Association of blood antioxidants and vitamins with risk of age-related cataract: a meta-analysis of observational studies¹⁻³

Yu-Hong Cui, Chun-Xia Jing, and Hong-Wei Pan

ABSTRACT

Background: Observational studies have been inconsistent regarding the association between blood antioxidants or vitamins and risk of age-related cataract.

Objective: We performed a meta-analysis to determine whether an association exists between blood levels of antioxidants or vitamins and age-related cataract in observational studies.

Design: We searched PubMed, EMBASE, and the Web of Science for relevant studies from inception to October 2012. Study-specific risk estimates were combined by using a random-effects model.

Results: A total of 13 studies with 18,999 participants were involved in this meta-analysis. A pooled estimate showed vitamin E (OR: 0.75; 95% CI: 0.58, 0.96), α-carotene (OR: 0.72; 95% CI: 0.59, 0.88), lutein (OR: 0.75; 95% CI: 0.65, 0.87), and zeaxanthin (OR: 0.70; 95% CI: 0.60, 0.82) were inversely associated with age-related cataract. Vitamins A (OR: 0.69; 95% CI: 0.58, 0.83) and C (OR: 0.67; 95% CI: 0.57, 0.78) were inversely associated with age-related cataract in Asian populations but not in Western populations. β-Carotene (OR: 0.90; 95% CI: 0.78, 1.05), lycopene (OR: 0.86; 95% CI: 0.65, 1.15), and β-cryptoxanthin (OR: 0.83; 95% CI: 0.68, 1.02) had no significant association with risk of cataract.

Conclusions: This meta-analysis provides additional evidence supporting the view that blood levels of certain antioxidants are inversely associated with risk of age-related cataract. However, the role of antioxidant or vitamin supplement intake in preventing cataract should be further investigated in interventional studies.


INTRODUCTION

Age-related cataract is the leading cause of blindness worldwide. The number of people with age-related cataract will increase dramatically in the next 20 y in US populations and the Western world because of an increasing life expectancy (1). Cataract is even more prevalent in developing countries, such as India and China (2–4). Because the incidence of cataract in the developing world far surpasses the cataract surgical rate, cataract blindness will continue to increase in coming decades. For instance, the surgical coverage in patients with cataract blindness was only 35.7% in the rural area in China in 2010 (5). It is estimated that the need for cataract extractions would be diminished by one-half if the onset of cataract could be delayed by only 10 y (5). Hence, the clarification of risk factors may define the best methods to prevent or delay age-related cataract.

Both in vitro and animal experiments have shown that oxidative stress is involved in cataragenesis, and antioxidants can limit lens damage after an oxidative insult (6, 7). It is theoretically reasonable to deduce that antioxidants might have a protective effect against cataract. Thus far, many observational studies or randomized controlled trials (RCTs) have been performed to investigate the role of antioxidant supplemental or dietary intake in the prevention of age-related cataract (8–24). However, food-frequency questionnaires used for the evaluation of dietary intake were greatly influenced by subjects’ poor memory, recall bias, and inaccurate estimation of the antioxidant content (25). The number of RCTs on such a topic is limited, and most RCTs involved only a few kinds of antioxidants and had a relatively short follow-up period in view of the long-term process in cataract development. Therefore, we think the current evidence regarding antioxidant intake and cataract has obvious weakness in revealing the intrinsic association between antioxidant and cataract risk.

Blood levels of antioxidants, which can be objectively measured, reflect the antioxidant status of the body. Observational studies that investigated the association of blood antioxidants with age-related cataract have helped to show potential risk factors. In the past 2 decades, many studies have been carried out, but the results were not consistent. To the best of our knowledge, thus far, there had been no meta-analysis on the association of blood antioxidants with risk of age-related cataract. In this article, we report the results of our meta-analysis with an aim to find potential risk factors for age-related cataract.

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METHODS

Search strategy

We followed recommendations made by the Meta-analysis of Observational Studies in Epidemiology group to report the present meta-analysis (26). We searched PubMed (http://www.ncbi.nlm.nih.gov/pubmed), EMBASE (http://www.embase.com/), and Web of Science (http://thomsonreuters.com/web-of-science/) (all-year time span) through October 2012 with a combination of 2 groups of key words to identify primary research studies. One group was for antioxidants, including antioxidants, vitamin A, vitamin C, vitamin E, α-carotene, β-carotene, lutein, zeaxanthin, lycopene, β-cryptoxanthin, retinol, ascorbic acid, α-tocopherol, carotenoid, and retinoids. The other group was for cataract, including cataract, age-related cataract, and lens opacity. No language restriction was applied. In addition, we also screened reference lists of retrieved studies for additional potentially relevant articles. We excluded studies if they were based on selected populations exposed to other cataract-related risk factors (eg, diabetes, glaucoma, smoking, drinking, or long-time exposure to sunlight).

Inclusion criteria

For inclusion, studies had to meet the following criteria: 1) be a cross-sectional, case-control, nested case-control, or cohort study; 2) the exposure of interest was blood levels of antioxidant nutrients (including vitamin A, vitamin C, vitamin E, α-carotene, β-carotene, lutein, zeaxanthin, lycopene, and β-cryptoxanthin); 3) the outcome of interest was the incidence or prevalence of age-related cataract; 4) and RRs or ORs with corresponding 95% CIs (or data to calculate them) for the highest compared with lowest categories of blood levels of antioxidant nutrients were reported.

Data extraction

We extracted all data by using a standardized data-collection form. Information was recorded as follows: the first author, date of publication, study location, study design, number of participants, antioxidants investigated, ORs or RRs from the most fully adjusted model for the highest compared with lowest categories of antioxidant blood levels and corresponding 95% CIs, and statistical adjustments for main confounding factors. Two authors independently conducted the study selection and data extraction. Any disagreements were resolved by discussion.

Quality evaluation

Because there is no universal scale available for the evaluation of the quality of observational studies, we created a modified scoring system that was based on a recently used system (designed with reference to Meta-analysis of Observational Studies in Epidemiology, Quality Assessment Tool for Systematic Reviews of Observational Studies, and Strengthening the Reporting of Observational studies in Epidemiology) that allowed a total score of 0–6 points (6 reflected the highest quality) (27). Two independent investigators evaluated the quality of included studies by using this system. With this system, one point each was allocated for 1) any justification given for the prospective study design, 2) when appropriate inclusion and exclusion criteria were used, 3) a diagnosis of age-related cataract was not solely based on self-reporting, 4) participant blood levels of antioxidants were measured by using a validated method, 5) adjustments were made for age and sex, and 6) any other adjustments were used (eg, BMI, smoking status, diabetes, blood pressure, physical activity, and dietary factors).

Statistical analysis

We evaluated the association between blood levels of antioxidants and risk of age-related cataract by pooling the results from individual studies. When factors of interest were reported by ≥2 studies, effect estimates were combined to yield pooled ORs and corresponding 95% CIs. Random-effects models (DerSimonian and Laird), which considered both within- and between-study variation, were used to estimate pooled ORs for associations of blood antioxidants with cataract risk. For each study, ORs or RRs from the most fully adjusted model for the highest compared with the lowest categories of antioxidant blood levels and corresponding 95% CIs were used to calculate pooled estimates. We converted RRs to ORs by using the following formula:

$$RR \times (1 - P) / [1 - (P \times RR)] \quad (I)$$

in which $P$ is the incidence of the outcome of interest in the nonexposed group. Results were expressed as pooled OR with 95% CIs. A homogeneity test was performed with the use of the Q statistic at the $P < 0.10$ level of significance. We also calculated the $I^2$ statistic, which is a quantitative measure of the inconsistency across studies. To explore the possible source of heterogeneity, we conducted a subgroup analysis stratified by populations to assess its effect on outcomes. We also conducted a sensitivity analysis to investigate the influence of a single study on the overall risk estimate by omitting one study in each turn.

Because funnel plots have several limitations and represent only an informal approach to detect publication bias, we carried out the testing by using Begg’s and Egger’s tests. All analyses were performed with the STATA software (version 12.0; StataCorp LP). $P < 0.05$ was considered statistically significant, except where otherwise specified.

RESULTS

Literature search

Of 1198 articles retrieved by the literature search, 1162 articles were excluded after a first screening on the basis of titles and abstracts, which left 36 articles for a full-text review. The manual searching of reference lists of these articles identified 3 additional articles. A full-text assessment of the 39 articles resulted in the exclusion of 26 articles for the following reasons: 1) 13 studies were excluded because they did not report ORs or RRs for the highest compared with lowest categories of blood levels of antioxidant nutrients, 2) 5 studies were excluded for unrelated outcome measures, 3) 4 studies were excluded because they were based on selected populations, 4) 2 studies were excluded because there was no exposure of interest, and 5) 2 studies were
excluded because they were updated by more-recent studies. Finally, 13 studies met the inclusion criteria (28–40) (Figure 1).

Study characteristics

Characteristics of the 13 included studies are shown in Table 1. Four studies were prospective studies (including one nested case-control study and 3 cohort studies), one study was a case-control study, and the other 8 studies were cross-sectional studies. Selected studies were published between 1992 and 2012, and the study population ranged from 141 to 5638, with a total of 7885 cases from 18,999 participants included in this meta-analysis. Except for one study that included women only (38), the other studies included both women and men. The age of participants in all studies was >47 y. Eleven studies were conducted in the United States and European countries, and 2 studies were conducted in Asian countries. The mean follow-up duration of prospective studies ranged from 4 to 15 y. The quality score of most included studies ranged from 4 to 5, which indicated that the quality was good in general.

All studies reported at least one antioxidant blood level as the exposure of interest, but in different manners of 3, 4, and 5 categories. With consideration of the heterogeneity in reporting and the measurement of blood levels of antioxidants, we decided to use the lowest and highest categories to measure the association of blood levels of antioxidants with risk of cataract. The cataract ascertainment and classification were largely based on lens photography, except by the self-reporting in one study (39), and cataract extraction was record in another study (28). The major adjusted confounders were age and sex, which were used in most studies, and other adjustment factors, including, eg, BMI, smoking, alcohol use, diabetes, and blood pressure, were used in some studies.

Association of antioxidant blood levels with risk of age-related cataract

In the 13 studies included in this meta-analysis, 7 studies reported the total incidence or prevalence of age-related cataract. The study by Knekt et al (28) reported an OR for lowest compared with highest categories, which could not be used directly in our meta-analysis, and thus, we recalculated the appropriate OR on the basis of primary data. Two studies reported the incidence or prevalence of different subtypes of age-related cataract, and we calculated the OR for all age-related cataract on the basis of primary data. For the other 4 studies in which only nuclear cataract was reported, we took the OR as approximately the same for the risk estimate of total age-related cataract and used it for the meta-analysis.

Vitamin A

The pooled estimate of the OR on the basis of 6 studies revealed that vitamin A had no significant association with risk of cataract (summary OR: 0.86; 95% CI: 0.66, 1.11) (Figure 2). Because substantial heterogeneity was observed across studies (I²-heterogeneity = 0.069, F² = 51.1%), we performed a stratified analysis according to the population. Results showed that vitamin A was inversely associated with cataract (OR: 0.69; 95% CI: 0.58, 0.83) in Asian but not Western populations (OR: 1.07; 95% CI: 0.82, 1.40). A sensitivity analysis showed the combined estimate was not significantly influenced by a single study (data not shown).

Vitamin C

The pooled estimate of the OR on the basis of 7 studies showed vitamin C was associated with significantly reduced risk of cataract (summary OR: 0.70; 95% CI: 0.56, 0.88) (Figure 2). Substantial heterogeneity was observed in the meta-analysis (I²-heterogeneity = 0.006, F² = 66.6%). A stratified analysis by population showed vitamin C was inversely associated with cataract in Asian (OR: 0.67; 95% CI: 0.57, 0.78) but not Western (OR: 0.73; 95% CI: 0.49, 1.08) populations. A sensitivity analysis by omitting one study at a time showed the combined estimate was not significantly influenced by a single study (data not shown).

Vitamin E

The pooled estimate of the OR on the basis of 9 studies showed vitamin E was inversely associated risk of cataract (summary OR: 0.75; 95% CI: 0.58, 0.96). Substantial heterogeneity was observed in the meta-analysis (I²-heterogeneity = 0.015, F² = 58.0%) (Figure 2). We showed the substantial heterogeneity resulted from the study by Ferrigno et al (34) after a subgroup analysis and sensitivity analysis. We omitted this study and performed a meta-analysis on the basis of remaining studies. The results verified the inverse association between the blood level of vitamin E and cataract without significant heterogeneity across studies (data not shown).

α-Carotene and β-carotene

The pooled estimate on the basis of 5 studies showed α-carotene was inversely associated with risk of cataract (summary OR: 0.72; 95% CI: 0.59, 0.88) (Figure 3). The pooled estimate on the basis of 9 studies showed β-carotene had no significant association with cataract (summary OR: 0.90; 95% CI: 0.78, 1.05) (Figure 3). No significant heterogeneity was observed across studies for α-carotene and β-carotene.
<table>
<thead>
<tr>
<th>First author, year of publication (reference)</th>
<th>Location</th>
<th>Study design</th>
<th>Quality score</th>
<th>Study population</th>
<th>Participant characteristics</th>
<th>Blood antioxidant measures</th>
<th>Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knekt, 1992 (28)</td>
<td>Finland</td>
<td>NCC</td>
<td>4</td>
<td>47 cases; 94 controls</td>
<td>47–83y F/M</td>
<td>A, E, and β-carotene</td>
<td>Age, sex, occupation, smoking, blood pressure, serum cholesterol concentration, BMI, and diabetes</td>
</tr>
<tr>
<td>Vitale, 1993 (29)</td>
<td>United States</td>
<td>Cohort</td>
<td>5</td>
<td>318 cases from 660 subjects</td>
<td>≥60 F/M ≤4</td>
<td>A, C, E, and β-carotene</td>
<td>Age, sex, and history of diabetes</td>
</tr>
<tr>
<td>Leske, 1998 (30)</td>
<td>United States</td>
<td>Cohort</td>
<td>5</td>
<td>177 cases from 744 subjects</td>
<td>63.8 ± 8.0y F/M 4.6 ± 1.6 LOCS III</td>
<td>E</td>
<td>Age, sex, race, education, and smoking</td>
</tr>
<tr>
<td>Lyle, 1999 (31)</td>
<td>United States</td>
<td>Cohort</td>
<td>5</td>
<td>57 cases from 252 subjects</td>
<td>50–86 F/M 5</td>
<td>E, β-cryp, α-carotene, β-carotene, lycopene, and lutein</td>
<td>Age, smoking, serum cholesterol, alcohol intake, hypertension, and BMI</td>
</tr>
<tr>
<td>Simon, 1999 (39)</td>
<td>United States</td>
<td>CS</td>
<td>3</td>
<td>416 cases from 4001 subjects</td>
<td>60–74 F/M NA</td>
<td>Self-report C</td>
<td>Age, sex, race, steroid use, BMI, physical activity, education, alcohol intake, smoking, and diabetes</td>
</tr>
<tr>
<td>Gale, 2001 (32)</td>
<td>UK</td>
<td>CS</td>
<td>3</td>
<td>188 cases from 372 subjects</td>
<td>66–75 F/M NA</td>
<td>C, E, β-cryp, α-carotene, β-carotene, lutein, and zeaxanthin</td>
<td>Age, sex, and other risk factors</td>
</tr>
<tr>
<td>Valero, 2002 (33)</td>
<td>Spain</td>
<td>CC</td>
<td>4</td>
<td>343 cases; 334 controls</td>
<td>55–74 F/M NA</td>
<td>A, C, E, β-cryp, α-carotene, β-carotene, and lutein</td>
<td>Age, sex, and energy intake</td>
</tr>
<tr>
<td>Ferrigno, 2005 (34)</td>
<td>Italy</td>
<td>CS</td>
<td>5</td>
<td>710 cases from 1120 subjects</td>
<td>55–75 F/M NA</td>
<td>A, C, E, and β-carotene</td>
<td>Age, sex, alcohol use, smoking, family history, diabetes, hypertension, sunlight index, and BMI</td>
</tr>
<tr>
<td>Delcourt, 2006 (35)</td>
<td>France</td>
<td>CS</td>
<td>5</td>
<td>241 cases from 815 subjects</td>
<td>≥60 F/M NA</td>
<td>β-cryp, α-carotene, β-carotene, lutein, and zeaxanthin</td>
<td>Age, sex, smoking, lipid-standardized α-tocopherol, HDL-cholesterol, and BMI</td>
</tr>
<tr>
<td>Dherani, 2008 (36)</td>
<td>India</td>
<td>CS</td>
<td>4</td>
<td>821 cases from 1112 subjects</td>
<td>≥50 F/M NA</td>
<td>A, C, E, β-cryp, α-carotene, β-carotene, lutein, and zeaxanthin</td>
<td>Age, sex, smoking, BMI, and average systolic blood pressure</td>
</tr>
<tr>
<td>Moeller, 2008 (38)</td>
<td>United States</td>
<td>CS</td>
<td>5</td>
<td>356 cases from 1778 subjects</td>
<td>60–74 F NA</td>
<td>Lutein and zeaxanthin</td>
<td>Age, smoking, iris pigmentation, physical activity, multivitamin use, HRT, pulse pressure, and BMI</td>
</tr>
</tbody>
</table>
Lutein and zeaxanthin

The pooled estimate of the OR on the basis of 7 studies revealed that lutein was associated with significantly reduced risk of cataract (summary OR: 0.75; 95% CI: 0.65, 0.87), and results of the meta-analysis on the basis of 6 studies showed that zeaxanthin was inversely associated with risk of cataract (summary OR: 0.70; 95% CI: 0.60, 0.82) (Figure 4). No significant heterogeneity was observed across studies for both lutein and zeaxanthin (P-heterogeneity = 0.837, $I^2 = 0.0%$; P-heterogeneity = 0.835, $I^2 = 0.0%$, respectively).

Lycopene and β-cryptoxanthin

Results of a meta-analysis on the basis of 5 studies showed both lycopene (summary OR: 0.86; 95% CI: 0.65, 1.15) and β-cryptoxanthin (summary OR: 0.83; 95% CI: 0.68, 1.02) had no significant association with cataract (Figure 5). No substantial heterogeneity was observed across studies (P-heterogeneity = 0.197, $I^2 = 33.6%$; P-heterogeneity = 0.945, $I^2 = 0.0%$, respectively).

Publication bias

There was little evidence of a publication bias with regard to the blood level of each antioxidant in relation to risk of age-related cataract as indicated by Begg’s ($P > 0.10$) and Egger’s ($P > 0.10$) tests (data not shown).

DISCUSSION

In this meta-analysis of 13 observational studies that involved 7885 cases from 18,999 participants, we showed the association of blood levels of antioxidants with risk of age-related cataract. Our results showed vitamin E, α-carotene, lutein, and zeaxanthin had inverse associations with cataract, and vitamins A and C were inversely associated with cataract in Asian but not Western populations; β-carotene, lycopene, and β-cryptoxanthin had no significant association with cataract. Our findings are of potential importance for additional research to explore the target for cataract prevention.

Except for those studies that investigated the association of blood antioxidants with cataract, there were also many observational studies that focused on the association between antioxidant intakes and cataract (9, 11–13, 15, 41–47). Results from these studies were inconsistent. Compared with blood antioxidants, the assessment of antioxidants intake was relatively imprecise, which was mainly on a self-reported basis instead of objective measurements. Moreover, many studies suggested that there is a poor correlation between dietary intake and blood levels for some antioxidants (48, 49). Therefore, blood levels of antioxidants might be a better marker for the antioxidant status of the body. Efforts should be dedicated to investigate the most-efficacious method to improve blood levels of antioxidants.

Because certain correlations exist between antioxidants, disentangling whether it is a combination of antioxidants or one specific antioxidant that exerts a protective effect is likely to be
difficult. Previous studies have shown that plasma lutein and zeaxanthin were correlated highly with each other (35, 40). Also, there is evidence that vitamin C acts synergistically with vitamin E in the antioxidant activity (50). However, an antioxidant or vitamin index was used in only a few studies (51, 52). We expect an antioxidant index that includes all blood antioxidants in the

<table>
<thead>
<tr>
<th>Study ID</th>
<th>OR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td>1.15 (0.55, 2.39)</td>
<td>9.08</td>
</tr>
<tr>
<td>Knecht 1992 [28]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitale 1993 [29]</td>
<td>1.21 (0.73, 2.00)</td>
<td>14.99</td>
</tr>
<tr>
<td>Valero 2002 [33]</td>
<td>1.27 (0.78, 2.06)</td>
<td>15.79</td>
</tr>
<tr>
<td>Ferrigno 2005 [34]</td>
<td>0.74 (0.44, 1.25)</td>
<td>14.32</td>
</tr>
<tr>
<td>Dherani 2008 [36]</td>
<td>0.58 (0.37, 0.91)</td>
<td>16.89</td>
</tr>
<tr>
<td>Ravindran 2011 [37]</td>
<td>0.72 (0.59, 0.88)</td>
<td>28.83</td>
</tr>
<tr>
<td>Subtotal (I-squared = 51.1%, p = 0.069)</td>
<td>0.66 (0.66, 1.11)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

| Vitamin C | 1.02 (0.70, 1.41) | 9.96 |
| Vitale 1993 [29] | | |
| Simon 1998 [39] | 0.74 (0.56, 1.07) | 17.55 |
| Gale 2001 [32] | 1.02 (0.68, 1.54) | 13.31 |
| Valero 2002 [33] | 0.30 (0.18, 0.51) | 10.55 |
| Ferrigno 2005 [34] | 0.70 (0.42, 1.15) | 10.94 |
| Dherani 2008 [36] | 0.64 (0.45, 0.98) | 17.19 |
| Ravindran 2011 [37] | 0.68 (0.57, 0.82) | 20.50 |
| Subtotal (I-squared = 66.6%, p = 0.005) | 0.70 (0.56, 0.88) | 100.00 |

| Vitamin E | 0.59 (0.29, 1.20) | 7.90 |
| Knecht 1992 [28] | | |
| Vitale 1993 [29] | 0.62 (0.36, 1.06) | 10.83 |
| Lyele 1999 [30] | 0.61 (0.28, 0.92) | 9.76 |
| Gale 2001 [32] | 0.50 (0.20, 1.00) | 6.25 |
| Valero 2002 [33] | 0.62 (0.40, 0.95) | 13.04 |
| Ferrigno 2005 [34] | 0.93 (0.56, 1.52) | 11.59 |
| Dherani 2008 [36] | 1.86 (1.08, 3.18) | 10.77 |
| Ravindran 2011 [37] | 0.58 (0.36, 0.94) | 11.99 |
| Subtotal (I-squared = 58.0%, p = 0.015) | 0.91 (0.72, 1.14) | 17.87 |

**FIGURE 2.** Summary ORs (95% CIs) of age-related cataract for the comparison of highest with lowest categories of blood levels of vitamin A, C, and E. Squares indicate study-specific estimates (the size of a square reflects the study’s statistical weight), horizontal lines indicate 95% CIs, and diamonds indicate summary OR estimates with corresponding 95% CIs. Study-specific risk estimates were combined by using DerSimonian and Laird’s random-effects model. ID, identifier.

**FIGURE 3.** Summary ORs (95% CIs) of age-related cataract for the comparison of highest with lowest categories of blood levels of α-carotene and β-carotene. Squares indicate study-specific estimates (the size of a square reflects the study’s statistical weight), horizontal lines indicate 95% CIs, and diamonds indicate summary OR estimates with corresponding 95% CIs. Study-specific risk estimates were combined by using DerSimonian and Laird’s random-effects model. ID, identifier.
same model can be established and used in future studies to investigate the overall effect of blood antioxidants.

Thus far, many interventional studies have been performed to explore the possibility of antioxidant intake for the prevention of cataract. Most of these RCTs focused on $\beta$-carotene, vitamin C, and vitamin E or a combination of these antioxidants. Doses used in these studies were 7.5–25 mg $\beta$-carotene/d (16–22), 250–750 mg vitamin C/d (16, 20–22), and 75–900 IU vitamin E/d (16, 17, 20–24). Only one study observed the change in blood levels of antioxidants, and the results proved supplement intake at the dose of 15 mg $\beta$-carotene/d, 500 mg vitamin C/d, and 400 IU vitamin E/d could remarkably increase the median serum value of participants. However, on the basis of the current evidence, it is difficult to determine what the most-
Efficacious dose for each antioxidant is because of the great difference in blood antioxidant levels in different populations. The majority of these studies had negative results (16, 17, 20, 21, 23, 24), except in only a few studies that had potentially positive results (22, 53). A recently published systematic review revealed that there was no evidence of an effect of \( \beta \)-carotene, vitamin C, and vitamin E on the incidence of cataract, and the authors did not recommend any additional studies to examine the role of \( \beta \)-carotene, vitamin C, and vitamin E in the prevention of cataracts (54). We think it is too early to draw such a conclusion. There are many possible reasons that might be responsible for the inconsistency between these interventional studies and our meta-analysis. First, blood levels of antioxidants might be influenced by lifestyle, environmental factors, and individual variances in the absorption and use other than of antioxidant intake. Second, we could not rule out the possibility that blood levels of antioxidants have threshold effects on risk of age-related cataract rather than a dose-response effect. Third, the protective effect of antioxidant vitamins perhaps may take decades of intake to manifest. The follow-up period of these interventional studies might not have been long enough to detect the potential effect of antioxidant intake. Fourth, most interventional studies were carried out in developed countries in apparently healthy individuals except in one study in India with a relatively short follow-up period.

In 2006, the Food and Drug Administration reviewed interventional and observational studies and concluded that no credible evidence existed for a health claim about the intake of lutein or zeaxanthin and risk of age-related macular degeneration or cataracts (55). Because many studies have been conducted thereafter, we think it is necessary to perform a meta-analysis again to update our knowledge on this topic.

We acknowledge the limitations of this meta-analysis. First, the studies in our meta-analysis were different in study designs and included case-control, cross-sectional, and cohort studies, which did not have the same risk estimates. Case-control and cross-sectional studies may overestimate the effect size of the association, which makes the relation between exposure and outcome less clear. Second, the efficiency of the analysis was limited because some items were combined from only 5 or 6 studies, such as the association of blood lycopene, \( \beta \)-cryptoxanthin, and \( \alpha \)-carotene with cataract. Third, the pooled risk estimate may have been affected by individual studies, especially the one study that was weighted the highest [ie, Ravindran et al (37)]. However, we performed a subgroup analysis and sensitivity analysis to verify the reliability and robustness of our findings. Finally, although most of the included studies adjusted for relevant factors that could have confounded the association between blood antioxidants and cataract, the potential confounding effect of these factors might still have been prevalent.

In conclusion, in consideration of the limitations of the study, any conclusions should be made with caution. Our results provide additional evidence in support of a significant inverse association between blood levels of certain antioxidants and risk of age-related cataract, suggesting the elevation of blood levels of related antioxidants by appropriate methods might bring a benefit in age-related cataract prevention, especially for people with low basic levels of blood antioxidants. However, it must be pointed out that the current evidence is insufficient to inform clinical decision making, policy, or practice guidelines. To further explore the association between antioxidants and risk of cataract, studies should aim to specify the population for which antioxidant levels are especially important to determine the antioxidant threshold for increased risk of cataract and explore the efficacious methods to increase blood levels of antioxidants. Moreover, large-scale, long-term RCTs should be carried out in different populations to investigate the efficacy of antioxidant intakes on cataract prevention.

The authors’ responsibilities were as follows—H-WP: conceived the study idea, designed the study, and had primary responsibility for final content of the manuscript; Y-HC and C-XJ: conducted the literature search, extracted data, and performed the statistical analysis; H-WP and Y-HC: interpreted results and wrote the manuscript; and all authors: read and approved the final manuscript. None of the authors had a conflict of interest.

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