The Association between Glaucoma Prevalence and Supplementation with the Oxidants Calcium and Iron

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PURPOSE. To investigate the relationship between supplementary consumption of the oxidants calcium and iron and the prevalence of glaucoma.

METHODS. This cross-sectional study included 3833 participants in the National Health and Nutrition Examination Survey (NHANES) for 2007 and 2008, ≥ 40 years of age, who reported a presence or absence of glaucoma. Participants were interviewed regarding the use of dietary supplements and antacids during the preceding 30-day period. Data pertaining to the supplementary intake of calcium and iron was aggregated and divided into quintiles. Information regarding the presence or absence of glaucoma and demographics, comorbidities, and health-related behavior was obtained via interview.

RESULTS. Participants who consumed ≥ 800 mg/d of supplementary calcium or ≥ 18 mg/d of supplementary iron had significantly higher odds of having been diagnosed with glaucoma than did those who had not consumed supplementary calcium or iron, after adjustment for potential confounders (odds ratio [OR] 2.44, 95% confidence interval [CI] 1.25–4.76 for calcium; OR 3.80, 95% CI 1.79–8.06 for iron). Concurrent consumption of both calcium and iron above these levels was associated with still greater odds of having been diagnosed with glaucoma (OR 7.24, 95% CI 2.42–21.62). A clear dose-response relationship between quintiles of supplementary calcium or iron intake and glaucoma prevalence was not found.

CONCLUSIONS. These results suggest that there may be a threshold intake of iron and calcium above which there is an increased risk of development of glaucoma. Prospective longitudinal studies are needed, to assess whether oxidant intake is a risk factor for development and progression of glaucoma. (*Invest Ophthalmol Vis Sci.* 2012;53:725–731) DOI:10.1167/iov.11-9038

Glaucoma is a chronic and irreversible optic neuropathy, characterized by the progressive loss of retinal ganglion cells.^{1,2} The only confirmed modifiable risk factor for glaucoma is intraocular pressure (IOP); consequently, the goal of all current medical and surgical therapies for this disease is to reduce IOP. The identification of modifiable risk factors other than IOP may provide additional therapeutic targets that would

be valuable in the management of patients, particularly those who continue to show substantial progression despite significant lowering of IOP.

A body of research has focused on elucidating the role of oxidative stress in the pathogenesis of neuronal death as well as aqueous humor outflow,³ with particular interest in the role that oxidants such as calcium and iron may play in disease pathogenesis. Iron is a potent oxidant that accumulates with aging and catalyzes the creation of highly reactive hydroxyl radicals, which can cause oxidative damage to DNA and adjacent lipids and proteins. In vitro studies have suggested that iron regulation plays a role in glaucoma's pathogenesis both in retinal ganglion⁴ and trabecular meshwork (TM)⁵ cells. Dysregulation of calcium homeostasis has also been implicated in some neurodegenerative diseases,⁶ including glaucoma.⁷ One study found that human TM cells from donors with glaucoma were defective in mitochondrial function, resulting in abnormal sensitivity to calcium-induced stress.⁸ Impaired calcium regulation and calcium overload have been found in lamina cribrosa cells of donors with glaucoma,⁹ and intriguing yet controversial evidence suggests that treatment of glaucoma patients with a calcium channel blocker may slow loss of visual fields.¹⁰

These previous animal and preliminary human studies have offered potential roles that calcium and iron may play in oxidative stress and the pathogenesis of glaucoma. However, there have been no epidemiologic studies investigating the relationship of calcium or iron consumption with glaucoma. The National Health and Nutrition Examination Survey (NHANES) is an annual national population study conducted by the Centers for Disease Control and Prevention (CDC) designed to assess the health status of the U.S. population. It not only includes an extensive interview related to a variety of health conditions and medication use, but a physical examination component as well, which includes a visual acuity examination and objective refraction. In addition, the 2007–2008 data release of NHANES included a calculated intake of a variety of nutrients from a detailed interview of participants' use of dietary supplements. We have used this extensive, nationally representative sample to study the association between glaucoma and the consumption of calcium and iron through dietary supplements.

METHODS

Sample and Population

We used publicly available data from the National Health and Nutrition Examination Survey (NHANES) for 2007 and 2008,¹¹ a cross-sectional series of interviews and examinations of the civilian, noninstitutionalized population of the United States, to assess the relationship between self-reported glaucoma and supplementary consumption of calcium and iron. NHANES is administered by the Centers for Disease Control and Prevention (CDC) for the purpose of providing U.S. health statistics, and includes interviews and examinations of approximately 5000 persons per year. NHANES uses a stratified multistage sampling design that requires a weighting scheme to provide optimal estimates of disease prevalence in the U.S. population.

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Our analysis included 3848 participants in NHANES in 2007 and 2008 who were 40 years of age or older and underwent both the interview and examination portions of the study. An additional 14 participants were excluded because of reported uncertainty regarding whether they had received a diagnosis of glaucoma, and 1 participant was excluded for not answering the question pertaining to glaucoma diagnosis.

Measures

The primary predictor variables were intake of calcium and iron from dietary supplements and antacids. NHANES included an interview about the use of prescription and nonprescription dietary supplements and antacids during the 30-day period before the interview. NHANES aggregated the intake of calcium and iron from all reported antacids and dietary supplements and determined the average daily intake for each nutrient. We then divided the population by quintiles of intake for each of the nutrients. The two highest quintiles of iron intake were classified into one intake category (≥ 18 mg/d), because the number of participants consuming exactly 18 mg/d of iron exceeded 20% of the population taking supplemental iron; consequently, both the 60th and 80th percentiles of iron intake were equal to 18 mg/d and participants in the 5th quintile could not be reliably distinguished from those in the 4th quintile.

The primary outcome variable was the presence or absence of self-reported glaucoma ($n = 248$). A 19-point suprathereshold screening test using N-30-5 frequency doubling technology (FDT) was also administered to the participants. In NHANES, abnormal FDT status was defined by using a 2-2-1 algorithm: two fields in the first test below the 1% threshold level, at least two fields in the second test below the 1% threshold level, and at least one failed field in the same location on both tests. FDT testing was considered unreliable if either of the two tests in each eye had at least two thirds false-positive or blind-spot errors or the technician supervising the test noted poor fixation.¹²

Potential confounding variables included age, sex, ethnicity, annual household income, and education; health-related behavior such as smoking (current, past, or never); alcohol use (number of alcoholic drinks per day over the past year); exercise (total number of metabolic equivalent tasks (MET); in minutes per week); basal metabolic index (BMI); comorbid medical conditions, such as self-reported history of osteoporosis, kidney failure, stroke, thyroid disease, emphysema, liver disease, cancer, congestive heart failure (CHF), diabetes, angina, coronary heart disease (CHD), myocardial infarction (MI), and chronic bronchitis; whether the patient had been treated for anemia in the prior 3 months; comorbid eye conditions, such as a self-reported history of cataract extraction, diabetic retinopathy, and macular degeneration; self-reported general health condition (self-rated as excellent or very good, fair, or poor or very poor); and spherical equivalent on objective refraction.

Data Analysis

We compared the distribution of possible confounding variables between participants with and without self-reported glaucoma using design-adjusted Rao-Scott Pearson-type χ^2 and Wald tests for categorical and continuous variables, respectively. Multivariate logistic regression models were created and refined by sequentially adding confounding variables. These models were used to examine the possible independent association of quintiles of iron and calcium intake with self-reported glaucoma. Potential confounding comorbidities not found to be significant at the $P < 0.1$ level in multivariate models were excluded from the final model. These excluded confounders were spherical equivalent on objective refraction; BMI; the comorbid eye condition of macular degeneration; comorbid medical conditions including kidney failure, stroke, CHF, diabetes, CHD, MI, thyroid disease, liver disease, emphysema, and chronic bronchitis; and treatment for anemia in the past 3 months. To most accurately calculate confidence intervals around estimates for the US national population, we performed all data analysis (Stata 12.0; Stata Statistical Software, College Station, TX) using weighted data, and standard errors of population estimates were calculated by Taylor linearization methods.

RESULTS

Population Characteristics

The 2007 and 2008 NHANES data yielded 3833 participants, 40 years of age or older, who participated in both the interview and examination portions of the study and were able to self-report presence or absence of glaucoma. Of these participants, 248 self-reported glaucoma, representing 4.7% (SE 0.44%) of the U.S. population.

Tables 1 and 2 present information on demographic characteristics, comorbidities, health-related behavior, and calcium and iron supplement intake between those with and without self-reported glaucoma. Many characteristics differed significantly between these two populations. The mean ages of those with and without glaucoma were 66.3 years (SE 1.51) and 56.6 years (SE 0.31), respectively ($P < 0.0001$). Smoking status and average daily number of alcoholic drinks did not differ between the two groups; however, those with glaucoma exercised significantly less on crude comparison ($P < 0.0098$).

Intake of Supplementary Calcium or Iron

Differences in calcium and iron intake by glaucoma status are presented in Table 2. Average daily calcium and iron intake from all antacids and dietary supplements for each participant were categorized into five quintiles of intake with an additional no-intake category. Intake of supplemental calcium differed between those with and without glaucoma, but the difference did not reach statistical significance in this unadjusted comparison ($P = 0.066$). Intake of supplemental iron differed significantly between those with and without glaucoma, with a higher proportion of participants with glaucoma consuming iron in the highest two quintiles compared with those without glaucoma (6.4% vs. 2.2%, respectively, $P = 0.0226$). The highest two quintiles of iron intake were combined into one category because the number of participants taking exactly 18 mg/d of iron exceeded 20% of the population taking supplemental iron; therefore, 18 mg/d represented both the 60th and the 80th percentiles of iron intake, and we could not readily discriminate between the top two quintiles.

We constructed multivariate logistic regression models to compare the odds of self-reported glaucoma between those consuming and not consuming supplemental calcium or iron (Tables 3, 4), while adjusting for confounders. Medical and ocular comorbidities were excluded as confounders in the multivariate model if they were not significant at $P < 0.1$; notably, kidney failure and treatment for anemia were among these excluded comorbidities. In contrast, the presence or absence of osteoporosis was included in the model as this variable was significant at the $P < 0.1$ level. The consumption of supplemental calcium at the highest quintile level (≥ 800 mg/d) was associated with significantly higher odds of glaucoma compared with no supplemental calcium consumption, even after adjustment for demographic characteristics, health-related behavior, comorbidities, and self-reported general health condition (odds ratio [OR] 2.44, 95% confidence interval [CI] 1.25–4.76). Similarly, consumption of supplemental iron in the highest two quintiles (≥ 18 mg/d) was also associated with significantly higher odds of glaucoma compared with no supplemental iron consumption, after adjustment for the same confounders (OR 3.80, 95% CI 1.79–8.06). We did not find significantly higher odds of glaucoma among other quintiles of supplemental calcium or iron intake, nor did we observe a clear dose-response relationship between increasing supplemental calcium or iron intake and odds of glaucoma.

In an effort to improve disease specificity beyond what might be expected with self-report, we performed a subgroup analysis, defining as our outcome a self-reported diagnosis of

TABLE 1. Demographic and General Health Characteristics of Participants with or without Self-reported Glaucoma

	No Glaucoma		Glaucoma		P†
	Mean*	SE	Mean*	SE	
Demographics					
Mean age, y	56.6	0.31	66.3	1.51	<0.0001
Female, %	53.0	0.9	50.2	4.0	0.5102
Race, %					0.395
Mexican	5.7	1.2	5.7	2.5	
Other Hispanic	4.0	1.1	5.2	2.2	
Non-Hispanic white	74.5	3.3	69.3	5.2	
Non-Hispanic black	10.3	1.9	14.1	3.5	
Other and multiracial	5.6	1.0	5.8	2.5	
Education, %					<0.0001
<9th Grade	7.8	0.9	20.0	4.5	
≥9th Grade, <HS graduate	12.6	1.2	15.0	2.7	
HS graduate or GED equivalent	26.1	1.6	28.3	4.0	
Some college	26.6	1.5	26.4	4.4	
College graduate and beyond	27.0	2.1	10.4	2.5	
Annual household income, %					0.0005
<\$20,000	14.9	1.3	25.8	4.0	
\$20,000–\$44,999	27.0	1.7	37.6	4.0	
\$45,000–\$74,999	20.0	1.5	18.0	4.4	
\$75,000 and up	34.5	2.3	13.5	4.2	
>\$20,000	3.6	0.7	5.2	1.5	
Comorbidities					
General health condition, %					<0.0001
Excellent or good	41.3	2.1	35.7	4.8	
Fair	39.6	1.2	20.8	3.4	
Poor or very poor	19.1	1.5	43.6	3.7	
Visual comorbidities, %					
History of cataract extraction	10.4	0.7	36.3	4.9	<0.0001
Self-reported age-related macular degeneration	3.1	0.3	7.4	1.5	0.0012
Self-reported diabetic retinopathy	2.4	0.4	12.2	1.7	<0.0001
Medical comorbidities, %					
Osteoporosis	8.0	1.0	20.7	2.6	<0.0001
Taking treatment for anemia	4.7	0.5	8.6	2.4	0.0293

* All means, proportions, and standard errors are weighted estimates of the U.S. population characteristics, taking into account NHANES's complex sampling design.

† All *P* values are unadjusted. *P* values were calculated using Wald test for continuous variables, and design-adjusted Rao-Scott Pearson χ^2 test for categorical variables.

glaucoma with a visual field defect detected by FDT screening ($n = 141$). Participants who self-reported glaucoma but had normal FDT screening results were excluded from this analysis. Although consumption of supplemental calcium at the highest quintile level (≥ 800 mg/d) continued to be associated with increased odds of glaucoma in this subgroup analysis, the association was not statistically significant (OR 1.91, 95% CI 0.94–3.88) in this smaller study sample. In contrast, consumption of supplemental iron ≥ 18 mg/d continued to be significantly associated with self-reported glaucoma confirmed by abnormal FDT screening results (OR 3.92, 95% CI 1.06–14.40). The wider confidence intervals in both subgroup analyses relative to the outcomes found when all self-reported glaucoma subjects were included are, of course, largely reflective of the smaller number of confirmed subjects determined to have glaucoma in the subgroup analyses.

Concurrent Intake of Supplementary Calcium and Iron

We next investigated whether concurrent consumption of calcium and iron would show an additive or synergistic association with the odds of having glaucoma (Table 5). Participants were categorized into those taking neither calcium nor iron supplements (no-intake group), those taking both calcium

<800 mg/d and iron <18 mg/d (low-intake group), and those taking both calcium ≥ 800 mg/d and iron ≥ 18 mg/d (high-intake group). Subjects with a high intake of one oxidant but no or low intake of the other were not included in this combined intake analysis. The low-intake group did not have significantly higher odds of glaucoma than the no-intake group (OR 1.27, 95% CI 0.44–3.63). In contrast, the high-intake group did have significantly higher odds of having a diagnosis of glaucoma than the no-intake group, which persisted after adjustment for confounders (OR 7.24, 95% CI 2.42–21.62). The high-intake group also had significantly higher odds of glaucoma than did the low-intake group, after adjustment for confounders (OR 5.77, 95% CI 2.10–15.89).

DISCUSSION

This study of a U.S. national population-based sample of adults 40 years of age and older found that participants who consumed ≥ 800 mg/d of supplementary calcium or ≥ 18 mg/d of supplementary iron had significantly higher odds of self-reported glaucoma than those who reported no supplemental intake, after adjustment for potential confounders. These nutrient intake levels were equivalent to the highest quintile of calcium intake and the highest two quintiles of iron intake in

TABLE 2. Health-Related Behavior and Supplement Use among Participants with and without Glaucoma

	No Glaucoma		Glaucoma		<i>P</i> †
	%*	SE	%*	SE	
<i>Health-Related Behavior</i>					
Smoking					0.0632
Current	19.5	1.5	16.0	3.9	
Past	29.6	1.0	39.8	3.8	
Never	50.9	1.2	44.2	4.6	
MET minutes of exercise per week					0.0098
None	27.7	1.9	42.5	3.1	
1st Quartile, <195	21.3	1.3	16.2	2.2	
2nd Quartile, <540	18.3	1.1	17.5	3.4	
3rd Quartile, <1320	16.9	1.3	14.3	2.5	
4th Quartile, ≥1320	15.7	0.8	9.5	2.6	
Average daily number of alcoholic drinks					0.5407
0	42.9	2.5	48.3	6.8	
>0 and <1	42.7	1.7	41.4	5.0	
≥1 and <2	7.7	1.0	6.0	2.2	
≥2 and <4	4.8	0.8	3.5	1.8	
≥4	1.9	0.4	0.8	0.4	
<i>Supplemental Nutrient Intake</i>					
Calcium					0.066
No intake	49.5	1.8	44.7	4.1	
1st Quintile, >0 mg/d and <100 mg/d	11.1	0.7	12.1	2.1	
2nd Quintile, ≥100 mg/d and <200 mg/d	11.1	1.2	7.0	2.0	
3rd Quintile, ≥200 mg/d and <375 mg/d	8.5	0.7	8.5	2.6	
4th Quintile, ≥375 mg/d and <800 mg/d	10.9	0.9	12.3	1.9	
5th Quintile, ≥800 mg/d	9.0	0.7	15.5	2.5	
Iron					0.0226
No intake	79.0	1.4	78.2	3.3	
1st Quintile, >0 mg/d and <6 mg/d	4.4	0.6	3.2	1.3	
2nd Quintile, ≥6 mg/d and <15 mg/d	4.6	0.6	3.2	1.4	
3rd Quintile, ≥15 mg/d and <18 mg/d	9.9	0.7	9.0	1.7	
4th and 5th Quintiles, ≥18 mg/d	2.2	0.3	6.4	1.9	

* All proportions and standard errors are weighted estimates of the U.S. population characteristics, taking into account NHANES' complex sampling design.

† All *P* values are unadjusted and were calculated using the design-adjusted Rao-Scott Pearson χ^2 test for categorical variables.

this population. Concurrent consumption of both calcium and iron at these levels was associated with even greater odds of glaucoma. We did not, however, find a clear dose-response relationship between quintiles of supplementary calcium or iron intake and self-reported glaucoma. Rather, the relationship appeared to suggest a threshold level of oxidant consumption above which there is substantially increased risk of glaucoma. While the concurrent consumption of calcium and iron below

threshold levels did not increase the odds of glaucoma, suggesting that there is no significant additive effect of oxidant supplementation below 800 mg/d of calcium and 18 mg/d of iron, the consumption of both oxidants above these threshold levels resulted in even greater odds of glaucoma. It is noteworthy that the threshold levels deemed to be associated with glaucoma risk in this population-based study are considerably lower than the tolerable upper intake levels of calcium (2000

TABLE 3. ORs for the Presence of Glaucoma among Supplementary Calcium Consumers, Compared with Consumers of No Supplementary Calcium

	1st Quintile (<100 mg/d) OR* (95% CI)	2nd Quintile (≥100 mg/d) OR* (95% CI)	3rd Quintile (≥200 mg/d) OR* (95% CI)	4th Quintile (≥375 mg/d) OR* (95% CI)	5th Quintile (≥800 mg/d) OR* (95% CI)
Unadjusted	1.21 (0.76–1.91)	0.69 (0.31–1.53)	1.10 (0.55–2.21)	1.25 (0.78–1.99)	1.90 (1.11–3.27)
Age	1.32 (0.82–2.13)	0.64 (0.29–1.43)	0.90 (0.49–1.68)	0.99 (0.59–1.67)	1.33 (0.72–2.45)
+Sex	1.32 (0.81–2.16)	0.63 (0.28–1.42)	0.89 (0.48–1.65)	1.08 (0.65–1.79)	1.50 (0.82–2.75)
+Ethnicity	1.42 (0.85–2.38)	0.68 (0.31–1.51)	1.00 (0.53–1.88)	1.19 (0.74–1.93)	1.76 (0.99–3.15)
+SES†	1.62 (0.92–2.86)	0.82 (0.35–1.92)	1.16 (0.54–2.52)	1.46 (0.88–2.44)	2.32 (1.28–4.21)
+HRB‡	1.55 (0.84–2.87)	0.63 (0.29–1.39)	1.19 (0.56–2.54)	1.38 (0.73–2.60)	2.28 (1.20–4.33)
+Comorbidities§	1.57 (0.77–3.21)	0.59 (0.25–1.42)	1.23 (0.56–2.72)	1.25 (0.67–2.72)	2.30 (1.16–4.55)
+General health condition	1.67 (0.78–3.54)	0.65 (0.27–1.52)	1.25 (0.58–2.68)	1.47 (0.70–3.08)	2.44 (1.25–4.76)

* Reference group: no intake of supplementary calcium.

† Socioeconomic status variables included annual household income and education level.

‡ Health-related behaviors include smoking status (current, past, or never), exercise (MET-minutes per week), alcohol intake (drinks per day).

§ Comorbidities include osteoporosis, angina, history of cataract operation, diabetic retinopathy.

TABLE 4. ORs for the Presence of Glaucoma among Consumers of Supplementary Iron by Quintile of Intake, Compared with Consumers of No Supplementary Iron

	1st Quintile (<6 mg/d) OR* (95% CI)	2nd Quintile (≥ 6 mg/d) OR* (95% CI)	3rd Quintile (≥ 15 mg/d) OR* (95% CI)	4th and 5th Quintile (≥ 18 mg/d) OR* (95% CI)
Unadjusted	0.74 (0.30–1.80)	0.72 (0.25–2.09)	0.92 (0.53–1.61)	2.98 (1.45–6.11)
Age	0.87 (0.37–2.04)	0.98 (0.33–2.88)	0.90 (0.55–1.47)	1.85 (1.31–6.21)
+Sex	0.91 (0.40–2.07)	1.01 (0.34–2.97)	0.92 (0.57–1.49)	2.95 (1.37–6.33)
+Ethnicity	0.97 (0.42–2.23)	1.06 (0.36–3.10)	0.98 (0.60–1.61)	3.03 (1.40–6.57)
+SES†	1.06 (0.46–2.44)	1.36 (0.49–3.80)	1.09 (0.63–1.91)	3.67 (1.85–7.28)
+HRB‡	0.63 (0.18–2.19)	1.42 (0.51–3.96)	1.08 (0.62–1.89)	4.20 (1.99–8.83)
+Comorbidities§	0.73 (0.21–2.50)	1.47 (0.49–4.43)	1.24 (0.64–2.39)	3.79 (1.83–7.85)
+General health condition	0.73 (0.21–2.49)	1.67 (0.55–5.05)	1.23 (0.63–2.40)	3.80 (1.79–8.06)

* Reference group: no intake of supplementary iron.

† Socioeconomic status variables included annual household income and education level.

‡ Health-related behaviors include smoking status (current, past, or never), exercise (MET-minutes per week), alcohol intake (drinks per day).

§ Comorbidities include osteoporosis, angina, history of cataract operation, diabetic retinopathy.

mg/d for those aged ≥ 51 years)¹² and iron (45 mg/d for those aged ≥ 19 years)¹³ established by the Institute of Medicine for total nutrient intake.

It can be hypothesized that the detrimental health effects of supplementary iron intake may be because it is a potent oxidant that accumulates in the body with age. Consumption of supplementary iron has recently been associated with increased total mortality among elderly women.¹⁴ Furthermore, prior *in vitro* studies have suggested potential biologic mechanisms by which intracellular iron may be related to glaucoma, with Lin et al.,⁵ observing that redox-active iron was elevated in TM cells that were chronically stressed in a hyperoxic model. Changes in expression of iron homeostasis genes were also observed, whereas intracellular chelation of iron protected against apoptosis caused by H₂O₂ oxidative stress.⁵ Farkas et al.⁴ observed differences in expression of iron-regulating genes and levels of iron-related proteins between the retinal ganglion cells of glaucomatous and nonglaucomatous eyes, both in monkeys and in humans. Affected proteins included the iron storage, uptake, and antioxidant proteins ferritin, transferrin, and ceruloplasmin, respectively. Our findings are consistent with the conclusions of these previous studies that the regulation of iron and the response to oxidative stress may play important roles in glaucoma pathogenesis by impacting aqueous humor outflow and/or retinal ganglion cell survival.

The role of calcium homeostasis in glaucoma and other neurodegenerative diseases, as well as aging, has also been studied. Influx and intracellular accumulation of high levels of calcium is known to trigger cell death through caspase-depen-

dent degradation.⁷ Furthermore, aging causes subtle changes in calcium homeostasis through mitochondrial dysfunction that renders neurons more vulnerable to oxidative stress.⁶ A background of age-related calcium dysregulation combined with environmental or genetic stressors has been hypothesized to be associated with neurodegenerative diseases.⁶ For example, Alzheimer's Disease (AD) research suggests that there is a positive feedback loop between calcium dysregulation and production of toxic amyloid- β , resulting in neuronal death.⁶ Research in Parkinson's Disease (PD) has also suggested that calcium dysregulation drives neuronal loss, with relationships demonstrated between α -synuclein aggregates and calcium dysregulation in sporadic PD^{15–17} and results indicating that higher levels of calcium-buffering proteins confer resistance to degeneration among dopaminergic neurons.^{18–20} Finally, calcium dysregulation and overload have been identified in both TM⁸ and lamina cribrosa cells.⁹ Considering the common neurodegenerative features between AD, PD, and glaucoma and a possible epidemiologic association between these three diseases,^{21–26} it would not be surprising if calcium dysregulation were found to increase the risk of glaucoma.

We acknowledge that our study conclusions are limited by the reliance on a self-report of a prior diagnosis of glaucoma that may be subject to recall bias and disease misclassification. One must consider the possibility that there is an association between supplemental oxidant consumption status and misclassification of glaucoma and that such a potential differential bias may amplify our results away from the null hypothesis, particularly if high consumers of iron or calcium supplements

TABLE 5. ORs for the Presence of Glaucoma among Consumers of Both Calcium and Iron Supplements, Compared with Consumers of Neither

	Low Intake: Calcium (<800 mg/d) and Iron (<18 mg/d) OR* (95% CI)	High Intake: Calcium ≥ 800 mg/d and Iron ≥ 18 mg/d OR* (95% CI)
Unadjusted	0.81 (0.36–1.85)	4.89 (1.58–15.11)
Age	0.87 (0.39–1.92)	4.85 (1.63–14.45)
+Sex	0.90 (0.41–1.98)	5.32 (1.83–15.42)
+Ethnicity	0.98 (0.45–2.16)	6.26 (2.21–17.68)
+SES†	1.21 (0.51–2.67)	7.37 (2.79–19.46)
+HRB‡	1.08 (0.41–2.83)	7.03 (2.44–20.24)
+Comorbidities§	1.20 (0.42–2.23)	7.15 (2.66–19.19)
+General health condition	1.27 (0.44–3.63)	7.24 (2.42–21.62)

* Reference group: no intake of supplementary calcium or iron.

† Socioeconomic status variables included annual household income and education level.

‡ Health-related behaviors include smoking status (current, past, or never), exercise (MET-minutes per week), alcohol intake (drinks per day).

§ Comorbidities include osteoporosis, angina, history of cataract operation, diabetic retinopathy.

are more likely to self-report glaucoma. In ideal circumstances, self-reported glaucoma should be confirmed or refuted by complete ophthalmic examination including structural and functional assessment of optic nerve status; lack of such testing leaves open the possibility that some subjects who self-report a diagnosis of glaucoma are in fact glaucoma suspects or ocular hypertensives. However, there is no compelling reason to believe that individuals taking a high level of supplementary oxidants would be systematically more or less likely to accurately recall a glaucoma diagnosis than would those taking lower levels of such supplements. If recall and misclassification with regard to glaucoma diagnosis is nondifferential among those consuming high and low levels of oxidants, as well as among those not using such supplements, one would expect the results to be biased toward the null, with resultant underestimation of the strength of the relationship between such consumption and glaucoma diagnosis.

An additional limitation of our study was the ascertainment of supplement intake information based on 30-day recall, which included both subjects who had been on long-term supplementation and those who had only recently begun receiving calcium or iron supplements. Furthermore, nutrient intake was aggregated only from supplement and antacid use and did not take into account natural dietary sources. However, dietary supplements are known to contribute substantially to the total intake of calcium and iron in the United States, particularly in elderly women.²⁷ There is also no compelling reason to suspect that these limitations in the measurement of supplemental oxidant intake would bias our results by differentially impacting subjects based on glaucoma status.

Much additional research elucidating the link between glaucoma and oxidant intake is required before we can advocate that patients discontinue supplemental calcium or iron therapy, particularly if such supplementation is necessary for a medical condition such as iron-deficiency anemia. As is the case with most population-based studies, our results do not shed light on the mechanism by which oxidant intake may increase the risk of glaucoma. Intraocular pressure measurements were not available, and their absence limited our ability to further hypothesize regarding the effects of calcium and iron intake on the TM outflow pathway. In addition, an association found in a cross-sectional study cannot determine the direction of causation; therefore, one must at least consider the possibility that a diagnosis of glaucoma could have led to increased calcium and/or iron supplementation. However, this scenario is unlikely, given that oxidant supplementation is generally used for the treatment of other clinical entities and is not recognized as an effective therapy for glaucoma.

Finally, one cannot rule out the possibility that the association we found between glaucoma and supplementation of calcium or iron actually represents a relationship between glaucoma and deficiency of calcium or iron. Iron deficiency, the surrogate for which may be recent treatment of anemia, was not a significant confounder and therefore was not included in the final model. Calcium deficiency as represented by a reported diagnosis of osteoporosis was significantly different between those with and without glaucoma on crude comparison, but this may be due to the age differences between the two groups. Osteoporosis was a significant confounder that was adjusted for in the multivariate model. It is also noteworthy that neither calcium nor iron deficiency is a proven risk factor for glaucoma and there is presently no plausible biologic mechanism that can support such a hypothesized association.

In summary, we found that after adjustment for confounding demographic factors, comorbidities, and health-related behaviors, consumption of supplementary calcium ≥ 800 mg/d or supplementary iron ≥ 18 mg/d was associated with significantly greater odds of self-reported glaucoma than was no

supplementary consumption of these oxidants. There may be a threshold level above which consumption of calcium or iron influences glaucoma, whereas consumption of these oxidants at lower levels has no such effect. The more than sevenfold greater odds of a glaucoma diagnosis in those with high levels of calcium and iron supplementation strongly suggest an important association that warrants further study. In addition to epidemiologic confirmation of our findings, further research is needed to determine whether calcium and iron intake may increase the risk of glaucoma progression and to elucidate the potential mechanisms by which consumption of these oxidants may influence glaucoma pathogenesis.

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