Antioxidant Intake and Primary Open-Angle Glaucoma: A Prospective Study

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The relation between dietary antioxidant intake and primary open-angle glaucoma risk was examined in participants aged over 40 years in the Nurses’ Health Study (n = 76,200) and the Health Professionals Follow-up Study (n = 40,284). They were followed biennially from 1980 and 1986, respectively, to 1996, during periods when they received an eye examination. Dietary intakes were measured repeatedly from 1980 in the Nurses’ Health Study and from 1986 in the Health Professionals Follow-up Study using validated food frequency questionnaires. The authors analyzed 474 self-reported glaucoma cases confirmed by medical chart review to have primary open-angle glaucoma with visual field loss. The authors used Cox proportional hazards models for cohort-specific multivariate analyses, and results were pooled using random effects models. The pooled multivariate rate ratios for primary open-angle glaucoma comparing the highest versus lowest quintile of cumulative updated intake were 1.17 (95% confidence interval (CI): 0.87, 1.58) for \( \alpha \)-carotene, 1.10 (95% CI: 0.82, 1.48) for \( \beta \)-carotene, 0.95 (95% CI: 0.70, 1.29) for \( \beta \)-cryptoxanthin, 0.82 (95% CI: 0.60, 1.12) for lycopene, 0.92 (95% CI: 0.69, 1.24) for lutein/zeaxanthin, 1.05 (95% CI: 0.59, 1.89) for vitamin C, 0.97 (95% CI: 0.62, 1.52) for vitamin E, and 1.11 (95% CI: 0.82, 1.51) for vitamin A. In conclusion, the authors did not observe any strong associations between antioxidant consumption and the risk of primary open-angle glaucoma.

Abbreviations: CI, confidence interval; RR, rate ratio.

Glaucoma, the second leading cause of blindness worldwide (1), is characterized by gradual loss of retinal ganglion cell axons (2, 3). The pathogenesis of primary open-angle glaucoma, the most common type, is poorly understood (4, 5). Intraocular pressure is the only risk factor identified that is modifiable (4, 5).

Oxidative stress may contribute to glaucoma etiology and progression (6–8). A variety of defensive mechanisms against free radicals formed by light-catalyzed reactions protect trabecular meshwork cells (9–12). In vitro studies have demonstrated a decrease in aqueous outflow facility after perfusion with hydrogen peroxide when pressure was elevated (13) or when glutathione was depleted (12). Posteriorly, oxidative processes may trigger and mediate the apoptotic death of retinal ganglion cells in glaucoma. For example, vascular ischemia in the optic nerve may lead to oxidative injury to the retinal ganglion cells during reoxygenation (14). In addition, nitric oxide, after reacting with superoxide anions, may damage retinal ganglion cells (15). Finally, various injurious triggers, such as excess glutamate, induce the fatal apoptotic cascade, which is mediated in part by free radical damage (8, 16, 17). Endogenous oxidation-reduction agents, such as glutathione, have been found to be protective against glutamate-induced toxicity (18).

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Antioxidant supplementation may enhance trabecular meshwork function and protect the optic nerve (6, 19–21). If increasing total dietary antioxidant intake is shown to be beneficial, this would be a promising means of primary prevention for primary open-angle glaucoma. However, to our knowledge, this hypothesis has not been evaluated previously. The present observational study prospectively examined the role of specific carotenoids and vitamins E and C in relation to primary open-angle glaucoma risk among 116,484 participants followed for at least 10 years.

MATERIALS AND METHODS

Population for current study

The Nurses’ Health Study started in 1976 with 121,701 US female registered nurses aged 30–55 years who responded to a mailed questionnaire on health information and medical history. The Health Professionals Follow-Up Study began in 1986 with the enrollment of 51,529 US male health professionals (dentists, veterinarians, pharmacists, optometrists, osteopaths, podiatrists) aged 40–75 years, who also responded to a mailed questionnaire. Participants were followed with biennial questionnaires on risk factors and newly diagnosed illnesses such as glaucoma. This study was approved by the human subject committees of the Brigham and Women’s Hospital and the Harvard School of Public Health.

Because the first dietary assessments occurred in 1980 for the Nurses’ Health Study and in 1986 for the Health Professionals Follow-up Study, the study period was restricted to 1980–1996 for the Nurses’ Health Study and 1986–1996 for the Health Professionals Follow-up Study. Person-time accrual began from the return date of the first questionnaire completed when a participant became eligible until the earliest occurrence of glaucoma, cancer (an event unrelated to glaucoma that can lead to great changes in eating behaviors), death, loss to follow-up, or 1996. To minimize possible detection bias, we included only the person-time during which a participant was aged 40 or more years (as glaucoma risk increases after the age of 40) and reported having had an eye examination. Person-years were accrued in approximate 2-year units, and exposures were defined on the basis of responses to the biennial questionnaires at the beginning of the interval or, if not completed, the most recent previous questionnaire.

Of the original cohort members, participants were excluded for the following reasons as of 1980 in the Nurses’ Health Study and 1986 in the Health Professionals Follow-up Study: 1) 23,239 women did not return the first semiquantitative food frequency questionnaire assessment in 1980; 2) 1,596 men and 5,994 women had inadequate diet information on the first food frequency questionnaire (“adequate” information for men was fewer than 70 of 131 items blank in the food frequency questionnaire, with a total caloric intake range of 800–4,200 kcal/day; for women, fewer than 10 of 61 items blank and 500–3,500 kcal/day); 3) 1,927 men and 3,625 women had prevalent cancers excluding nonmelanoma skin cancer; 4) 787 men and 767 women had a prevalent diagnosis of glaucoma or suspected glaucoma; 5) 1,029 men and 795 women were later lost to follow-up; 6) 18 men and four women had missing age; and 7) 5,507 men and 9,686 women never reported an eye examination during follow-up. After these exclusions, 40,665 men and 77,591 women remained. However, at each specific 2-year period, some of these participants were considered ineligible. For example, the number of participants who contributed person-time for the first 2 years (1986–1988 in the Health Professionals Follow-up Study; 1980–1982 in the Nurses’ Health Study) was 29,835 men and 44,767 women, as those who were aged less than 40 years (221 men and 16,160 women) and who did not report receiving an eye examination when first asked (see below; 10,609 men and 16,664 women) were temporarily ineligible. At later observation periods, these participants became eligible if they reached 40 or more years of age and later reported receiving eye examinations. Hence, by 1996, a total of 30,306 men and 76,199 women had contributed person-time. Follow-up rates were high: Greater than 95 percent of the total possible person-time was observed in both cohorts.

We determined eligibility for the eye examination on the basis of positive responses to the question of receiving an eye examination in the previous 2 years. For example, if a subject answered positively only in 1994 and 1996, then she contributed person-time only during 1992–1994 and 1994–1996. Because this question was first asked in 1990 in both cohorts, we determined eye examination eligibility in this way from 1988. However, for the initial periods 1986–1988 in the Health Professionals Follow-up Study and 1980–1988 in the Nurses’ Health Study, eye examination eligibility was based on responses to the 1990 question. For example, a Nurses’ Health Study participant eligible in 1980 contributed 8 years from 1980 to 1988 if the response to the 1990 eye examination question was positive and 0 years if negative.

Measurement of antioxidant intake from foods and supplements

Food frequency questionnaires assessed the intake of antioxidants from foods (22–26). The 1980 Nurses’ Health Study food frequency questionnaire included 61 foods found to maximally discriminate intakes of specific fats, fiber, and 12 other nutrients. The 1984 Nurses’ Health Study food frequency questionnaire was expanded to 116 foods to include more fruits and vegetables, and versions of it were used from 1986 onward in both the Nurses’ Health Study (126 foods) and the Health Professionals Follow-up Study (131 foods). For each food item, a common serving size is specified, and respondents are asked to estimate the average frequency of consuming that amount in the past year, ranging from “almost never” to “6 or more times a day.”

In 1980 for the Nurses’ Health Study and 1986 for the Health Professionals Follow-up Study, we asked participants about their use of multivitamins and other supplements of vitamins A, C, and E, including dose and duration of use. With each biennial questionnaire, participants’ supplement use was updated in both cohorts.

We calculated the total intakes of antioxidants by adding the contributions from vitamin supplements and foods. For
vitrins C, E, and A and β-carotene, separate calculations were also made using contributions from foods only. Food intakes were computed by multiplying the frequency of consumption by the nutrient content of specified portions. The nutrient composition of various foods was obtained from US Department of Agriculture sources (27) and food manufacturers’ data. For carotenoid contents specifically, the US Department of Agriculture-National Cancer Institute carotenoid food composition databases were used (28, 29). In our databases, the data for lutein and zeaxanthin have been combined.

In both the Nurses’ Health Study and the Health Professionals Follow-up Study, validation studies of food frequency questionnaires have been conducted using dietary records or plasma nutrient values as standards for evaluation. Pearson’s correlations between the 1980 Nurses’ Health Study food frequency questionnaire and four 1-week dietary records were 0.84 for orange or grapefruit juice, 0.80 for apples, 0.69 for broccoli, 0.73 for tomatoes, and 0.40 for raw carrots (24). For vitamins A and C from foods, the correlations were 0.36 and 0.66, respectively (22). The correlations between vitamin E values from the food frequency questionnaire and from plasma were 0.34 in one study (30) and 0.52 in a larger study (31). The correlations between dietary carotenoids and plasma levels among nonsmoking women were \( r = 0.21 \) for lycopene, 0.27 for β-carotene and lutein, 0.32 for β-cryptoxanthin, and 0.48 for α-carotene (32).

In the Health Professionals Follow-up Study, the correlations between the dietary record values and the food frequency questionnaire values were 0.92 for both vitamins C and E (25). Correlations between plasma concentrations and the food frequency questionnaire assessments were 0.35 for α-carotene, 0.40 for lutein, 0.43 for β-cryptoxanthin, 0.47 for α-carotene, and 0.51 for α-tocopherol (26, 32). These estimates were similar to those found between plasma levels of these nutrients and food records estimates (25). Although the correlations between dietary vitamin intake and plasma vitamin levels were not high, they would not be highly correlated even if dietary measurements were perfect, because many factors other than diet (such as genetic differences in absorption or homeostatic mechanisms) influence between-person variations in plasma vitamin levels (33).

**Case definition and ascertainment**

We asked participants about glaucoma diagnosis from 1986 onward. From all who reported glaucoma, we requested permission to review their ophthalmic records. We then requested that the diagnosing clinician(s) send copies of records or complete a brief questionnaire about glaucomatous signs, the dates of diagnosis, and whether the glaucoma was primary or secondary. For the participants whose optometrists or ophthalmologists indicated primary open-angle glaucoma with glaucomatous visual field loss, we obtained complete ocular records, including visual fields, from visits since the original date of diagnosis. These records were examined independently by two ophthalmologists, who were masked to participants’ antioxidant intake. Cases for analysis were those that both reviewers agreed were either “definite” or “probable primary open-angle glaucoma.” The standardized criteria for these designations are described below. For the date of diagnosis, we used the date of onset of the earliest glaucomatous sign in either eye.

For **definite primary open-angle glaucoma** cases, we required that 1) gonioscopy results confirmed that angles were open and not occludable in both eyes; 2) slit-lamp biomicroscopy showed no indication of secondary causes of glaucoma; and 3) visual field defects were consistent with glaucoma in the most recently available visual fields (i.e., nasal step, nasal depression, paracentral scotoma, arcuate defect, blind spot enlargement, or temporal wedge), reproduced on at least one prior set of reliable visual fields, and not due to other ocular conditions or optic disc pathology. Although there was no requirement for the type of perimetry performed, static automated perimeters had to have an age-matched normal database, and visual field tests had to be reliable for the affected eye(s). For static threshold or suprathreshold testing, we considered a field reliable if the fixation loss was less than 33 percent, the false positive rate was less than 20 percent, and the false negative rate was less than 20 percent. For kinetic visual fields, we considered a field reliable unless there was notation by the examiner to the contrary. **Probable primary open-angle glaucoma** cases met the above criteria for slit-lamp examination and visual fields but did not have gonioscopy. In these cases, we required a documentation of pupil dilation without any subsequent adverse events.

Differences in reviewer assessments occurred for 8.9 percent of the cases (42 of 474), primarily because of errors in calculating visual field test reliability parameters or omissions in reading a few visual fields in the charts. The two reviewers adjudicated their differences after an open discussion of the available information.

A total of 1,274 men and 2,897 women self-reported a diagnosis of glaucoma during follow-up. These self-reports were confirmed by questionnaires completed by the diagnosing physicians to have primary open-angle glaucoma with visual field loss for only 317 men and 693 women. The others had increased intraocular pressure only, cupping only, or other types of glaucoma. After chart review of these 317 men and 693 women, 188 men (59.4 percent) and 320 women (47.3 percent) met the criteria for “definite” or “probable” case designation. The remaining patients were excluded for having only one visual field showing abnormality, only elevated intraocular pressure, other glaucomas, no glaucomatous signs, or insufficient documentation. Finally, after excluding those without complete dietary information or with a history of cancer, we included 173 men and 301 women in the analysis.

**Statistical analysis**

We derived incidence rates of primary open-angle glaucoma by dividing the number of cases by the number of person-years in each quintile of nutrient intake. For age-adjusted analyses, we calculated Mantel-Haenszel adjusted incidence rate ratios using 5-year age categories. For multivariate analyses, we used Cox proportional hazards models stratified by period at risk and age (34). Potential
confounders were age (years), African-American heritage (yes/no), body mass index (kg/m²), alcohol intake (g/day), physical activity (quartiles of activity intensity/day), report of a physician examination (yes/no), self-reported history (yes/no) of hypertension, diabetes (recent diagnoses within 4 years), cataract, or age-related macular degeneration diagnoses. The categorization of these variables is provided in the footnotes to table 2. We calculated rate ratios as the measure of association and their 95 percent confidence intervals. We performed tests for trend by including continuous variables of the median values within each category in multivariate models and evaluating their statistical significance. All $p$ values are two sided.

For supplements of vitamins E, C, and A, we examined the duration of use and the current dose. For nutrients, we adjusted intake values for total caloric intake using the nutrient residual method (35). Intake values were calculated by cumulatively averaging intakes from all available dietary questionnaires up to the start of each 2-year follow-up interval. We used these cumulative average values for our primary analyses because they represent averaged long-term diet, and because they tend to have the least within-person variation in dietary intake (36). For lycopene in the Nurses’ Health Study, the analyses began in 1984, when the food frequency questionnaire included its significant sources. We also evaluated the relation between specific antioxidant-rich foods and food groups and primary open-angle glaucoma risk. The six food groups examined were citrus foods, cruciferous vegetables, yellow vegetables, green leafy vegetables, all fruits combined, and all vegetables combined.

We first analyzed the data from each cohort separately and performed heterogeneity tests of the cohort-specific results.
TABLE 2. Cohort-specific and pooled multivariate* analyses of carotenoid intake in relation to risk of primary open-angle glaucoma for participants of the Nurses’ Health Study from 1980 and the Health Professionals Follow-up Study from 1986 onward

<table>
<thead>
<tr>
<th>α-Carotene (mg/day)</th>
<th>Quintile 1</th>
<th>Quintile 2</th>
<th>Quintile 3</th>
<th>Quintile 4</th>
<th>Quintile 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medians (W, M)[§]</td>
<td>(237, 313)</td>
<td>(397, 499)</td>
<td>(553, 677)</td>
<td>(852, 1034)</td>
<td>(1,444, 1,789)</td>
</tr>
<tr>
<td>NHS§</td>
<td>1.00 (referent)</td>
<td>1.04 ± 0.71, 1.53</td>
<td>0.94 ± 0.64, 1.40</td>
<td>1.10 ± 0.76, 1.61</td>
<td>1.18 ± 0.82, 1.70</td>
</tr>
<tr>
<td>HPFS§</td>
<td>1.00 (referent)</td>
<td>1.51 ± 0.90, 2.54</td>
<td>1.40 ± 0.83, 2.35</td>
<td>1.15 ± 0.67, 1.95</td>
<td>1.16 ± 0.68, 1.97</td>
</tr>
<tr>
<td>Pooled#</td>
<td>1.00 (referent)</td>
<td>1.20 ± 0.84, 1.72</td>
<td>1.10 ± 0.76, 1.61</td>
<td>1.12 ± 0.82, 1.52</td>
<td>1.17 ± 0.87, 1.58, 0.71 ± 0.21</td>
</tr>
<tr>
<td>Pooled 4-year lag**</td>
<td>1.00 (referent)</td>
<td>1.11 ± 0.79, 1.57</td>
<td>1.01 ± 0.71, 1.43</td>
<td>1.40 ± 1.01, 1.93</td>
<td>1.17 ± 0.84, 1.62, 0.27 ± 0.28</td>
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<thead>
<tr>
<th>β-Carotene (mg/day)</th>
<th>Pooled 4-year lag</th>
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<tbody>
<tr>
<td>Medians (W, M)</td>
<td>(1,852, 2,197)</td>
</tr>
<tr>
<td>NHS</td>
<td>1.00 (referent)</td>
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<tr>
<td>HPFS</td>
<td>1.00 (referent)</td>
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<tr>
<td>Pooled</td>
<td>1.00 (referent)</td>
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<tr>
<td>Pooled 4-year lag</td>
<td>1.00 (referent)</td>
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<tr>
<th>β-Cryptoxanthin (mg/day)</th>
<th>Pooled 4-year lag</th>
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<tbody>
<tr>
<td>Medians (W, M)</td>
<td>(1,836, 2,171)</td>
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<tr>
<td>NHS</td>
<td>1.00 (referent)</td>
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<td>HPFS</td>
<td>1.00 (referent)</td>
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<tr>
<td>Pooled</td>
<td>1.00 (referent)</td>
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<tr>
<td>Pooled 4-year lag</td>
<td>1.00 (referent)</td>
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<tr>
<th>Lycopene (mg/day)††</th>
<th>Pooled 4-year lag</th>
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<tr>
<td>Medians (W, M)</td>
<td>(22, 15)</td>
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<tr>
<td>NHS</td>
<td>1.00 (referent)</td>
</tr>
<tr>
<td>HPFS</td>
<td>1.00 (referent)</td>
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<tr>
<td>Pooled</td>
<td>1.00 (referent)</td>
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<tr>
<td>Pooled 4-year lag</td>
<td>1.00 (referent)</td>
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<tr>
<th>Lutein/zeaxanthin (mg/day)</th>
<th>Pooled 4-year lag</th>
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<tr>
<td>Medians (W, M)</td>
<td>(1,476, 1,419)</td>
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<tr>
<td>NHS</td>
<td>1.00 (referent)</td>
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<tr>
<td>HPFS</td>
<td>1.00 (referent)</td>
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<tr>
<td>Pooled</td>
<td>1.00 (referent)</td>
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<tr>
<td>Pooled 4-year lag</td>
<td>1.00 (referent)</td>
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</table>

* Multivariate rate ratios based on Cox proportional hazards. All models have been controlled for the following: African heritage (yes/no), diagnosis of diabetes in the current or previous cycle (yes/no), history of hypertension (yes/no), body mass index (indicators for <22, 22–23, 24–25, 26–27, ≥28 kg/m²), indicators for quartiles of daily physical activity, alcohol intake (indicators for 0, 1–4, 5–14, 15–29, ≥30 g/day), and pack-years of smoking (indicators for 0, 1–9, 10–19, 20–29, ≥30 years). ‡ phet is the p value for the test for heterogeneity of the two cohort estimates of the linear trends. § RR, rate ratio; CI, confidence interval; NHS, Nurses’ Health Study; HPFS, Health Professionals Follow-up Study. ¶ Medians (W, M), median for quintile from women in the NHS and median for quintile from men in the HPFS. † Pooled estimate is the statistical significance of the pooled estimate for the linear values, consisting of the medians of nutrients. ‡‡ Pooled estimates of the 4-year lagged nutrient effects, with follow-up from 1984 to 1996 for the NHS and from 1990 to 1996 for the HPFS, with 400 total cases (282 NHS cases and 118 HPFS cases). ** Lycopene was inadequately assessed until 1984 in the NHS. Thus, for this nutrient, the analysis was from 1984 to 1996 with 400 cases.
of the highest versus lowest category comparisons and the linear trend analyses to check for appropriateness of pooling the results. Then, we pooled the results using the meta-analytical methods incorporating random effects of DerSimonian and Laird (37).

Because glaucoma is an insidious disease with signs appearing generally only after substantial damage to the optic nerve cells occurs (38, 39), the etiologically relevant exposure may be intake several years prior to the date of diagnosis, rather than the most recently reported intake. We have thus additionally conducted analyses to examine lagged intakes. For the 4-year lagged analyses in the Nurses’ Health Study from 1980 and the Health Professionals Follow-up Study from 1986 onward.

Table 3 presents the distribution of potential risk factors for glaucoma by intake level of vitamins C and E and of β-carotene. Age and African heritage are two established risk factors for primary open-angle glaucoma, and those with the lowest intakes were younger and less likely to be of African heritage. Those with the lowest antioxidant intakes tended to have a higher body mass index, to have a generally higher prevalence of diabetes or hypertension, to drink more alcohol, to engage in less physical activity, and to have a greater smoking history. These differences were accounted for by controlling for these variables in multivariate analyses.

RESULTS

Table 1 presents the distribution of potential risk factors for glaucoma by intake level of vitamins C and E and of β-carotene. Age and African heritage are two established risk factors for primary open-angle glaucoma, and those with the lowest intakes were younger and less likely to be of African heritage. Those with the lowest antioxidant intakes tended to have a higher body mass index, to have a generally higher prevalence of diabetes or hypertension, to drink more alcohol, to engage in less physical activity, and to have a greater smoking history. These differences were accounted for by controlling for these variables in multivariate analyses.

During 1,077,099 person-years of follow-up, we identified 474 cases of primary open-angle glaucoma. Adjusting for other covariates, we found that the risk of primary open-angle glaucoma was not materially related to β-carotene, total β-carotene, dietary β-carotene, β-cryptoxanthin, lycopene, or lutein/zeaxanthin in the primary analyses (table 2). The 4-year lagged analyses showed more inverse associa-
Intakes of total vitamin C, dietary vitamin C, total vitamin A, and total vitamin E were not significantly associated with the risk of primary open-angle glaucoma in the primary or 4-year lagged analyses (table 3). The rate ratios comparing the 4-year lagged analyses of the highest versus the lowest quintiles were 0.80 (95 percent CI: 0.58, 1.10) for total vitamin C, 0.97 (95 percent CI: 0.69, 1.37) for total vitamin A, and 0.81 (95 percent CI: 0.59, 1.10) for total vitamin E. With dietary vitamin E, we observed inverse associations (RR = 0.67, 95 percent CI: 0.50, 0.90; \( p \) for linear trend = 0.02 for the primary analyses and RR = 0.71, 95 percent CI: 0.53, 0.97; \( p \) for linear trend = 0.08 for the lagged analyses). As antioxidants tend to act synergistically (40), a composite score was constructed by summing the quintile scores 0–4 of the five carotenoids with vitamin C and vitamin E. No significant associations were observed between the composite antioxidant score and primary open-angle glaucoma risk.

When we excluded supplement users and examined intakes solely from foods, we found very similar results. For example, the rate ratios for top to bottom quintile using 4-year lagged intakes were 0.69 (95 percent CI: 0.44, 1.08) for lutein/zeaxanthin and 1.00 (95 percent CI: 0.60, 1.69) for the composite antioxidant score.

We also evaluated the risk of high-tension glaucoma specifically (defined as maximum intraocular pressure of \( \geq 22 \) mmHg; total of 358 cases, 221 from the Nurses’ Health Study and 137 from the Health Professionals Follow-up Study). In general, we observed no marked differences, with the exception of a greater inverse association with lutein/zeaxanthin in the 4-year lagged analyses: The rate ratio for the highest quintile was 0.58 (95 percent CI: 0.40, 0.84; \( p \) for linear trend = 0.17).

Supplement use was not associated with primary open-angle glaucoma risk. Comparing primary open-angle glaucoma risk.

### TABLE 3. Continued

<table>
<thead>
<tr>
<th>Antioxidant Intake and Open-Angle Glaucoma</th>
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</thead>
<tbody>
<tr>
<td>Quintile 1</td>
<td>Quintile 2</td>
<td>Quintile 3</td>
<td>Quintile 4</td>
<td>Quintile 5</td>
<td>( \beta_{\text{trend}} )</td>
<td>( \beta_{\text{rel}} )</td>
</tr>
<tr>
<td>Vitamin E (mg/day)</td>
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<td></td>
</tr>
<tr>
<td>Medians (W, M)</td>
<td>(6, 8)</td>
<td>(8, 10)</td>
<td>(10, 13)</td>
<td>(16, 22)</td>
<td>(125, 186)</td>
<td></td>
</tr>
<tr>
<td>NHS</td>
<td>1.00 (referent)</td>
<td>0.72</td>
<td>0.49, 1.04</td>
<td>0.77</td>
<td>0.54, 1.11</td>
<td>0.86</td>
</tr>
<tr>
<td>HPFS</td>
<td>1.00 (referent)</td>
<td>1.70</td>
<td>0.98, 2.93</td>
<td>1.47</td>
<td>0.85, 2.55</td>
<td>1.14</td>
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<tr>
<td>Pooled</td>
<td>1.00 (referent)</td>
<td>1.08</td>
<td>0.46, 2.50</td>
<td>1.03</td>
<td>0.55, 1.94</td>
<td>0.93</td>
</tr>
<tr>
<td>Pooled 4-year lag</td>
<td>1.00 (referent)</td>
<td>0.74</td>
<td>0.53, 1.02</td>
<td>0.85</td>
<td>0.63, 1.17</td>
<td>0.79</td>
</tr>
<tr>
<td>Vitamin E from foods only (mg/day)</td>
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</tr>
<tr>
<td>Medians (W, M)</td>
<td>(6, 8)</td>
<td>(7, 9)</td>
<td>(8, 10)</td>
<td>(8, 11)</td>
<td>(10, 14)</td>
<td></td>
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<tr>
<td>NHS</td>
<td>1.00 (referent)</td>
<td>0.81</td>
<td>0.57, 1.16</td>
<td>0.74</td>
<td>0.51, 1.06</td>
<td>0.76</td>
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<tr>
<td>HPFS</td>
<td>1.00 (referent)</td>
<td>0.79</td>
<td>0.47, 1.32</td>
<td>0.75</td>
<td>0.46, 1.25</td>
<td>0.83</td>
</tr>
<tr>
<td>Pooled</td>
<td>1.00 (referent)</td>
<td>0.80</td>
<td>0.60, 1.08</td>
<td>0.74</td>
<td>0.55, 1.00</td>
<td>0.79</td>
</tr>
<tr>
<td>Pooled 4-year lag</td>
<td>1.00 (referent)</td>
<td>0.66</td>
<td>0.28, 1.57</td>
<td>0.68</td>
<td>0.50, 0.94</td>
<td>0.69</td>
</tr>
</tbody>
</table>

†† Antioxidant score is a composite measure of the intakes of vitamin E, vitamin C, and carotenoids (α-carotene, β-carotene, β-cryptoxanthin, lutein/zeaxanthin, lycopene) derived by summing the quintile score of 0–4 for each of these nutrients.
coma risk in long-term supplement users with 10 or more years’ duration (>5 years for vitamin A) with risk in never users, we found that the rate ratios were 0.91 (95 percent CI: 0.69, 1.19) for multivitamins, 1.17 (95 percent CI: 0.89, 1.54) for vitamin C, 0.77 (95 percent CI: 0.53, 1.14) for vitamin E, and 0.96 (95 percent CI: 0.48, 1.89) for vitamin A. When these associations were examined among those consuming less than the median values for each vitamin, or when 4-year lagged relations were explored, we observed no material differences (data not shown). We also did not see associations between the current dose consumed and the risk of primary open-angle glaucoma (data not shown).

We also examined the major food sources for these nutrients. In both the primary and 4-year lagged analyses, no single food appeared to be strongly related to primary open-angle glaucoma risk.

We assessed the possibility of detection bias in various ways: controlling for other predictors of more frequent eye examinations (cataract diagnoses, macular degeneration diagnoses, report of physician examination, or total number of eye examination reports); limiting analyses only to those receiving eye examinations for screening or those who are 65 or more years; and restricting analyses to those consistently reporting eye examinations during follow-up. Although such restrictions limited the statistical power, we found no appreciable differences with the primary results (data not shown).

**DISCUSSION**

In our two prospective cohorts, we found little evidence that higher total intake of vitamin C, vitamin E, or vitamin A substantially reduced risks of primary open-angle glaucoma. Similarly, intakes of specific carotenoids did not appear to be materially related to primary open-angle glaucoma risk, with the possible exception of lutein/zeaxanthin. No specific fruits and vegetables or food groups were strongly associated with primary open-angle glaucoma risk. The use of multivitamins or supplements of vitamins C, E, and A, analyzed by either dose or duration, was unrelated to primary open-angle glaucoma risk.

To our knowledge, no previous longitudinal data are available on the relation between dietary antioxidants and primary open-angle glaucoma. The carotenoids examined are effective antioxidants (41–43), but they differ in concentration among ocular tissues (44). Carotenoids other than lutein/zeaxanthin are found only in trace amounts in ocular tissues, except for the ciliary body, where the aqueous humor is generated (44). In contrast, lutein and zeaxanthin are present in high concentrations in specific ocular tissues, such as the macula, retina, lens, and ciliary body (42). The inverse association observed with lutein/zeaxanthin in the 4-year lagged analyses may be a chance finding, but it deserves further evaluation, particularly in relation to high-tension glaucoma.

Vitamin C neutralizes oxygen radicals and singlet oxygen and is a reductant of oxidized vitamin E (45). In addition, ascorbic acid, which is 15 times higher in concentration in the aqueous humor than in plasma (46), may reduce intraocular pressure by the depolymerization of the trabecular meshwork’s hyaluronic acid component (47). Considerable reductions in intraocular pressure have been observed in glaucoma patients after administration of ascorbic acid in some (48–50), but not all (51, 52), studies. However, the high doses used were beyond ordinary consumption (0.5 g/kg of body weight per day (48, 49) or 3 g/day (50)) and thus could not be addressed here. In the only study to evaluate dietary factors with 38 glaucoma patients and 12 controls, no differences were found in either the dietary intake (measured by 1-week dietary record after diagnosis) or the postdiagnosis plasma levels of vitamin C (53). Another study (54) found no significant differences between the aqueous humor ascorbic acid concentrations in primary open-angle glaucoma patients and normal controls.

Vitamin E, a fat-soluble antioxidant, is important in protecting cell membranes from lipid peroxidation (55). In the anterior chamber, the aqueous humor vitamin E content is low, but an increasing intake of vitamin E may affect the antioxidant defenses in the aqueous humor by increasing the concentration of glutathione (56). In our study, the largest contributor to vitamin E intake is supplements, and we observed no clear associations with duration or dose. The inverse associations with dietary vitamin E thus may be due to chance or to foods with high vitamin E content containing other nutrients that may protect against primary open-angle glaucoma risk.

Our study has several strengths. The prospective design and high follow-up rates make recall or selection biases less likely. Multiple dietary assessments reduce measurement error and allowed us to examine the relations with nutrients over time. The range of intake, especially for supplement use, was large and generally comparable to intakes found in another US elderly population (57). We were able to control for several primary open-angle glaucoma risk factors, such as age, African heritage, and hypertension. Finally, there was little apparent detection bias, in that subanalyses restricted to those who received consistent eye examinations gave results that did not differ materially from the main findings.

The specific limitations of our study include the possibility of confounding by other variables, such as family history of primary open-angle glaucoma. Although we were unable to control for family history, it is unlikely that antioxidant intake differs by family history of primary open-angle glaucoma, as the antioxidant hypothesis has been little studied. We were also limited in our ability to detect modest associations, and longer follow-up of these cohorts will be necessary.

Participants’ error in dietary reporting would result in biases toward null associations. However, previously from these cohorts, inverse associations were reported between antioxidant intake and several major diseases (58–60). Therefore, if a true strong association between dietary antioxidant and primary open-angle glaucoma risk exists, we would be able to detect it.

Because conducting repeated eye examinations in these large cohorts was prohibitive, we had to rely on participants’ self-reports and medical records for case identification. As population-based studies found that only about 50 percent of persons with glaucoma are aware of their condition (1, 61), we restricted the sample of participants analyzed to those...
who had access to eye examinations in the past 2 years and, for confirmation, required that two glaucoma specialists independently use an objective standardized protocol when reading visual fields from the medical records. The eye examination restriction would also minimize biases from multivitamin users’ possibly receiving more eye examinations and thus being more likely to get diagnosed with primary open-angle glaucoma. Thus, we believe that this method was essential to the internal validity of our study.

Because of the insidious nature of the disease, the heterogeneous nature of eye examinations for detecting primary open-angle glaucoma, and our requirement of reproducible visual field defects, our protocol may have resulted in a greater percentage of cases with moderate-to-severe disease than would have been detected in a direct standardized ophthalmologic survey of this cohort.

In summary, using data from two large prospective cohorts, we found little evidence that intakes of dietary carotenoids, vitamin C, vitamin E, and fruits and vegetables or supplements substantially reduce the risk of developing primary open-angle glaucoma.

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REFERENCES


