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The Association of Dietary Lutein/Zeaxanthin and B Vitamins with Cataracts in the Age- Related Eye Disease Study AREDS Report No. 37

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Abstract

Purpose—To evaluate whether dietary intake of lutein/zeaxanthin and B vitamins is associated with cataract prevalence and incidence.

Design—Clinic-based, baseline cross-sectional and prospective cohort study designs.

Participants—3115 (6129 eyes) persons enrolled in the Age-Related Eye Disease Study, aged 55 to 80 years, followed for mean of 9.6 years.

Methods—Participants completed baseline food frequency questionnaires. Baseline and annual lens photographs were graded centrally. Multivariable models controlling for previously identified risk factors for cataracts were used to measure the association of cataracts with reported dietary intake, using the lowest quintile as reference.

Main Outcome Measures—Cataract surgery, cataract status (type and severity) at baseline, development of cataracts.

Results—At baseline, increased dietary riboflavin and B12 were inversely associated with nuclear and cortical lens opacities. In comparisons of persons with and without cataract, persons with the highest riboflavin intake vs. those with the lowest intake had the following associations: odds ratio (OR): 0.78, 95% confidence interval (CI): 0.63–0.97 for mild nuclear, OR: 0.62, 95% CI: 0.43–0.90 for moderate nuclear, and OR: 0.80, 95% CI: 0.65–0.99 for mild cortical cataracts. For B12, the results were: OR: 0.78, 95% CI: 0.63–0.96 for mild nuclear, OR: 0.62, 95% CI:

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0.43–0.88 for moderate nuclear, and OR: 0.77, 95% CI: 0.63–0.95 for mild cortical cataracts. Highest dietary B6 intake was associated with a decreased risk of developing moderate nuclear lens opacity compared with the lowest quintile, OR: 0.67, 95% CI: 0.45–0.99. Highest dietary intake levels of niacin and B12 were associated with a decreased risk of development of mild nuclear or mild cortical cataracts in participants not taking Centrum® multivitamin. For participants taking Centrum® during the study, highest intake of dietary folate was associated with an increased risk of development of mild posterior subcapsular lens opacity. No statistically significant associations were found between lutein/zeaxanthin intake and presence at baseline or development of nuclear or cortical lens opacity outcomes.

Conclusions—Findings from our study are consistent with earlier studies suggesting that dietary intake of B vitamins may affect the occurrence of age-related lens opacities. Further investigations are warranted.

Cataract is the leading cause of blindness worldwide; the World Health Organization has estimated 20 million people are affected with vision loss from cataract.[1] In the United States, age-related cataracts remain the leading cause of vision loss, with Medicare spending over 2 billion dollars annually on cataract surgery.[2,3] Because the total number of people with cataracts in the US is expected to increase to 30 million by 2020 in an aging population[3], identification of factors associated with the development of age-related cataracts is an important step in developing approaches to reduce visual impairment and healthcare costs.

Risk factors for cataract development include increasing age, diabetes,[4,5] smoking[6], alcohol use, trauma, and prolonged exposure to UV light.[7–9] A greater understanding of the underlying processes involved in cataract formation, particularly the role of oxidative stress,[10,11] led to numerous observational studies[12–19] with a focus on vitamins and small molecules with antioxidant properties. Many of these studies reported inverse relationships between the development of age-related cataract or the occurrence of cataract surgery and dietary intake or serum levels of micronutrients with antioxidant properties. Micronutrients of interest included vitamins A, C, and E, niacin, thiamin, riboflavin, and carotenoids. However, results from the observational studies have not been consistent and, in the absence of any consensus about the importance of specific micronutrients, several controlled clinical trials[20–23] tested high doses of what were thought to be the most promising of the antioxidants (vitamins C, E, beta-carotene and lutein/zeaxanthin), but found no statistically significant effects on cataract development.[20,24] A randomized trial of vitamins C and E in two simultaneous trials in the United States and in the United Kingdom showed mixed results.[25]

The Age-Related Eye Disease Study (AREDS) was a randomized controlled clinical trial of vitamins C, E, and beta-carotene and zinc for the treatment of age-related macular degeneration (AMD) and age-related cataracts.[20] While AREDS found no statistically significant effect of vitamins C, E, and beta-carotene on the progression of lens opacities in the controlled randomized trial,[20] observational data from AREDS suggest that daily use of Centrum®, a multivitamin and mineral supplement, may decrease the progression of nuclear opacities.[26] In AREDS a food frequency questionnaire was administered at baseline and lens

photographs were taken at baseline, year 2 and annually thereafter. We examined relationships of baseline lutein/zeaxanthin and B vitamin intake with cataract prevalence, incidence, and cataract surgery. We chose these nutrients on the basis of antioxidant potential,[10,27–29] presence in the lens,[30–32] and reported protective associations with cataracts in observational[33–35] and interventional studies.[36]

Methods

AREDS, a long-term multi-center, prospective study of individuals aged 55–80 years was designed to evaluate the risk factors, clinical course, and prognosis of AMD and cataract. The project included a randomized controlled clinical trial of the AREDS formulation (vitamins C, E, beta-carotene, zinc, and copper). Details of the study design have been published elsewhere[37] and are briefly summarized here. Eleven retinal specialty clinics enrolled 4757 individuals and followed them at 6-month intervals in the clinical trial between 1992 and 2001. Participants were followed annually an additional 5 years in an observational study until 2005. Institutional review board approval was obtained at each clinical site, and participants signed informed consents for the study.

Based upon fundus photographs graded at a central reading center, best-corrected visual acuity, and ophthalmologic evaluations, participants were enrolled in one of several AMD categories.[38] However, there were no specific eligibility criteria for lens opacities except the lens had to be sufficiently clear to allow for adequate fundus photographs and visual acuity had to be 20/30 or better in at least one eye. Participants who had advanced AMD in one eye were excluded from these analyses because more advanced severity of lens opacities was allowed in these eyes, creating the possibility of an ascertainment bias. Excluded from the current study were eyes that were aphakic or pseudophakic at baseline. Participants less than 60 years of age were excluded from the prevalence analyses to ensure that the cataract is the age-related type. For the cataract incidence analyses of cataract development, eyes with moderate (type specific) cataracts at baseline were excluded from the progression to moderate cataract analyses, and eyes with mild or moderate (type-specific) cataracts at baseline were excluded from the development ofat least mild cataract analyses.

Participant screening and data collection

Baseline data and information regarding risk factors for the development of age-related cataract were obtained by examination and interview. As 55% of enrolled participants were already users of multivitamin supplements or at least one ingredient in the AREDS formulation at the time of screening, a standard daily multivitamin-mineral supplement, Centrum® was offered to all participants to standardize the use of non-study supplements. Sixty-six percent of study participants opted to take Centrum®. We evaluated baseline dietary intake calculated from a self-administered, 90-item, semi-quantitative food frequency questionnaire (FFQ), which assessed dietary intake (nutrients, vitamins, and minerals) during the year prior to randomization. Details of the FFQ and its validation have been described previously.[38]

Standard lens photographs, taken at baseline and annually beginning two years after enrollment, were graded centrally and used to assess the presence and progression of lens

opacities. The AREDS cataract grading scale is a modified version of the Wisconsin Cataract Grading System.[39] Nuclear opacities were graded on a decimal scale using a series of 7 standard photographs with increasingly severe nuclear opacification. A grid overlay on retroillumination lens photographs was used to estimate the area of lens involvement for PSC and cortical lens opacities. History of cataract surgery was determined by patient report, slit-lamp examination during study visits, and evidence of aphakia or pseudophakia on lens photographs.

Outcome measures

A standardized and validated grading system was used to establish a three-step severity scale for each type of opacity.[39,40] The controls and the severity of the 3 types of cataract using the AREDS standard for lens classification are described in table 1A. The baseline cross-sectional analyses compared controls with persons with mild and moderate nuclear or cortical opacities. PSC opacities were not included in the baseline cross-sectional analyses because they were uncommon in the cohort at baseline (only 2.5% of persons had PSC > 5% of the central 5 mm in at least one eye). The outcomes examined in the incidence analyses include development of and moderate lens opacities of all three types, or cataract surgery.

Analyses

Nutrient intake values were adjusted for total energy intake (TEI) by computing nutrient densities (nutrient intake/TEI). For cataract prevalence, gender-adjusted quintiles were then calculated. For the analysis of cataract progression and advancement to cataract surgery, the vitamin intake amounts for participants taking Centrum® during the study (n= 3143, 66%) were calculated by combining the contributions from multivitamins (Table 2, available at http://aaojournal.org) with the vitamin intake from food only. As Centrum® use was found to be significantly associated with nuclear opacities in our modeling, participants were then stratified into Centrum® users and non-users and gender-adjusted quintiles were calculated separately. Since Centrum ingredient amounts were added to the nutrient intake values, stratification of Centrum-users and non-users allowed for more accurate quintile comparisons. AREDS participants who completed a FFQ at baseline (n=4751) were included in the quintile comparisons. The analyses exclude participants at the extremes of caloric intake, less than the first percentile and greater than the 99th percentile (<677 or >1995 reported kcal/day for females, and <794 or >2771 kcal/day for males), as these participants were less likely to have submitted accurate dietary intake estimates.

Multivariable analyses, controlling for risk factors previously identified in AREDS,[41] were performed to assess the associations between B vitamins and lutein/zeaxanthin intake and the cataract outcomes. Repeated-measures logistic regression utilizing generalized estimating equations was performed to analyze the baseline cross sectional data.[42] The unit of analysis is an eye, and each participant could contribute either one eye or both eyes. We accounted for the correlation between eyes using an exchangeable covariance structure. Regression models were applied separately for nuclear and cortical opacities, controlling for risk factors found to be significant in AREDS Report 5.[41] Goodness of fit was determined with the QICu statistic (quasi-likelihood under the independence model criterion) for the purpose of selecting a nutrient-free final model. Each nutrient was then included separately

in each best-fit model to evaluate association with our endpoints. Proportional hazards regression was used to analyze the opacity-specific progression and cataract surgery outcomes. The Wei-Lin-Weissfeld method was implemented to take into account the correlation of the two eyes per participant, [43] and regression models used were derived from AREDS report 32.[44] Mortality analysis of AREDS participants comparing the highest and lowest intake groups of each nutrient was performed using life-table analyses. We did not adjust for multiplicity of analyses. The GENMOD and PHREG procedures were used in the cross-sectional and incidence analyses, respectively. All analyses were performed with the SAS software version 9.3 (SAS Inc., Cary NC).

Results

There were a total of 5582 and 3840 eyes of 2939 and 2358 participants included in the baseline cross sectional analysis of mild and moderate nuclear cataract, respectively and 5296 and 2681 eyes of 2788 and 1852 participants were included in the baseline cross sectional analysis of mild and moderate cortical cataracts, respectively. Table 1B and C also display the number of participants and eyes that have progressed to the outcome. In this study, about 40% of the participants were older than 70 years of age, more than 50% were women, about 95 % were Caucasians, about 40% were college graduates, and about 40% had intermediate AMD (Tables 3 and 4 available at http://aaojournal.org). Tables 5 and 6 (available at http://aaojournal.org) display demographic characteristics of participants included in the incident analyses for nuclear, cortical, and PSC cataracts.

Table 7 contains the odds ratios (ORs) for the baseline cross sectional outcomes of nuclear and cortical cataracts adjusted for non-nutrient-based predictors and correlates, which had been determined previously.[44] An OR greater than 1 indicates an increased likelihood of having the outcome among participants reporting nutrient intake within the highest quintile of nutrient intake compared to those reporting within the lowest quintile, whereas an OR less than one indicates a decreased likelihood. Individuals reporting highest dietary intake of riboflavin had a 22% and 38% lower likelihood of mild and moderate nuclear cataracts at baseline, respectively, compared with participants reporting the lowest dietary intake, OR: 0.78, 95% CI: 0.63–0.97, p=0.02 and OR: 0.62, 95% CI: 0.43 – 0.90, p=0.01. A similar reduction in likelihood of having mild and moderate nuclear cataracts was seen for individuals reporting the highest intake of B12, OR: 0.78, 95% CI: 0.63–0.96, p=0.02 and OR: 0.62, 95% CI: 0.43–0.88, p=0.01, respectively. Additionally, people reporting intake in the highest quintile of vitamin B6 showed a 33% reduction in the odds of having moderate nuclear cataract at baseline, OR: 0.67, 95% CI: 0.45–0.99. Participants reporting the highest intake of riboflavin and B12 were 20% and 23% less likely to have mild cortical cataract at baseline, OR: 0.80, 95% CI: 0.65–0.99, p=0.04, OR: 0.77, 95% CI: 0.63–0.95, p=0.01, respectively. In addition to statistically significant findings in comparisons of the highest vs. the lowest quintile of dietary intake of these B vitamins, statistically significant results were demonstrated in comparisons of other quintiles vs. the lowest quintile of dietary intake (Table 8). Table 7A provides the individual odds ratio for each of the comparison of quintiles with quintile one in those nutrients found to be statistically significant (available at http://aaojournal.org). There was no statistically significant association between B vitamin intake and the risk of having moderate cortical cataract at baseline. Findings for lutein/

zeaxanthin were in a protective direction for both mild and moderate prevalent nuclear and cortical opacities but not statistically significant.

Tables 9 and 10 contain the hazards ratios (HRs), comparing the highest with the lowest quintiles of reported dietary intake, for development of the three cataract types and/or cataract surgery adjusted for possible risk factors as described in AREDS report 32 and stratified by Centrum® use.[44] For Centrum® non-users, niacin was associated with a 31% reduction in the risk of developing mild nuclear cataract and vitamin B12 was associated with a 44% reduction in the risk of developing mild cortical cataract, OR: 0.69, CI: 0.52, 0.92, p=0.01 and OR: 0.56, CI: 0.37, 0.83, p<0.01, respectively. In Centrum® users, those reporting the highest intake of folate had a 61% increased risk of at least mild PSC cataract compared with those with the lowest folate intake, OR: 1.61, CI: 1.08, 2.41, p=0.02. Aside from folate, there were no statistically significant harmful associations between the highest dietary intake of any vitamin examined and development of nuclear, cortical, or PSC cataracts. Again, the various odds ratios for each of the quintiles of the nutrients that were found to be statistically significantly associated with the cataract development are also displayed in Table 7A [sections B and C] (available at http://aaojournal.org). There was no excess mortality risk associated with the highest versus the lowest level of intake for any of the nutrients investigated (P-value > 0.05) (Table 11, available at http://aaojournal.org).

Discussion

Our findings add to previous literature on the possible role of nutritional factors in the development of lens opacities. The clinical trial component of AREDS found that high doses of vitamin C, E and beta carotene and/or zinc had no apparent effect on the development or progression of lens opacities.[20] The Age-Related Eye Disease Study 2 (AREDS2), a randomized controlled clinical trial, also found no beneficial or harmful effect of treatment with lutein and zeaxanthin on the occurrence of cataract surgery or progression of lens opacities.[24] Theoretical considerations, observational studies and a few clinical trials suggest that micronutrients other than those studied in the AREDS clinical trials might affect cataract development. Testing the many potential candidates in clinical trials requires large, long-term, and prohibitively expensive studies, so that observational studies are the most common source of information on this association.

In this report cross sectional and prospective data from AREDS were used to examine associations between age-related lens opacities and dietary intake of B vitamins and lutein/zeaxanthin, micronutrients for whom protective associations have been reported.[13,14,16,33,35,36,45] We found that increased dietary intake of riboflavin and B12 were inversely associated in the cross sectional baseline comparison for both nuclear and cortical cataracts. The association with B12 intake was seen when comparing several of the higher quintiles to the lowest quintile of intake levels (Table 8). B6 intake was also associated with a decreased risk of moderate nuclear lens opacities in the baseline cross sectional analyses. Highest intake levels of niacin and B12 were associated with a decreased risk of development of nuclear and mild cortical lens opacities, but only in participants not taking Centrum® multivitamin. In agreement with recently published results from the AREDS2

cohort[24], no statistically significant associations were found between highest lutein/zeaxanthin intake level and the nuclear or cortical cataract outcomes.

A large body of evidence suggests that micronutrients with antioxidant potential may affect cataract development. Aging lenses are thought to lose their capacity to neutralize free radicals and minimize oxidative damage as the efficacy of protective enzymes such as superoxide dismutase and levels of compounds with antioxidant capabilities such as glutathione and ascorbic acid decrease.[46,47] Radical oxygen species increase within the lens secondary to environmental ultraviolet exposure, the formation of cholesterol oxide derivatives and mitochondrial dysfunction. [47,48] The accumulation of reactive oxygen species results in lipid peroxidation, protein denaturation and crosslinking, which aggregate within the lens and lead to cataract formation. B vitamins may help to maintain the cellular response to oxidative stress by functioning as cofactors in the enzymatic activation of antioxidants. Riboflavin (B2) and niacin (B3), once converted to their biologically active forms as flavin adenine dinucleotide (FAD) and nicotinamide adenine dinucleotide phosphate (NADPH), contribute to the reduction of glutathione by acting as the cofactor and reducing equivalent, respectively, for the enzyme glutathione reductase.[11,31] The possible role of vitamins B6 and B12 in the prevention of oxidative damage is less clear. It is biologically plausible that their importance may be attributed to their function in the metabolic pathway that eliminates homocysteine, wherein B12 and B6 act as enzymatic cofactors.

The Linxian Cataract Studies, two randomized, double-masked trials conducted in rural China in an undernourished population, found a protective effect of supplementation with riboflavin and niacin vitamins on the occurrence of nuclear cataracts.[36] Observational studies have also reported a decrease in the prevalence and progression of nuclear [13,16] and cortical lens opacities[18] in participants with the highest dietary intake of niacin, thiamin, and riboflavin. While most studies suggest no effect or a beneficial effect on cataract development of vitamin supplementation, some studies have raised the possibility of a possible harmful effect of supplementation, particularly for PSC cataract. The Linxian Cataract trials found that riboflavin and niacin supplementation were associated with a slowing in the progression of nuclear lens opacities, but were associated with an increase in the progression of PSC cataract and had no effect on cortical cataract.[36] In our study we found that in Centrum users, among whom there was a thousand-fold increase in the highest quintile range for folate compared with non- Centrum users, the highest level of folate intake was associated with an increased risk of mild PSC cataract, possibly the result of chance or uncontrolled confounding in the high dietary folate group. Two other studies of dietary and serum levels of folate showed conflicting results.[49,50] A randomized placebo-controlled trial of Centrum found that those taking the multivitamin had a two-fold increased risk in PSC events.[51] No increased mortality risk was associated with any B vitamin or lutein/zeaxanthin intake levels.

Theoretical considerations and some observational studies have suggested that carotenoids, in particular lutein/zeaxanthin, may play a role in cataract prevention. Lutein, and its structural isomer zeaxanthin, are the only carotenoids found within the human lens.[32] They have the ability to filter and absorb potentially damaging short wave-length light and reduce

oxidative stress.[29] Their unique structure, with an ionone ring and conjugated polyene chain, allows for several types of reactions that can neutralize reactive oxygen species.[29] Incubation of human lens epithelial cells with lutein and zeaxanthin prior to exposure to hydrogen peroxide or ultraviolet-B light irradiation (UVB) protects lens cells from protein oxidation, lipid peroxidation, and DNA damage, and also results in increased levels of glutathione in response to oxidative stress.[27,28] Clinical studies have reported that high dietary intake of lutein/zeaxanthin is protective against the development and progression of nuclear cataract,[34,35] as well as all cataracts, [33] and reduces the risk of cataract extraction.[12,52] High levels of plasma lutein have also been associated with a reduced risk of nuclear cataract.[45]

However, other studies and our study found no relationship between lutein/zeaxanthin intake and cataracts. Analysis of a small cohort from the Nurse's Health Study, which incorporated 15 years of food frequency questionnaire data, found that the protective association between high lutein/zeaxanthin intake and nuclear cataract disappeared after adjusting for vitamin C intake.[53] In the population-based Pathologies Oculaires Liées à l'Age (POLA) Study, which had fewer than 100 eyes with any cataract type, only serum levels of zeaxanthin, but not lutein, were associated with a reduced risk of nuclear cataract, and neither lutein nor zeaxanthin were associated with a reduced risk of cortical, PSC, mixed cataracts, or cataract surgery.[14] Most recently, analysis of data from the AREDS2 clinical trial showed that lutein/zeaxanthin supplementation did not significantly reduce progression to cataract surgery.[24]

It is unclear why, riboflavin, B6, and B12 are associated with a protective effect in the baseline cross sectional analysis for nuclear and cortical lens opacities, but only B12 intake had a statistically significant association on the development of cortical lens opacities. One possibility for this discrepancy is that the power to detect an association was much larger in the cross sectional baseline data compared to the incidence data, where the duration of difference in vitamin intake, although unknown, may have been present for decades, and likely much longer than for the duration of AREDS. Additionally, our population represents a relatively healthy and well-nourished cohort with baseline levels of nutrient intake that are higher than the general population. For all of the nutrients studied, the lowest intake quintile for the AREDS patient population was greater than the lowest intake quintile calculated from the National Health and Nutrition Examination Survey (NHANES) data acquired during the same time period (Table 11 available at http://aaojournal.org).

For lutein and zeaxanthin, the difference between the lowest intake quintile and the highest intake quintile was much less than the corresponding NHANES quintiles, making the identification of differences in the risk of cataract progression more difficult than if comparisons were being made across more widely divergent population.

Our observational study had strengths and some potential weaknesses. The strengths of the study include its size, with large numbers of each cataract type included, the use of standardized evaluation of lens photographs longitudinally, and the long duration of follow-up. Self-reported dietary intake is subject to recall bias, which we attempted to minimize by comparing only the highest and lowest quintiles of nutrient intake. However, self-reported measurements of nutritional intake are limited in that they are unable to account for changes

in nutritional intake over time and instead make an averaged approximation of dietary habits. While we adjusted for known risk factors in the logistic and proportional hazards regression models, there is the possibility of unadjusted confounding from other factors. Participants with higher self-reported levels of micronutrient intake may be healthier overall compared to those with the least nutrient intake, or the accuracy of diet recall may have differed in individuals with and without more significant cataracts and worse vision. Previous analysis of AREDS data has shown that PSC cataracts are associated with increased risk of nuclear and cortical cataracts, suggesting that one cataract type may be associated with the development of other lens opacity types.[44] We attempted to adjust for this in our lens opacity progression modeling but it is unlikely that we could fully account for this possible effect, as we did not separate eyes with multiple types of cataracts from those with only one type of cataract. Lastly, because of the multiple comparisons made between nutrient intake and lens opacity outcomes, it is possible that some of our findings are due to chance. This is less likely for those vitamins that demonstrated a dose-response effect on cataract risk with increasing intake level and for those that had similar findings in both the cross sectional and prospective analyses,

The totality of evidence from our study and other studies suggests that B vitamins may have a role in slowing cataract development. However, additional evidence would be needed to make definitive clinical recommendations. Identification of micronutrients that retard cataract progression would serve as a cost-effective way to reduce the disease burden of age-related cataracts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The Age-Related Eye Disease Study (AREDS): Directory of Participating Centers

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National Institutes of Health

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AREDS Research Group

A complete list of the members of the AREDS Research Group appears in:

AREDS Research Group. Associations of mortality with ocular disorders and an intervention of high-dose antioxidants and zinc in the Age-Related Eye Disease Study: AREDS Report No. 13. *Archives of Ophthalmology* 2004 May; 122(5): 716–726.

Table 1

Definition of Cataract and Number of Participants and Eyes in Analyses

A. Definition of controls and cataract types evaluated in the Age-Related Eye Disease Study (AREDS)			
Cataract type	**Mild**	**Moderate**	**Controls**
Nuclear	AREDS nuclear grade >2 and ≤4	AREDS nuclear grade ≥4	AREDS nuclear grade ≤2
Cortical	Cortical >0% and <10%	Cortical ≥10%	Cortical = 0%
Posterior Subcapsular (PSC)	PSC >0% and <5%	PSC ≥5%	PSC = 0%

1B. Numbers of participants and eyes included in the prevalence analyses of the lutein/zeaxanthin and vitamin B and cataracts analyses						
	Nuclear			**Cortical**		
	N participants	**N eyes**	**N (%) eyes with event**	**N eyes**	**N participants**	**N (%) eyes with event**
Mild	2939	5582	2279 (40.8)	2788	5296	3294 (62.2)
Moderate	2358	3840	537 (14.0)	1852	2618	616 (23.5)

1C. Numbers of participants and eyes included in the incidence analyses of the lutein/zeaxanthin and vitamin B and cataracts analyses							
		Centrum=No			**Centrum=Yes**		
	Opacity	**N participants**	**N eyes**	**N (%) eyes with event**	**N eyes**	**N participants**	**N (%) eyes with event**
Mild	Nuclear	639	1045	734 (70.2)	1190	1963	1279 (65.2)
	Cortical	470	658	312 (47.4)	903	1245	619 (49.7)
	PSC	939	1727	185 (10.7)	1807	3315	347 (10.5)
Moderate	Nuclear	505	674	326 (48.4)	966	1354	617 (45.6)
	Cortical	583	825	293 (35.5)	1132	1597	590 (36.9)
	PSC	951	1716	161 (9.4)	1842	3326	313 (9.4)
Cat surgery		1043	2047	558 (27.3)	2025	3985	1009 (25.3)

Table 7

Odds ratios for prevalence of nuclear and cortical cataracts adjusted for risk factors for cataract prevalence by highest vs. lowest energy-adjusted intake quintiles of dietary lutein/zeaxanthin and B vitamins.

	Quintile 5 vs. Quintile 1, OR (95% CI)			
	Mild Nuclear[1]	Mild Cortical[2]	Moderate Nuclear[1]	Moderate Cortical[2]
Lutein/zeaxanthin	0.89 (0.71–1.11)	0.89 (0.72–1.11)	0.81 (0.55–1.20)	0.79 (0.55–1.16)
B1	0.98 (0.79–1.23)	0.89 (0.72–1.09)	0.73 (0.49–1.09)	1.44 (0.98–2.13)
Riboflavin	**0.78 (0.63–0.97)***	**0.80 (0.65–0.99)***	**0.62 (0.43–0.90)***	1.06 (0.73–1.53)
Niacin	0.95 (0.76–1.18)	0.92 (0.75–1.13)	0.83 (0.58–1.20)	1.16 (0.80–1.68)
B6	0.87 (0.70–1.08)	0.90 (0.73–1.10)	**0.67 (0.45–0.99)***	1.00 (0.69–1.44)
Folate	0.89 (0.71–1.11)	0.86 (0.70–1.07)	0.85 (0.57–1.27)	1.14 (0.78–1.67)
B12	**0.78 (0.63–0.96)***	**0.77 (0.63–0.95)***	**0.62 (0.43–0.88)***	0.86 (0.60–1.24)

[1]Covariates included in this model were age, gender, race, level of education, smoking status, eye color, refractive error, and anti-inflammatory use

[2]Covariates included in this model were age, race, gender, level of education, and beta-blocker use *P≤ .05.

OR: Odds Ratio, CI: Confidence Interval

Table 8

Heat map depicting protective nutrients for prevalence of nuclear and cortical cataracts by comparing highest vs. lowest energy adjusted intake quintiles[1]

Nutrient	Mild Nuclear	Mild Cortical	Moderate Nuclear	Moderate Cortical
Lutein/zeaxanthin				
B1				
Riboflavin	0.78 (0.63–0.97)	0.80 (0.65–0.99)	0.62 (0.43–0.90)[a]	
Niacin				
B6			0.67 (0.45–0.99)[b]	
Folate				
B12	0.78 (0.63–0.96)[c]	0.77 (0.63–0.95)[d]	0.62 (0.43–0.88)[e]	

[1] Odds Ratios (95% confidence intervals) for 5th vs 1st quintile represented, all quintiles compared to the 1st quintile

Q5 vs Q1 not significant

Q5 only significant

Q5 and 1 other quintile significant

Q5, Q4 and Q3/Q2 significant

Q5, Q4, Q3 and Q2 significant

Table 9

Hazard Ratios for Incidence of different cataract types and cataract surgery in Centrum® non-users adjusted for cataract risk factors for cataract incidence[a] by highest vs. lowest energy-adjusted intake quintiles of dietary lutein/zeaxanthin and B vitamins.

	Quintile 5 vs. Quintile 1, HR (95% CI)						
	Mild Nuclear[1]	Mild Cortical[2]	Mild PSC[3]	Moderate Nuclear[1]	Moderate Cortical[2]	Moderate PSC[3]	Cataract Surgery[4]
Lutein/zeaxanthin	0.94 (0.69, 1.28)	0.88 (0.57, 1.37)	0.97 (0.55, 1.69)	1.01 (0.69, 1.47)	1.11 (0.73, 1.72)	0.93 (0.49, 1.78)	1.08 (0.74, 1.57)
B1	0.88 (0.67, 1.17)	1.05 (0.69, 1.59)	1.09 (0.66, 1.79)	0.98 (0.65, 1.48)	0.87 (0.54, 1.41)	1.29 (0.62, 2.68)	1.14 (0.78, 1.67))
Riboflavin	1.02 (0.79, 1.33)	0.72 (0.49, 1.07)	1.17 (0.71, 1.90)	0.88 (0.60, 1.30)	1.03 (0.65, 1.62)	0.81 (0.46, 1.43)	0.96 (0.68, 1.36)
Niacin	**0.69 (0.52, 0.92)***	1.26 (0.81, 1.98)	1.05 (0.60, 1.84)	0.79 (0.51, 1.20)	1.13 (0.72, 1.80)	1.10 (0.56, 2.14)	1.06 (0.75, 1.49)
B6	0.93 (0.70, 1.24)	1.09 (0.72, 1.66)	0.99 (0.57, 1.71)	1.00 (0.66, 1.51)	1.02 (0.65, 1.62)	1.22 (0.64, 2.32)	1.35 (0.93, 1.97)
Folate	0.88 (0.67, 1.16)	0.85 (0.55, 1.33)	1.35 (0.78, 2.31)	0.74 (0.48, 1.13)	1.10 (0.69, 1.75)	1.01 (0.57, 1.79)	0.92 (0.64, 1.32)
B12	1.02 (0.77, 1.34)	**0.56 (0.37, 0.83)***	1.06 (0.64, 1.76)	1.13 (0.75, 1.69)	1.14 (0.73, 1.80)	0.66 (0.38, 1.16)	1.17 (0.81, 1.68)

[1] Covariates included in this model are age, gender, refractive error, nuclear cataract at baseline (for moderate only), cortical and PSC cataract at time of event, total energy intake and BMI (for moderate only)

[2] Covariates included in this model are age, gender, race, education, smoking status, diabetes, weight change, cortical cataract at baseline (for moderate only), nuclear and PSC cataract at time of event, total energy intake and BMI (for moderate only)

[3] Covariates included in this model are age, gender, diabetes, weight change since age 20 yr, refractive error, thyroid hormone use, total energy intake, PSC cataract at baseline (for moderate only), and nuclear and cortical cataract at time of event

[4] Covariates included in this model are age, gender, race, smoking status, diabetes, refractive error, anti-inflammatory use, AMD category, total energy intake, and nuclear, cortical, and PSC cataract at baseline (for moderate only).

* P≤ .05.

HR: Hazard Ratio, CI: Confidence Interval

Table 10

Hazard Ratios for Incidence of different cataract types and cataract surgery in Centrum® users adjusted for cataract risk factors for cataract incidence[a] by highest vs. lowest energy-adjusted intake quintiles of dietary lutein/zeaxanthin and B vitamins.

	Quintile 5 vs. Quintile 1, HR (95% CI)						
	Mild Nuclear[1]	Mild Cortical[2]	Mild PSC[3]	Moderate Nuclear[1]	Moderate Cortical[2]	Moderate PSC[3]	Cataract Surgery[4]
Lutein/zeaxanthin	1.06 (0.86, 1.31)	1.08 (0.80, 1.47)	1.19 (0.81, 1.75)	1.16 (0.88, 1.52)	0.79 (0.57, 1.10)	1.17 (0.75, 1.81)	0.94 (0.72, 1.23)
B1	0.89 (0.72, 1.09)	1.19 (0.89, 1.60)	1.35 (0.92, 2.00)	0.90 (0.67, 1.21)	1.02 (0.74, 1.40)	0.95 (0.63, 1.45)	1.08 (0.83, 1.41)
Riboflavin	0.83 (0.68, 1.01)	1.00 (0.75, 1.33)	1.20 (0.83, 1.75)	0.78 (0.59, 1.04)	0.74 (0.54, 1.02)	1.28 (0.82, 2.00)	0.99 (0.76, 1.30)
Niacin	0.94 (0.75, 1.17)	1.08 (0.80, 1.44)	0.97 (0.66, 1.43)	0.88 (0.64, 1.19)	0.88 (0.65, 1.19)	0.71 (0.46, 1.11)	1.00 (0.77, 1.30)
B6	0.93 (0.75, 1.16)	0.95 (0.71, 1.27)	1.22 (0.83, 1.79)	1.07 (0.78, 1.47)	0.90 (0.65, 1.23)	1.07 (0.69, 1.66)	1.13 (0.85, 1.49)
Folate	1.01 (0.82, 1.24)	1.22 (0.90, 1.66)	**1.61 (1.08, 2.41)***	1.04 (0.78, 1.39)	1.05 (0.76, 1.44)	1.12 (0.73, 1.74)	1.00 (0.76, 1.32)
B12	0.86 (0.69, 1.06)	0.99 (0.75, 1.30)	1.29 (0.87, 1.91)	0.98 (0.73, 1.32)	1.00 (0.72, 1.38)	1.28 (0.82, 2.00)	1.22 (0.92, 1.60)

[1] Covariates included in this model are age, gender, refractive error, nuclear cataract at baseline (for moderate only), cortical and PSC cataract at time of event, total energy intake and BMI (for moderate only)

[2] Covariates included in this model are age, gender, race, education, smoking status, diabetes, weight change, cortical cataract at baseline (for moderate only), nuclear and PSC cataract at time of event, total energy intake and BMI (for moderate only)

[3] Covariates included in this model are age, gender, diabetes, weight change since age 20 yr, refractive error, thyroid hormone use, total energy intake, PSC cataract at baseline (for moderate only), and nuclear and cortical cataract at time of event

[4] Covariates included in this model are age, gender, race, smoking status, diabetes, refractive error, anti-inflammatory use, AMD category, total energy intake, and nuclear, cortical, and PSC cataract at baseline (for moderate only).

* P≤ .05.

HR: Hazard Ratio, CI: Confidence Interval