake.¹⁸

This aim of this review was to examine the literature on the association between dietary intake and the risk of oxidative-stress related eye conditions taking a whole diet approach.

METHODS

Google Scholar and key references from texts and publications were searched using search terms (eye disease, antioxidants), (vision, nutrition), no date restriction, only articles in English were included. Research involving case-control, observational and randomised control design were included, if they investigated food components (including vitamins C, E, A, calcium, folate, iron) and its derivatives or fruit and vegetable intake on the incidence of ocular disease (CAT, AMD, GLA). Ethical approval was not required.

RESULTS AND DISCUSSION

Oxidative stress and the pathophysiology of cataracts

The pathogenesis of cataracts is poorly understood, however oxidative stress appears to aid the progression of age-related cataracts by facilitating damage to cellular components and accumulating advanced glycation end products (AGEs).¹⁹ AGEs induce conformational changes in lens protein causing increased opacity.

The role of diet in cataracts

Participants with diets highest in fruit and vegetable intake appear to be at the lowest risk of cataracts (all types).^{17,20-22} Three studies using a case-control design demonstrated fruit and vegetables lower CAT risk, as seen by Jacques and Chylack²¹ (OR=0.57) or independent of each other as seen by Theodoropoulou et al¹⁷ (OR=0.53; OR=0.47 respectively). Tavani, Negri and La Vecchia²² further highlight the reduced risk of cataracts with individual fruit and vegetable items such as spinach (OR=0.6), peppers (OR=0.7), and citrus fruit (OR=0.5) (See Table 1).

Higher intakes of meat conversely appear to increase the risk of cataracts. This is observed in research by Theodoropoulou et al¹⁷ where participants with the highest meat intake had the greatest risk of cataracts (all types) (OR=1.46), and research by Appleby, Allen and Key¹⁴ where the risk of cataracts decreased with progressively lower intakes of meat (See Table 2).

The protective association identified between higher intakes of fruit and vegetables with reduced risk of cataracts may be attributed to their composition, as they are dietary sources rich in antioxidants. Antioxidants have a key role in reduction of oxidative stress by inhibition of oxidative reactions and removal of free radical intermediates.²³

Higher dietary consumptions of vitamins C and E either in isolation or combined, are most consistently observed with reduced risk of cataracts (see Table 3). In two case-control studies, high vitamin C consumption reduced CAT risk (OR=0.4 and 0.3 respectively).^{17,24} The protective impact of a high vitamin E intake in comparison was best observed by Robertson, Donner and Trevithick²⁵ and Tavani et al²² both presenting odds ratio

of 0.5 and 0.5 respectively. Supplemental intake of vitamins C and E in the prevention of CAT were also addressed by Robertson et al²⁵ showing reduced risk across three groups assessed (excluding controls) of: vitamin C (approximately 300–600 mg) only (OR=0.3), vitamin E (approximately 400 mg) only (OR=0.44), and a combination of the two (OR=0.32).²⁵ In addition Jacques and Chylack²¹ identified that participants with a low intake of vitamin C were more likely to develop cortical or posterior subcapsular cataracts (PSC CAT) (OR=3.7 and 11.0 respectively). Those with a low plasma vitamin C status in this study were at a greater risk of CAT (OR=11.3), as with participants that had low plasma carotene (OR=7.2). Of cohort studies examined Tan et al²⁶ and Jacques et al²⁷ identified participants with the highest quintile of vitamin C intake had the lowest odds ratio (OR=0.55 and 0.31 respectively) of developing CAT of nuclear origin (see Table 3).

Tan et al²⁶ further identified that participants with a median intake of combined antioxidants (vitamins C and E, zinc and β -carotene) had a reduced risk of nuclear CAT by 49% (OR=0.51). Jacques et al²⁷ showed in a separate study that only vitamin C had a significant association with a reduced risk of developing nuclear CAT after adjusting for vitamin E, riboflavin, folate, β -carotene, and lutein and zeaxanthin. Supplement use was assessed by Jacques et al²⁷ and Hankinson et al²⁸ with findings from both studies suggesting greater than 10-year use of vitamin C supplements are associated with decreased risk of nuclear CAT by 45% (OR=0.55) and 64% (OR=0.36) respectively. The findings in Jacques et al,²⁷ however were only applicable to female participants. Although greater than 10 year supplementation of vitamin C provided similar results between Hankinson et al²⁸ and Jacques et al²⁷ the overall findings by Hankinson et al²⁸ were vastly different than the other cohort studies. Hankinson et al²⁸ suggested that there was no association between the dietary intake of vitamins C, E and riboflavin with nuclear opacities, while a high intake of carotenoids is inversely associated with nuclear opacities (OR=0.61).

Jacques et al²⁹ examined the impact of long term vitamin C supplements use on age-related lens opacities from a sample of the nurses health study cohort also used by Jacques et al²⁷ and Hankinson et al.²⁸ Findings suggest the use of vitamin C supplements is associated with a 77% lower prevalence of early lens opacities (OR=0.23) and 83% lower prevalence of moderate lens opacities at any lens site.²⁹ A cross-sectional design was employed by Ravindran et al³⁰ examining the association between plasma vitamin C status and CAT, with findings suggesting an inverse relationship between plasma vitamin C and CAT (OR=0.61), with minor attenuation upon inclusion of other antioxidants such as lutein and zeaxanthin, retinol, β -carotene (OR=0.68). These findings for an inverse association with vitamin C and CAT are present across all three types with nuclear (OR=0.66), cortical (OR=0.7) and PSC (OR=0.58) presenting reduced risk.³⁰

Two randomised control trials were evaluated with conflicting findings around vitamin E supplementation. Seth and Kharb³¹ examined the impact of antioxidant supplementation on participants diagnosed with CAT of both

Table 1. Table identifying key characteristics, associations, and findings of Fruits and Vegetables and ocular pathology, listed from beneficial to harmful effects, each disease type separated

Author	Ocular disease examined	Study design and sample size	Participant age (yrs.)	Method of data collection	Key findings
Theodoropoulou, 2014 ¹⁷	CAT: CX, PSC, NUC	Case-control Cases=314 Controls=314	Between 45-85	Dietary FFQ	↓ risk CAT (all types) with high consumption of fruits (OR=0.53; 95% CI: 0.39, 0.72; $p<0.001$), and vegetables (OR=0.47; 95% CI: 0.38, 0.59; $p<0.001$)
Jacques, 1991 ²¹	CAT: CX, PSC, NUC, both or either lens	Case-control Cases=77 Controls=35	Between 40-89	Plasma levels and Dietary FFQ for of vitamin C, E, and carotenoids	↑ risk CAT (any) with ≤ 1.5 servings/day of fruits (OR=3.4), ≤ 2.0 servings/day of vegetables (OR=3.6), and ≤ 3.5 servings/day of fruits and/or vegetables (OR=5.7)
Tavani, 1996 ²²	CAT	Case-control Cases=207 Controls=706	Median age Cases=63, Controls=62	Dietary FFQ	↓ risk CAT with higher intakes of cruciferae (OR=0.5; 95% CI: 0.3,0.8; $p<0.001$), spinach (OR=0.6; 95% CI: 0.4, 0.9; $p<0.005$), tomatoes (OR=0.5; 95% CI: 0.4, 0.8; $p<0.001$), peppers (OR=0.7; 95% CI:0.4, 1.1, $p<0.05$), citrus fruit (OR=0.5; 95% CI: 0.2, 1.3, $p<0.001$), and melon (OR=0.5; 95% CI: 0.4, 0.8, $p<0.001$)
Coleman, 2008 ⁴⁷	Glaucoma	Cross-sectional cohort n=1,155, with 95 developing GLA	Mean age=79.4	Dietary FFQ	Statistically non-significant ↓ risk of GLA with ≥ 3 servings/day of all fruits and fruit juices (OR=0.98; 95% CI: 0.44, 2.19; $p=0.963$). Statistically non-significant ↑ risk of GLAU with ≥ 3 servings/day of all vegetables (OR=1.44; 95% CI: 0.47, 4.36; $p=0.524$).
Giaconi, 2012 ⁴⁸	Glaucoma	Cross-sectional study n=584, with 77 developing GLA	Mean age=75.3	Dietary FFQ	↓ risk of GLA with ≥ 3 servings/day of all fruits and fruit juices (OR=0.21; 95% CI: 0.08, 0.60; $p=0.023$). Statistically non-significant ↓ risk of GLA with ≥ 3 servings/day of all vegetables (OR=0.97; 95% CI:0.37, 2.54; $p=0.965$)
Seddon, 1994 ³⁷	AMD	Case-control Cases=356 Controls=350	Mean age Cases=71 Controls=68	Dietary FFQ	↓ risk of AMD with higher frequency of consumption/week of spinach or collard greens (OR=0.12, 95% CI: 0.01, 0.09; $p<0.001$)
Vanden Langenberg, 1998 ³⁵	AMD	Retrospective cohort n=1,586	Ages 43-84 y	Dietary FFQ	↓ risk of large drusen with high past intake of fruits and vegetables (OR=0.47; 95% CI: 0.2,1.0; $p<0.05$). Statistically non-significant ↓ risk of large drusen with high baseline intakes of fruits and vegetables (OR=0.77; 95% CI: 0.4,1.7). Statistically non-significant
Cho, 2004 ³⁶	AMD	Prospective cohort n=77,562 women and 40,866 men, with 464 total cases of AMD after follow up (up to 18 years)	≥ 50	Dietary FFQ	↓ risk of AMD with ≥ 3 servings fruit/day (OR=0.64; 95% CI: 0.44, 0.93; $p=0.04$). Similar findings for both sexes.

AMD: age-related macular degeneration; CAT: cataracts; CX: cortical cataracts; PSC: posterior subcapsularcataracts; NUC: nuclear cataracts; GLA: glaucoma; NTG: normal tension glaucoma; FFQ: food frequency questionnaire.

Table 2. Table identifying key characteristics, associations, and findings of meat intake and ocular pathology, listed from beneficial to harmful effects, each disease type separated

Author	Ocular disease examined	Study design and sample size	Participant age (yrs.)	Method of data collection	Key findings
Theodoropoulou, 2014 ¹⁷	CAT: CX, PSC, NUC	Case-control Cases=314 Controls=314	Between 45-85	Dietary FFQ	↑ risk CAT with high meat intake (OR=1.46; 95% CI: 1.17, 1.81; <i>p</i> =0.001)
Appleby, 2011 ¹⁴	CAT	Cohort n=27,670, with 1,484 developing cataracts at follow up	≥40	Dietary FFQ	↓ risk CAT with progressively less daily dietary meat intake seen with moderate intake (50-99 g) (OR=0.96; 95% CI: 0.84, 1.11; <i>p</i> <0.001), low intake (<50 g) (OR=0.85; 95% CI: 0.72, 0.99; <i>p</i> <0.001), fish (OR=0.79; 95% CI: 0.65, 0.97; <i>p</i> <0.001), vegetarian diet (OR=0.7; 95% CI: 0.58, 0.84; <i>p</i> <0.001), and vegan diet (OR=0.6; 95% CI: 0.38, 0.96; <i>p</i> <0.001)
Chong, 2009 ¹⁶	AMD	Cohort n=6,734, with 1,680 cases early AMD, and 77 cases of late AMD at follow up of 9 to 16 years	40-69	Dietary FFQ	↑ risk of early AMD (drusen ≥63 μm) with red meat ≥ 10 times/week (OR=1.47; 95% CI: 1.21, 1.79; <i>p</i> <0.001), fresh meat ≥6.5 times/week (OR=1.34; 95% CI: 1.10, 1.65; <i>p</i> =0.006), and processed meat ≥4 times/week (OR=1.13; 95% CI: 0.94, 1.37; <i>p</i> =0.040). ↑ risk of early AMD (drusen ≥125 μm) with red meat ≥10 times/week (OR=1.39; 95% CI: 1.09, 1.78; <i>p</i> =0.019), fresh meat ≥6.5 times/week (OR=1.31; 95% CI: 1.01, 1.69; <i>p</i> =0.044). ↑ risk of late AMD with chicken ≥3.5 times/week (OR=0.43; 95% CI: 0.20, 0.91; <i>p</i> =0.007)
Ersoy, 2014 ¹⁵	AMD	Case-control Cases=1,147 Controls=1,773	Mean age Cases=77.06 Controls=69.55	Dietary FFQ	↑ risk AMD with red meat intake daily (OR=2.34; 95% CI: 1.610, 3.400; <i>p</i> <0.001) and 2-6x/week (OR=1.67; 95% CI: 1.296, 2.162; <i>p</i> <0.001)

AMD: age-related macular degeneration; CAT: cataracts; CX: cortical cataracts; PSC: posterior subcapsular cataracts; NUC: nuclear cataracts; NTG: normal tension glaucoma; FFQ: food frequency questionnaire.

Table 3. Table identifying key characteristics, associations, and findings of vitamin C, A, and E, and ocular pathology, listed from beneficial to harmful effects, each disease type separated

Author	Ocular disease examined	Study design and sample size	Participant age (yrs.)	Method of data collection	Key findings
Jacques, 1991 ²¹	CAT: CX, PSC, both or either lens	Case-control Cases= 7 Controls=35	40-89	Dietary FFQ, and plasma levels of vitamin C, E, and carotenoids	Plasma level: (OR=11.3; $p<0.10$) PSC with ↓ plasma vitamin C. ↑ risk CX and PSC cataract with ↓ dietary intake (OR=3.7; $p<0.1$) (OR=11.0; $p<0.05$) respectively
Robertson, 1991 ²⁵	CAT	Case-control Cases=152 Controls=152	≥55	Interview regarding supplementation	↓ risk CAT with vitamin C supplementation (OR=0.3; 95% CI: 0.12, 0.75; $p=0.01$), and combined vitamin C and E supplementation (OR=0.32; 95% CI=0.11, 0.99; $p=0.05$)
Theodoropoulou, 2014 ¹⁷	CAT: CX, PSC, NUC	Case-Control Cases= 14 Controls=314	45-85	Dietary FFQ	↓CAT risk with high dietary intake of vitamin C (OR=0.50; 95% CI: 0.39, 0.64; $p<0.001$)
Leske, 1991 ²⁴	CAT: CX, PSC, NUC, Mixed	Case-Control Cases=945 Controls=435	Median age Cases=65.9 Controls=59.7	Dietary FFQ	↓ risk NUC with high dietary intake of vitamin C (OR=0.48; 95% CI; 0.24, 0.99; $p\leq 0.05$) statistically non-significant ↓ risk with high dietary vitamin C intake for PSC (OR=0.73; 95% CI; 0.31, 1.73), CX (OR=0.80; 95% CI; 0.50, 1.29), and mixed CAT (OR=0.72; 95% CI; 0.46, 1.12)
Tan, 2008 ²⁶	CAT: CX, PSC, NUC	Cohort n=2,464, with 389 cases developing cataracts upon follow up (5 or 10 y)	≥49	Dietary FFQ	↓ CAT risk with highest intake of vitamin C (supplements and diet) (OR=0.55; 95% CI: 0.36, 0.86; $p=0.05$), combined above median intake vitamin C, E, β-carotene, and zinc (OR=0.51; 95% CI: 0.34, 0.76; $p=0.0012$)
Jacques, 2001 ²⁷	CAT: NUC	Cohort n=478 women, with 163 developing nuclear opacities after 13-15y	Ages 53-73 with a mean age of 61	Dietary FFQ	↓ risk NUC with higher intake of vitamin C (OR=0.31; 95% CI: 0.16, 0.58; $p=0.003$), and lower nuclear opacity prevalence with longest duration vitamin C supplements use of ≥10y (OR =0.36; 95% CI: 0.18, 0.72; $p=0.04$). ↓ risk cataracts with highest plasma vitamin C concentration (OR=0.54; 95% CI: 0.28, 1.02; $p=0.04$)
Hankinson, 1992 ²⁸	CAT	Cohort n = 50,828 women 493 develop cataracts after follow up of 8 years	45-67	Dietary FFQ	↓ risk CAT with vitamin C supplementation ≥ 10 years, (OR=0.55; 95% CI: 0.32, 0.96; $p=0.1$ for trend)
Jacques, 1997 ²⁹	CAT: NUC, CX, PSC	Cross-sectional n=247	56-71	Dietary FFQ	↓ risk CAT with vitamin C supplement use for ≥ 10 years at any lens site, for early (OR=0.23; 95% CI: 0.09, 0.60; $p=0.02$), and moderate (OR 0.17; 95% CI: 0.03, 0.85; $p=0.03$) grade opacities.
Ravindran, 2011 ³⁰	CAT: PSC, CX, NUC	Cross-sectional n=5,638	≥60	Dietary FFQ, Plasma samples, and lifestyle assessment questionnaire	↓ Overall risk of CAT with highest plasma vitamin C (OR=0.61; 95% CI, 0.57, 0.82; $p<0.0001$). Also seen by type of CAT: NUC (OR= 0.66; 95% CI: 0.54, 0.80; $p<0.0001$), CX (OR=0.70; 95% CI: 0.54, 0.90; $p<0.002$), and PSC (OR= 0.58; 95% CI: 0.45, 0.74; $p<0.00003$). ↓ risk CAT with highest dietary intake vitamin C (OR=0.78; 95% CI: 0.62, 0.98; $p=0.006$).

AMD: age-related macular degeneration; CAT: cataracts; CX: cortical cataracts; PSC: posterior subcapsular cataracts; NUC: nuclear cataracts; GLA: glaucoma; NTG: normal tension glaucoma; FFQ: food frequency questionnaire.

Table 3. Table identifying key characteristics, associations, and findings of vitamin C, A, and E, and ocular pathology, listed from beneficial to harmful effects, each disease type separated (cont.)

Author	Ocular disease examined	Study design and sample size	Participant age (yrs.)	Method of data collection	Key findings
Wang, 2013 ⁵¹	GLA	Cross-sectional n=2,912	Mean age Cases=67.4 Controls=56.5	Dietary supplement questionnaire, serum measurements	↓ risk GLA with highest intake of vitamin C supplements (OR=0.47; 95% CI: 0.23-0.97; <i>p</i> =0.227 for trend)
Giaconi, 2012 ⁴⁸	GLA	Cross-sectional n=662	Mean age=75.3	Dietary FFQ	↓ risk GLAU with high dietary intake vitamin C (OR=0.30; 95% CI: 0.13, 0.7; <i>p</i> =0.018)
Seddon, 1994 ³⁷	AMD	Case-control 356 cases, 350 controls	Mean age Cases=71 Controls=68	Dietary FFQ	Statistically non-significant ↓ risk AMD with high dietary intake vitamin C (excluding supplements)(OR=0.83; 95% CI: 0.52, 1.33; <i>p</i> =0.31)
van Leeuwen, 2005 ³⁸	AMD	Cohort n=4,170, with 560 cases after mean follow up of 8 years	Mean age of AMD cases=68.2, those without mean age=66.4	Dietary FFQ	↓ risk AMD with above median intake of combined nutrients of vitamin C, E, zinc, and β-carotene (OR=0.65; 95% CI: 0.46-0.92)
Flood, 2002 ⁴⁰	AMD	Cohort n=1,989, with 192 developing cataracts after follow up of 5 years	Mean age cohort=64.2	Dietary FFQ	↑AMD risk with high dietary and supplement intake of vitamin C , (OR=2.3; <i>p</i> =0.002)
Christen, 1999 ⁴¹	AMD	Cohort n=21,120, with 279 developing CAT after average follow up of 12.5 y	40-84	Dietary FFQ	↑ AMD risk with vitamin c supplement use, (OR=1.03; 95% CI: 0.71, 1.50)
Theodoropoulou, 2014 ¹⁷	CAT: CX, PSC, NUC	Case-control 314 Cases and 314 controls	Between 45-85	Dietary FFQ	↓CAT risk with high dietary intake carotenoids, (OR=0.56; 95% CI: 0.45, 0.69; <i>p</i> <0.001)
Jacques, 1991 ²¹	CAT: CX, PSC, NUC, both or either lens	Case-control Cases=77 Controls=35	Between 40-89	Plasma levels and dietary FFQ for of vitamin C, E, and carotenoids	↑risk CX with low plasma carotenoids, (OR=7.2; <i>p</i> <0.05)
Leske, 1991 ²⁴	CAT: CX, PSC, NUC, Mixed	Case-Control Cases=945 Controls=435	Median age Cases=65.9 Controls=59.7	Dietary FFQ	↓risk with high vitamin A intake (OR=0.45; 95% CI: 0.23, 0.66), (OR=0.60; 95% CI: 0.37, 0.96) for NUC and mixed CAT respectively. Statistically non-significant ↓ risk with high vitamin A intake (OR=0.86; 95% CI: 0.52, 1.42) for CX cataracts. Statistically non-significant ↑ risk PSC with high vitamin A intake (OR=1.35; 95% CI: 0.59, 3.08)
Hankinson, 1992 ²⁸	CAT	Cohort n=50,828 women 493 develop CAT after follow up of 8 years	45-67	Dietary FFQ	↓ risk CAT with high intake dietary carotenoids and vitamin A (OR=0.61; 95% CI: 0.45, 0.81). Statistically non-significant ↓ risk cataracts ≥ 10 years supplementation (OR=0.2; 95% CI: 0.03, 1.57; <i>p</i> =0.3)

AMD: age-related macular degeneration; CAT: cataracts; CX: cortical cataracts; PSC: posterior subcapsular cataracts; NUC: nuclear cataracts; GLA: glaucoma; NTG: normal tension glaucoma; FFQ: food frequency questionnaire.

Table 3. Table identifying key characteristics, associations, and findings of vitamin C, A, and E, and ocular pathology, listed from beneficial to harmful effects, each disease type separated (cont.)

Author	Ocular disease examined	Study design and sample size	Participant age (yrs.)	Method of data collection	Key findings
Ramdas, 2012 ⁴⁹	GLA	Cohort n=3052, with 91 cases developing GLA after mean follow up of 9.7 y	≥55	Dietary FFQ	↓ risk GLA with high intake dietary retinol (OR=0.45; 95% CI: 0.23, 0.9; <i>p</i> =0.023)
Giaconi, 2012 ⁴⁸	GLA	Cross-sectional n=662	Mean age=75.3	Dietary FFQ	↓ risk GLA with high dietary intake vitamin A, (OR=0.37; 95% CI:0.15, 0.90; <i>p</i> =0.011)
Seddon, 1994 ³⁷	AMD	Case-control Cases=356 Controls=350	Mean age Cases=71 Controls=68	Dietary FFQ	↓ risk AMD with high dietary intake carotenoids (OR=0.57; 95% CI: 0.35, 0.92; <i>p</i> =0.02), and total vitamin A (including supplements) (OR=0.56; 95% CI: 0.35, 0.96; <i>p</i> =0.02)
Vanden Langenberg, 1998 ³⁵	AMD	Retrospective cohort n=1,586	Ages 43-84	Dietary FFQ	↓ risk of large drusen with high past intakes of α -carotene (OR=0.52; 95% CI: 0.3, 1.0; <i>p</i> =0.02), high past and baseline intakes of Pro-A carotenoids (OR=0.53; 95% CI: 0.3, 1.0; <i>p</i> =0.03) (OR=0.45; 95% CI: 0.2, 1.0; <i>p</i> =0.03) respectively, and statistically non-significant ↓ risk with high past intake of β -carotene (OR=0.62; 95% CI: 0.3, 1.3; <i>p</i> =0.05). ↓ risk pigment abnormalities with higher past intake of pro-A carotenoids (fourth quartile) (OR=0.24; 95% CI: 0.1, 0.8; <i>p</i> =0.69).
van Leeuwen, 2005 ³⁸	AMD	Cohort n=4,170, with 560 cases after mean follow up of 8 years	Mean age cases with AMD=68.2, those without mean age=66.4	Dietary FFQ	↓ risk AMD with above median intake of combined nutrients of vitamin C, E, zinc, and β -carotene (OR=0.65; 95% CI=0.46-0.92)
Robertson, 1991 ²⁵	CAT	Case-control Cases=152, Controls=152	≥55	Interview regarding supplementation	↓ risk CAT with vitamin E supplementation (OR=0.44; 95% CI: 0.24, 0.77; <i>p</i> =0.004), and combined vitamin C and E supplementation (OR=0.32; 95% CI =0.11, 0.99; <i>p</i> =0.05)
Theodoropoulou, 2014 ¹⁷	CAT: CX, PSC, NUC	Case-control Cases=314, Controls=314	Between 45-85	Dietary FFQ	↓ risk CAT with high dietary intake vitamin E (OR=0.50; 95% CI: 0.39, 0.64; <i>p</i> <0.001)
Tavani, 1996 ²²	CAT	Case-control Cases=207, Controls=706	Median age Cases=63 Controls=62	Dietary FFQ	↓ risk CAT with high dietary intake vitamin E (OR=0.5; 95% CI: 0.3, 1.0; <i>p</i> <0.05)
Leske, 1991 ²⁴	CAT: CX, PSC, NUC, Mixed	Case-control Cases=45 Controls=435	Median age Cases=65.9 Controls=59.7	Dietary FFQ	↓ risk CX and mixed CAT with high intake vitamin E and tocopherol equivalents (OR=0.59; 95% CI: 0.35, 0.99; <i>p</i> ≤0.05) (OR=0.58; 95% CI: 0.37, 0.93; <i>p</i> ≤0.05), respectively

AMD: age-related macular degeneration; CAT: cataracts; CX: cortical cataracts; PSC: posterior subcapsular cataracts; NUC: nuclear cataracts; GLA: glaucoma; NTG: normal tension glaucoma; FFQ: food frequency questionnaire.

Table 3. Table identifying key characteristics, associations, and findings of vitamin C, A, and E, and ocular pathology, listed from beneficial to harmful effects, each disease type separated (cont.)

Author	Ocular disease examined	Study design and sample size	Participant age (yrs.)	Method of data collection	Key findings
Tan, 2008 ²⁶	CAT: CX, PSC, NUC	Cohort n=2,464, with 389 cases developing CAT upon follow up (5 or 10 y)	≥49	Dietary FFQ	↓ risk NUC with an above median intake vitamin C, E, β-carotene, and zinc (OR=0.51; 95% CI: 0.34, 0.76; p=0.0012)
Jacques, 2001 ²⁷	CAT: NUC	Cohort n=478 women, with 163 developing nuclear opacities after 13-15 y	Ages 53-73 with a mean age of 61	Dietary FFQ	↓ risk NUC with high total intake vitamin E (food and supplements), however statistically non-significant (OR=0.45; 95% CI: 0.23, 0.86; p=0.06). Long term vitamin E intake ≥ 10y associated with decrease risk nuclear opacities, prior to adjusting for vitamin C and multivitamin supplements (OR=0.49; 95% CI: 0.22, 1.09; p=0.03)
Vanden Langenberg, 1998 ³⁵	AMD	Retrospective cohort n=1,586	Ages 43-84	Dietary FFQ	↓ risk AMD of large drusen with high past intakes of dietary vitamin E (excluding supplements) (OR=0.4; 95% CI: 0.2, 0.9; p=0.04)
van Leeuwen, 2005 ³⁸	AMD	Cohort n=4,170, with 560 cases after mean follow up of 8 years	Mean age cases with AMD=68.2, those without mean age=66.4	Dietary FFQ	↓ risk AMD with high dietary intake vitamin E (OR per standard deviation increase=0.91; 95% CI: 0.83, 0.98). ↓ risk AMD with above median intake of combined nutrients of vitamin C, E, zinc, and β-carotene (OR=0.65; 95% CI=0.46-0.92)
Christen, 1991 ⁴¹	AMD	Cohort n=21,120, with 279 developing CAT after average follow up of 12.5 y	40-84	Dietary FFQ	Use of vitamin E supplements had statistically non-significant ↓ risk AMD (OR=0.87; 95% CI: 0.53, 1.43)

AMD: age-related macular degeneration; CAT: cataracts; CX: cortical cataracts; PSC: posterior subcapsular cataracts; NUC: nuclear cataracts; GLA: glaucoma; NTG: normal tension glaucoma; FFQ: food frequency questionnaire.

nuclear and cortical origin, with the outcomes of changes to reduced GSH, vitamin E, MDA (oxidative stress biomarker) and GSH peroxidase. Findings show increase in vitamin E of both lens homogenates, an increase in GSH peroxidase activity, and a decrease in the level of MDA with α -tocopherol use compared to placebo. Observed changes were to a larger degree in participants with cortical CAT, and there were no changes to the level of reduced GSH in nuclear CAT, as observed in cortical CAT.³¹ Conversely, McNeil et al¹⁰ randomised vitamin E (500 IU) and placebo supplementation in a cohort of 1,193 healthy participants, and found at a 4-year follow up no observed differences in the rate of cataract extraction and lens characteristics between the two groups. These findings may be the result of over-reporting supplement use and other factors unaccounted for.

The impacts of dietary vitamin A, calcium and folate intake on the outcome of cataracts were investigated and presented conflicting findings. Higher intakes of folate and calcium were observed by Tavani et al²² to reduce the risk of CAT (OR 0.4 and 0.5 respectively). This same study did not identify any associations between retinol, methionine, β -carotene, vitamins A, D and E, and the outcome of CAT. Folate intake was not associated with CAT however in a separate study.¹⁴ Higher intakes of vitamin A appeared protective towards nuclear and mixed CAT (OR=0.45, OR=0.6, respectively) in research by Leske, Chylack Jr and Wu,²⁴ but increased the risk of CAT in research by Theodoropoulou et al¹⁷ These conflicting findings however may be related to dietary sources of folate, calcium, and vitamin A as different components within food may attenuate the impact of other components on CAT.

Overall the evaluation of literature indicates that higher dietary consumption of fruit and vegetables, and vitamin C (including supplementation) was associated with the most consistent risk reduction of CAT. Vitamin E dietary intake and supplementation was also consistent with risk reduction in majority of studies, however findings on vitamin E supplementation by McNeil presented no observed differences in rate cataract extraction and lens characteristics between groups. Higher dietary intakes of meat conversely appear to increase the risk of CAT. We are still uncertain about the impact of higher dietary folate, calcium, and vitamin A intake on the outcome of CAT as findings present mixed results. In regards to vitamin A, findings by Theodoropoulou and colleagues¹⁷ identified a harmful association (OR=1.47) with higher intakes of retinol and a protective association with carotene (OR=0.56). However it may be possible that the harmful association identified with retinol may be related to dietary meat intake as retinol is the form of vitamin A found in animal products such as liver, kidneys, and eggs, and dietary meat intake was further identified in this study to increase the risk of CAT (OR=1.46).

Age-related macular degeneration

The role of oxidative stress (and drusen) in AMD

There is evidence indicating a clear link between cumulative oxidative stress and AMD development. Rabin, Rabin, Blenkinsop, Temple and Stern³² demonstrated that patients with AMD exhibit a greater amount of oxidative

modifications to proteins and DNA in the Bruch's membrane, drusen, and RPE compared to age matched controls. Human retinal pigment epithelium cells exposed to a regimen of reactive oxygen species showed an increased concentration of drusen, which are associated with a poor AMD prognosis. Earlier studies suggest that the observed levels of these markers were associated with AMD and its risk factors.^{33,34}

The role of diet in AMD

As with cataracts, dietary intake of certain food groups may influence the outcome and/or progression of AMD due to the role of oxidative stress. The impact of fruit and vegetables, meat intake, and micronutrient intake has been investigated in earlier research.

Participants with a diet higher in fruit and vegetable may have a lower risk of AMD, however findings are not as clear as cataracts.^{25,35-37} For example findings presented by Vanden Langenberg et al³⁵ indicate participants with the highest past intake of fruits and vegetables had reduced risk of large drusen (OR=0.47), and participants with the highest baseline intake of fruit and vegetables had reduced risk of large drusen (OR=0.77). However both findings were not statistically significant.

The impacts of different food items and groups on AMD were identified in two studies. In one study participants of a prospective cohort who consumed greater than or equal to 3 servings of fruit per day had a reduced risk of AMD (OR=0.64).³⁶ In the other study participants consuming spinach or collard greens more frequently per week had a reduced risk of AMD (OR=0.12)³⁷ (See Table 1).

Frequent consumption of meat has been observed to increase the risk of AMD. Red meat consumption of greater than or equal to 10 times per week increased the risk of early AMD of both smaller and larger drusen types (OR=1.47 for drusen ≥ 63 μm and OR=1.39 for drusen ≥ 125 μm), with similar findings were present for frequent fresh meat consumption weekly.¹⁶ In a separate case-control study participants consuming red meat daily, and two to six times per week had increased risk of AMD (OR=2.43 and OR=1.67, respectively).¹⁵

The relationship between dietary antioxidant intake and the risk of AMD is uncertain.

Nine studies were reviewed to examine relationship between intake of antioxidants and the outcome of AMD. Four studies exhibited an inverse association with antioxidant intake, while five were unable to establish an association. A further three studies examined the relationship between plasma antioxidant status with AMD. Two determined an inverse association of risk with a higher plasma antioxidant status, while one was unable to establish a clear association (See Table 3).

Two of the studies that exhibited an inverse association followed a cohort design. Findings between them had certain similarities as both Vanden Langenberg et al³⁵ and van Leeuwen et al³⁸ determined that a high intake of vitamin E had an inverse association with AMD. The inverse association with vitamin E in the study by Vanden Langenberg et al³⁵ however were only found among participants with a higher past intake (approximately 10 years ago) that was measured at baseline, and was strong-

er among men (OR for men=0.31; 95 % CI, 0.1-0.9) (OR for women=0.86; 95% CI, 0.4-2.1). Furthermore Vanden Langenberg et al³⁵ determined that a high intake of combined pro-vitamin A carotenoids was inversely associated with large drusen at baseline and 5 year follow up, and no significant associations were identified between lycopene, lutein and zeaxanthin and vitamin C with AMD. A contrasting find by van Leeuwen et al³⁸ was that a high intake of zinc showed an inverse association with AMD (OR=0.91), which was not shown by Vanden Langenberg et al.³⁵ (See Table 2). van Leeuwen et al³⁸ also identified that a median intake of β -carotene, vitamins C and E, and zinc were associated with a 35% reduction in risk of AMD.

The case-control study by Seddon et al³⁷ exhibited an inverse association between dietary antioxidant intake and advanced age-related macular degeneration (advanced AMD), however the findings were inconsistent with the cohort studies mentioned prior. Statistically significant associations were unable to be identified between advanced AMD the intakes of vitamins E, C and preformed vitamin A.³⁷ Carotenoid intake however was inversely associated with advanced AMD as participants with the highest quintile of intake showed a 43% reduced risk compared to the lowest quintile (OR=0.57). Of the carotenoids, lutein and zeaxanthin were most strongly associated ($p=0.001$),³⁷ which was not consistent findings by Vanden Langenberg et al³⁵ and van Leeuwen et al.³⁸ Finally Bibiloni Mdel et al³⁹ used a cross-sectional approach and compared antioxidant intake among participants with AMD, with their recommended dietary intake (RDI) values specified for the Spanish population. Findings indicate that less than two thirds met the RDI for antioxidant intake, with approximately 60% of all participants showing a serious deficiency in lutein and zeaxanthin intake. However the findings by Bibiloni Mdel et al³⁹ are from a small sample of 52 participants and therefore only an estimation of antioxidant intake can be considered. Literature presented in Table 3 suggests that while the dietary data on vitamin C is unclear with a trend to decreasing disease risk, supplemental vitamin-C appears to increase AMD risk.

Five studies were unable to establish an association between the dietary intake and supplementation of antioxidants and the primary outcome of AMD. All five studies featured a cohort design but varied in whether they assessed antioxidants as an entire group or specific antioxidants such as lutein and zeaxanthin, or zinc (a cofactor for antioxidant processes). Dietary intake of antioxidants did not appear to be associated with AMD in research by Cho et al³⁶ and Flood et al⁴⁰. Although authors did not identify significant association with antioxidant intake, Cho et al³⁶ established an inverse association between ≥ 3 serves of fruit per day (compared to ≤ 1.5 serves of fruit per day) and AMD with a pooled multivariate risk of 0.64. Christen et al⁴¹ assessed antioxidant supplementing on a sample from the physicians health study, involving a 12.5 year median follow up and identified that participants supplementing with vitamin E a 13% reduced risk (OR=0.87) of developing AMD, and participants taking a multivitamin supplement had a 10% reduced risk (OR=0.9) of developing AMD.³⁶ Both findings however

were not statistical significant.⁴¹ Cho et al assessed lutein and zeaxanthin,⁴² and zinc⁴³ intake on AMD with inconclusive findings.

Dietary or supplementary intake of calcium however may modulate the risk of AMD. Findings by Gopinath et al⁴⁴ indicate lower dietary intake of dairy and calcium intake was independently associated with increased risk of late AMD over the observed 15-year period assessed. Supplemental intake of calcium however of greater than 800 mg/d is associated with greater odds of AMD compared to participants' not self-reporting supplementary calcium consumption (OR=1.85).⁴⁵

Overall the evaluation of literature provides little evidence that dietary intake of fruit and vegetables, and dietary antioxidants impact the risk of AMD (See Table 1). The dietary intake of meat in contrast appears to increase the risk of AMD when consumed in greater frequency. Of the antioxidants examined vitamin E and carotenoids (precursors of vitamin A found primarily in fruits and vegetables) may influence the risk of AMD. Calcium intake either dietary or supplementary may modulate the risk of AMD. Further research in the area of dietary intake on age-related macular degeneration is required before making any definitive conclusion.

Glaucoma

Oxidative stress and pathophysiology of glaucoma

Oxidative stress may have role in the pathogenesis of GLA, through degradation of the trabecular network, or direct damage to the retinal ganglion cells.⁴⁶ Degradation of the trabecular meshwork results in increased intraocular pressure due to a build-up of aqueous humour. Analysis of the trabecular meshwork from the eyes of calves treated with the reactive oxygen species hydrogen peroxide (H_2O_2) show evidence of altered aqueous humour drainage.⁴⁷ Human cells treated in vitro with H_2O_2 show altered adhesion and cellular integrity.⁴⁸ Human in vivo research provides convincing evidence of greater oxidative damage among glaucomatous individuals. Additionally increases in visual-field damage and intracranial pressure (IOP) have been attributed to greater extents of trabecular meshwork (TM) cell oxidative damage.⁴⁹

Although oxidative stress has been recognized as an etiopathogenic factor for primary open-angle glaucoma (POAG) through its ability to alter components of the TM, biological systems carry antioxidant defence mechanisms against free radicals. In the eye the major antioxidants that have a protective role are ascorbic acid, reduced glutathione (GSH), and superoxide dismutase-catalase.⁵⁰⁻⁵² Ascorbic acid is found in high concentrations in various areas that include: the cornea, central corneal epithelium, lachrymal film, vitreous humour and aqueous humour.⁵³ GSH is a tripeptide comprised of three amino acids (L-cysteine, glycine and glutamic acid) found in the aqueous humour and TM, and has a role in protecting against damage from low concentrations of H_2O_2 . In contrast, the superoxide dismutase-catalase system has a role in protection from high concentrations of H_2O_2 .^{50,52} Under normal physiological conditions reactive oxygen species such as H_2O_2 are neutralised by antioxidant systems before they impact outflow pathways, however this equilibrium may shift over time with age allowing for the accu-

mulation of oxidative stress within the TM.⁴⁷ This was a finding noted by Alvarado, Murphy, Polansky and Juster⁴⁶ demonstrating a linear reduction in TM cells correlating with age. This equated to a loss of approximately 0.58% of total TM cells per year. Furthermore in a separate study by De La Paz and Epstein,⁵⁴ TM samples from cadavers display an age-related decline of superoxide dismutase believed to be the result of a progressive increase in oxidative stress.

The role of diet in glaucoma

Coleman et al⁵⁵ presents mixed findings with a decreased risk of glaucoma with greater than or equal to three servings of fruit and fruit juices per day (OR=0.98), but an increased risk of glaucoma with greater than or equal to 3 servings per day of all vegetables (OR=1.44). Both findings however are not statistically significant. Giaconi et al⁵⁶ also suggest a decreased risk of glaucoma with greater than or equal to three serving of fruit and fruit juices per day (OR=0.21), which is statistically significant. In contrast findings further suggest a statistically non-significant decrease in risk of Glaucoma with greater than or equal to three servings of vegetables per day (OR=0.97) (See Table 1).

Seven studies were evaluated regarding dietary intake or supplement of antioxidants on the outcome of glaucoma. Four studies showed a reduction in risk with a higher quintile of intake, while three showed no statistically significant effect regardless of intake (See Table 3).

Coleman et al⁵⁵ conducted a cross sectional cohort study on 1155 women and reported a 50% risk reduction of POAG [OR=0.5; 95% CI, 0.24 to 1.03; $p=0.61$] in those with a daily intake of at least 1400 retinol equivalents (RE) of vitamin A, compared to those consuming less than 800 RE daily. Furthermore women who consumed at least 2 mg vitamin B-2 (riboflavin) from natural food sources had a 61% risk reduction of POAG (OR 0.39; 95% CI, 0.17 to 0.86; $p=0.019$) compared with those consuming less than 1 mg.⁵⁵ The dietary intake of fruit and vegetables was analysed for a subgroup of African American women of this cohort as various associations in the prior study appeared stronger among this ethnic group, but the sample size was small ($n=144$).⁵⁶ The entire cohort of African American women ($n=662$) showed a 63% risk reduction (OR=0.37; 95% CI, 0.15 to 0.9, $p=0.11$) among the group with the highest quintile of intake for vitamin A, compared to the lowest quintile of intake.⁵⁶ Although higher consumption of vitamin B2 showed a risk reduction of 25% (OR=0.75; 95% CI, 0.35-1.62) among the highest quintile of intake, the impact was non-significant. Furthermore in both studies there was no statistical significant association between dietary intake of β -carotene, folate, lutein and zeaxanthin, vitamins B-1, B-3, B-6, D, E, K and lycopene, and the outcome of GLA.⁵⁶ A high intake of vitamin C however was identified in this population to be associated with a 70% POAG risk reduction (OR=0.3), which was not present in the total population.⁵⁶

The Rotterdam population-based cohort study followed 3,502 participants and examined their dietary intake with a mean follow-up time of 9.7 years.⁵⁷ Findings illustrated similar results to Coleman et al,⁵⁵ with a 55% risk reduc-

tion (OR=0.45; 95% CI, 0.23-0.9) among those with the highest consumption of vitamin A (expressed as retinol equivalents). However Ramdas et al⁵⁷ also identified a 50% risk reduction (OR=0.5; 95% CI, 0.24-0.98) among those with the highest tertile of intake for vitamin B-1, compared to the lowest tertile of intake.

In mice, that the cohorts exposed to α -lipoic acid (ALA) from birth or at 6 months expressed a greater proportion of antioxidant genes and proteins, showed less damage to retinal ganglion cells and increased retrograde transport in comparison to controls. Both mice models further presented with lower levels of lipid peroxidation, protein nitrosylation and DNA oxidation in the retina compared to controls.⁵⁸

In contrasting results in humans, Garcia-Medina et al¹² and Wang et al⁵⁹ investigated the impact of antioxidant supplementation on participants diagnosed with GLA. Garcia-Medina et al¹² conducted a randomised control trial with two oral antioxidant supplements (OAS) varying only in omega-3 content and a control supplement, and followed a cohort of 117 participants with POAG over a period of two years. Participants in the trial showed no differences in visual global indices, peripapillary retinal nerve fibre layer (RNFL) thickness and macular ganglion cell complex (GCC), between the groups with OAS and the control group. Wang, Singh and Lin⁵⁹ conducted a cross sectional design examining the association between GLA prevalence and supplemental as well as serum levels of vitamins A, C and E. Findings from this study illustrated no association between supplementary or serum levels of vitamins A and E with GLA prevalence, however both high and low dose supplementary vitamin C consumption was associated with decreased odds (OR=0.47; 95% CI 0.23-0.97) of GLA prevalence. There was no significant association with serum levels of vitamin C and GLA prevalence.

Meanwhile Kang et al¹¹ implemented a prospective cohort design to examine the relationship between dietary antioxidant intake and the primary outcome of GLA. This study followed the Nurses Health Study ($n=76,200$) and Health Professionals Follow-up Study ($n=40,284$) biennially from 1980 and 1986 respectively to 1996, and was unable to establish any strong associations between antioxidant consumption and the risk of POAG.

The dietary and supplemental intake of calcium and iron appear to modulate the risk of glaucoma. Findings by Wang, Singh and Lin⁶⁰ indicate that participants with the highest dietary intake of calcium and iron have the lowest adjusted odds ratio of glaucoma (OR=0.39 and OR=0.30, respectively). However consumption of iron and calcium including supplementation increased the risk of glaucoma. Adjusted odds ratio for glaucoma were significantly higher at the third and fourth quintiles for total calcium (OR=1.58 and OR=1.21 respectively), and at the fourth and fifth quintiles for total iron (OR=2.95 and OR=1.58, respectively). The finding of increased risk of glaucoma with high supplemental intake of calcium and iron was observed in another study where participants consuming ≥ 800 mg/d of supplemental calcium or ≥ 18 mg/d of supplemental iron had significantly higher risk after adjusting for confounders (OR=2.44 and OR=3.80, respectively).⁶¹

Overall, a higher dietary consumption of vitamins A

and C was associated with the most consistent risk reduction of GLA. Dietary sources vitamin E appears to have no significant association based on the literature evaluated. Dietary intake of calcium and iron may reduce the risk of glaucoma, however supplemental intake of both micronutrients elevates the risk of glaucoma. Further research on the effect of vitamins A and C on the risk of disease and disease progression is warranted.

Conclusions

There is probable evidence for a protective effect of fruits and vegetables, vitamins C and E on CAT and AMD, however AMD risk increases with higher intakes of supplemental vitamin C. Higher intakes of meat also increase the risk of CAT and AMD. Dietary intake of vitamin A and its derivatives appear protective against CAT, but not in supplemental form. Vitamin A in both diet and supplement form appears to be protective against AMD. Due to the low number of published studies, the evidence regarding the prevention of GLA through higher consumption of antioxidant supplements and/or vegetables and fruit is unclear, with more research warranted. A higher intake of fruit and vegetables is protective against AMD, but otherwise unclear. There is limited evidence that dietary iron and calcium are protective against GLA. Based on the literature to date, it would be safe to advise patients with a family history of oxidative stress related ocular disease to consume a diet high in particularly those rich in vitamins C and E. There is some evidence that high intakes of supplemental forms of antioxidants are damaging and we would recommend further investigation into appropriate dose, form and timing of antioxidant consumption.

AUTHOR DISCLOSURES

All authors declare no conflict of interest or funding sources.

REFERENCES

- Pascolini D, Mariotti SP. Global estimates of visual impairment: 2010. *Br J Ophthalmol*. 2012;96:614-8. doi: 10.1136/bjophthalmol-2011-300539.
- Cook HL, Patel PJ, Tufail A. Age-related macular degeneration: diagnosis and management. *Br Med Bull*. 2008;85:127-49. doi: 10.1093/bmb/ldn012.
- Taylor P, Mapp K. Clear Focus — The economic impact of vision loss in New Zealand in 2009. Melbourne, Australia: Vision 2020 Australia; 2010.
- Mitchell P, Deloitte Access Economics. Eyes on the future: a clear outlook on age-related macular degeneration. Sydney, Australia: Macular Degeneration Foundation; 2011.
- Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol*. 2006;90:262-7. doi: 10.1136/bjo.2005.0.
- Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. *JAMA*. 2014;311:1901-11. doi: 10.1001/jama.2014.3192.
- Sies H. Oxidative stress: oxidants and antioxidants. *Experimental Physiology*. 1997;82:291-5. doi: 10.1113/expphysiol.1997.sp004024.
- Cao G, Booth SL, Sadowski JA, Prior RL. Increases in human plasma antioxidant capacity after consumption of controlled diets high in fruit and vegetables. *Am J Clin Nutr*. 1998;68:1081-7.
- Age-Related Eye Disease Study Research Group. 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.
- McNeil JJ, Robman L, Tikellis G, Sinclair MI, McCarty CA, Taylor HR. Vitamin E supplementation and cataract: Randomized controlled trial. *Ophthalmology*. 2004;111:75-84. doi: 10.1016/j.ophta.2003.04.009.
- Kang JH, Pasquale LR, Willett W, Rosner B, Egan KM, Faberowski N et al. Antioxidant Intake and Primary Open-Angle Glaucoma: A Prospective Study. *Am J Epidemiol*. 2003;158:337-46. doi: 10.1093/aje/kwg167.
- Garcia-Medina JJ, Garcia-Medina M, Garrido-Fernandez P, Galvan-Espinosa J, Garcia-Maturana C, Zanon-Moreno V et al. A two-year follow-up of oral antioxidant supplementation in primary open-angle glaucoma: an open-label, randomized, controlled trial. *Acta Ophthalmol*. 2014;93:546-54. doi: 10.1111/aos.12629.
- Mares-Perlman JA, Brady WE, Klein R, Klein BE, Bowen P, Stacewicz-Sapuntzakis M et al. Serum antioxidants and age-related macular degeneration in a population-based case-control study. *Arch Ophthalmol*. 1995;113:1518-23. doi: 10.1001/archophth.1995.01100120048007.
- Appleby PN, Allen NE, Key TJ. Diet, vegetarianism, and cataract risk. *Am J Clin Nutr*. 2011;93:1128-35. doi: 10.3945/ajcn.110.004028.
- Ersoy L, Ristau T, Lechanteur YT, Hahn M, Hoyng CB, Kirchhof B et al. Nutritional risk factors for age-related macular degeneration. *Biomed Res Int*. 2014;2014:6. doi: 10.1155/2014/413150.
- Chong EW-T, Simpson JA, Robman LD, Hodge AM, Aung KZ, English DR et al. Red Meat and Chicken Consumption and Its Association With Age-related Macular Degeneration. *Am J Epidemiol*. 2009;169:867-76. doi: 10.1093/aje/kwn393.
- Theodoropoulou S, Samoli E, Theodossiadi P, Papathanassiou M, Lagiou A, Lagiou P, Tzonou A. Diet and cataract: a case-control study. *Int Ophthalmol*. 2014;34:59-68. doi: 10.1007/s10792-013-9795-6.
- Boeing H, Bechthold A, Bub A, Ellinger S, Haller D, Kroke A et al. Critical review: vegetables and fruit in the prevention of chronic diseases. *Eur J Nutr*. 2012;51:637-63. doi: 10.1007/s00394-012-0380-y.
- Beebe DC, Holekamp NM, Shui Y-B. Oxidative damage and the prevention of age-related cataracts. *Ophthalmic Res*. 2010;44:155-65. doi: 10.1159/000316481.
- Wang N, Chintala SK, Fini ME, Schuman JS. Activation of a tissue-specific stress response in the aqueous outflow pathway of the eye defines the glaucoma disease phenotype. *Nat Med*. 2001;7:304-9. doi: 10.1038/85446.
- Jacques PF, Chylack LT. Epidemiologic evidence of a role for the antioxidant vitamins and carotenoids in cataract prevention. *Am J Clin Nutr*. 1991;53:352S-5S.
- Tavani A, Negri E, La Vecchia C. Food and nutrient intake and risk of cataract. *Ann Epidemiol*. 1996;6:41-6. doi: 10.1016/1047-2797(95)00099-2.
- Pham-Huy LA, He H, Pham-Huy C. Free radicals, antioxidants in disease and health. *Int J Biomed Sci*. 2008;4:89-96.
- Leske M, Chylack LT Jr, Wu S. The lens opacities case-control study: risk factors for cataract. *Arch Ophthalmol*. 1991;109:244-51. doi: 10.1001/archophth.1991.01080020090051.
- Robertson JM, Donner AP, Trevithick JR. A possible role for vitamins C and E in cataract prevention. *Am J Clin Nutr*. 1991;53:346S-51S.

26. Tan AG, Mitchell P, Flood VM, Burlutsky G, Rochtchina E, Cumming RG, Wang JJ. Antioxidant nutrient intake and the long-term incidence of age-related cataract: the Blue Mountains Eye Study. *Am J Clin Nutr.* 2008;87:1899-905.
27. Jacques PF, Chylack LT Jr, Hankinson SE, Khu PM, Rogers G, Friend J et al. Long-term nutrient intake and early age-related nuclear lens opacities. *Arch Ophthalmol.* 2001;119:1009-19. doi: 10.1001/archoph.119.7.1009.
28. Hankinson SE, Stampfer MJ, Seddon JM, Colditz GA, Rosner B, Speizer FE, Willett WC. Nutrient intake and cataract extraction in women: a prospective study. *BMJ.* 1992;305:335-9.
29. Jacques PF, Taylor A, Hankinson SE, Willett WC, Mahnken B, Lee Y, Vaid K, Lahav M. Long-term vitamin C supplement use and prevalence of early age-related lens opacities. *Am J Clin Nutr.* 1997;66:911-6.
30. Ravindran RD, Vashist P, Gupta SK, Young IS, Maraini G, Camparini M et al. Inverse association of vitamin C with cataract in older people in India. *Ophthalmology.* 2011;118:1958-65.e2. doi: 10.1016/j.ophtha.2011.03.016.
31. Seth RK, Kharb S. Protective function of alpha-tocopherol against the process of cataractogenesis in humans. *Ann Nutr Metab.* 1999;43:286-9. doi: 10.1159/000012796.
32. Rabin DM, Rabin RL, Blenkinsop TA, Temple S, Stern JH. Chronic oxidative stress upregulates drusen-related protein expression in adult human RPE stem cell-derived RPE cells: A novel culture model for dry AMD. *Aging (Albany NY).* 2013;5:51-66. doi: 10.18632/aging.100516.
33. Sharma RK, Orr WE, Schmitt AD, Johnson DA. A functional profile of gene expression in ARPE-19 cells. *BMC Ophthalmol.* 2005;5:25. doi: 10.1186/1471-2415-5-25.
34. Ablonczy Z, Dahrouj M, Tang PH, Liu Y, Sambamurti K, Marmorstein AD, Crosson CE. Human retinal pigment epithelium cells as functional models for the RPE in vivo. *Invest Ophthalmol Vis Sci.* 2011;52:8614-20. doi: 10.1167/iops.11-8021.
35. Vanden Langenberg GM, Mares-Perlman JA, Klein R, Klein BEK, Brady WE, Palta M. Associations between antioxidant and zinc intake and the 5-Year incidence of early age-related maculopathy in the Beaver Dam Eye Study. *Am J Epidemiol.* 1998;148:204-14.
36. Cho E, Seddon JM, Rosner B, Willett WC, Hankinson SE. Prospective study of intake of fruits, vegetables, vitamins, and carotenoids and risk of age-related maculopathy. *Arch Ophthalmol.* 2004;122:883-92. doi: 10.1001/archoph.122.6.883.
37. Seddon JM, Ajani UA, Sperduto RD, Hiller R, Blair N, Burton TC et al. Dietary carotenoids, vitamins A, C, and E, and advanced age-related macular degeneration. Eye Disease Case-Control Study Group. *JAMA.* 1994;272:1413-20. doi: 10.1001/jama.1994.03520180037032.
38. van Leeuwen R, Boekhoorn S, Vingerling JR, Witteman JC, Klaver CC, Hofmann A, de Jong PT. Dietary intake of antioxidants and risk of age-related macular degeneration. *JAMA.* 2005;294:3101-7. doi: 10.1001/jama.294.24.3101.
39. Bibiloni Mdel M, Zapata ME, Aragon JA, Pons A, Olea JL, Tur JA. Estimation of antioxidants dietary intake in wet age-related macular degeneration patients. *Nutr Hosp.* 2014;29:880-8. doi: 10.3305/nh.2014.29.4.7078.
40. Flood V, Smith W, Wang JJ, Manzi F, Webb K, Mitchell P. Dietary antioxidant intake and incidence of early age-related maculopathy. *Ophthalmology.* 2002;109:2272-8. doi: 10.1016/S0161-6420(02)01263-0.
41. Christen WG, Ajani UA, Glynn RJ, Manson JE, Schaumberg DA, Chew EC, Buring JE, Hennekens CH. Prospective cohort study of antioxidant vitamin supplement use and the risk of age-related maculopathy. *Am J Epidemiol.* 1999;149:476-84.
42. Cho E, Hankinson SE, Rosner B, Willett WC, Colditz GA. Prospective study of lutein/zeaxanthin intake and risk of age-related macular degeneration. *Am J Clin Nutr.* 2008;87:1837-43.
43. Cho E, Stampfer MJ, Seddon JM, Hung S, Spiegelman D, Rimm EB, Willett WC, Hankinson SE. Prospective study of zinc intake and the risk of age-related macular degeneration. *Ann Epidemiol.* 2001;11:328-36. doi: 10.1016/S1047-2797(01)00217-4.
44. Gopinath B, Flood VM, Louie JCY, Wang JJ, Burlutsky G, Rochtchina E, Mitchell P. Consumption of dairy products and the 15-year incidence of age-related macular degeneration. *Br J Nutr.* 2014;111:1673-9. doi: 10.1017/S000711451300408X.
45. Kakigi CM, Singh K, Wang SY, Enanoria WT, Lin SC. Self-reported calcium supplementation and age-related macular degeneration. *JAMA Ophthalmol.* 2015;133:746-54. doi: 10.1001/jamaophthalmol.2015.0514.
46. Alvarado J, Murphy C, Polansky J, Juster R. Age-related changes in trabecular meshwork cellularity. *Invest Ophthalmol Vis Sci.* 1981;21:714-27.
47. Kahn MG, Giblin FJ, Epstein DL. Glutathione in calf trabecular meshwork and its relation to aqueous humor outflow facility. *Invest Ophthalmol Vis Sci.* 1983;24:1283-7.
48. Zhou L, Li Y, Yue BY. Oxidative stress affects cytoskeletal structure and cell-matrix interactions in cells from an ocular tissue: the trabecular meshwork. *J Cell Physiol.* 1999;180:182-9.
49. Saccà SC, Pascotto A, Camicione P, Capris P, Izzotti A. Oxidative DNA damage in the human trabecular meshwork: Clinical correlation in patients with primary open-angle glaucoma. *Arch Ophthalmol.* 2005;123:458-63.
50. Costarides AP, Riley MV, Green K. Roles of catalase and the glutathione redox cycle in the regulation of anterior-chamber hydrogen peroxide. *Ophthalmic Res.* 1991;23:284-94.
51. Giblin FJ, McCready JP, Kodama T, Reddy VN. A direct correlation between the levels of ascorbic acid and H₂O₂ in aqueous humor. *Expe Eye Res.* 1984;38:87-93.
52. Riley MV. Physiologic neutralization mechanisms and the response of the corneal endothelium to hydrogen peroxide. *CLAO J.* 1990;16(Suppl 1):S16-S21.
53. Agarwal R, Gupta SK, Agarwal P, Saxena R, Agrawal SS. Current concepts in the pathophysiology of glaucoma. *Indian J Ophthalmol.* 2009;57:257-66.
54. De La Paz MA, Epstein DL. Effect of age on superoxide dismutase activity of human trabecular meshwork. *Invest Ophthalmol Vis Sci.* 1996;37:1849-53.
55. Coleman AL, Stone KL, Kodjebacheva G, Yu F, Pedula KL, Ensrud KE et al. Glaucoma risk and the consumption of fruits and vegetables among older women in the study of osteoporotic fractures. *Am J Ophthalmol.* 2008;145:1081-9.
56. Giacony JA, Yu F, Stone KL, Pedula KL, Ensrud KE, Cauley JA; Study of Osteoporotic Fractures Research Group. The association of consumption of fruits/vegetables with decreased risk of glaucoma among older African American women in the study of osteoporotic fractures. *Am J Ophthalmol.* 2012;154:635-44. doi: 10.1016/j.ajo.2012.03.048.
57. Ramdas WD, Wolfs RCW, Kiefte-de Jong JC, Hofman A, de Jong PTVM, Vingerling JR, Jansonijs NM. Nutrient intake and risk of open-angle glaucoma: the Rotterdam Study. *Eur J Epidemiol.* 2012;27:385-93. doi: 10.1007/s10654-012-9672-z.

58. Inman DM, Lambert WS, Calkins DJ, Horner PJ. α -lipoic acid antioxidant treatment limits glaucoma-related retinal ganglion cell death and dysfunction. *PLoS One*. 2013;8:e65389.
59. Wang SY, Singh K, Lin SC. Glaucoma and vitamins A, C, and E supplement intake and serum levels in a population-based sample of the United States. *Eye*. 2013;27:487-94.
60. Wang SY, Singh K, Lin SC. Glaucoma prevalence and the intake of iron and calcium in a population-based study. *Curr Eye Res*. 2013;38:1049-56. doi: 10.3109/02713683.2013.803124.
61. Wang SY, Singh K, Lin SC. The association between glaucoma prevalence and supplementation with the oxidants Calcium and iron. *Invest Ophthalmol Vis Sci*. 2012;53:725-31.