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## Centrum Use and Progression of Age-Related Cataract in the Age-Related Eye Disease Study:

A Propensity Score Approach. AREDS Report No. 21

Age-Related Eye Disease Study Research Group\*

### Abstract

**Purpose**— To evaluate the effect of the multivitamin Centrum on the development and progression of age-related lens opacities.

**Design**—Clinic-based prospective cohort study.

**Participants**— Four thousand five hundred ninety individuals with at least one natural lens and photographic follow-up (median, 6.3 years) were assessed for development or progression of lens opacities.

**Main Outcome Measures**— Progression of “any” lens opacity or type-specific opacity was ascertained from lens photographs taken at baseline and at annual visits beginning at year 2.

**Methods**— The Age-Related Eye Disease Study (AREDS) showed no statistically significant effect of a high-dose antioxidant formulation on progression of lens opacities. Centrum also was provided to approximately two thirds of the study participants. Because Centrum use was elective, a logistic regression model of baseline characteristics was used to generate a propensity score for Centrum use. Repeated-measures logistic regression, adjusted for propensity score and other covariates, was used to evaluate associations of Centrum use and lens opacity.

**Results**— Centrum use, adjusted for propensity score and other covariates, was associated with a reduction in “any” lens opacity progression (odds ratio [OR] = 0.84, 95% confidence interval [CI] = 0.72–0.98,  $P = 0.025$ ). Results for individual lens opacity types suggested that Centrum use was protective for nuclear opacity events (OR = 0.75, 95% CI = 0.61–0.91,  $P = 0.004$ ).

**Conclusion**— Observational data from the AREDS and other studies suggest that use of a multivitamin may delay the progression of lens opacities. A National Eye Institute–sponsored clinical trial scheduled for completion in 2007 will provide additional data on Centrum use and cataract development.

Prospective epidemiological studies have reported a lower occurrence of cataract in users of multivitamin supplements.<sup>1–3</sup> In 2 observational studies assessing specific cataract types, regular or long-term use of multivitamins was associated with a reduced risk of nuclear<sup>2,3</sup> and cortical<sup>3</sup> opacification. Unadjusted confounding is a major concern in interpreting the results

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from these and other observational studies of supplement use and cataract risk, because of the likelihood that supplement users are different from nonusers in unrecognized ways that affect the risk of cataract. Significant unadjusted confounding is less likely to occur in well-designed randomized clinical trials.

A few clinical trials have tested the effect of high-dose formulations of selected antioxidants (vitamin C, vitamin E, or  $\beta$ -carotene) on cataract development.<sup>4–7</sup> These 3 nutrients, which have antioxidant attributes, have been selected for testing largely because of speculation that they may protect against oxidative damage, an important proposed risk factor for cataract development. The cumulative evidence from trials conducted to date suggests that high-dosage formulations of these antioxidants do not affect cataract risk when tested for relatively short periods in older relatively well-nourished populations. One trial, conducted in a nutritionally deprived population in China, tested the effect of a broad-spectrum low-dosage multivitamin supplement on cataract risk.<sup>8</sup> The Linxian Cataract Study reported that, after 5 to 6 years of treatment, there was a significant 36% reduction in the prevalence of nuclear cataract among persons 65 to 74 years old assigned to daily use of 2 multiple vitamin/mineral tablets (Centrum, Wyeth Consumer Healthcare, Madison, NJ), each containing the recommended daily allowance of nutrients, and one 15-mg  $\beta$ -carotene capsule compared with those receiving matching placebos. It is not clear whether this result can be generalized to better-nourished populations.

The Age-Related Eye Disease Study (AREDS) included a clinical trial designed to evaluate the effect of a high-dose antioxidant formulation (vitamin C, 500 mg; vitamin E, 400 IU; and  $\beta$ -carotene, 15 mg) on cataract development and progression.<sup>4</sup> The study reported no statistically significant effect on the 7-year risk of development or progression of lens opacities. At the time of enrollment into the AREDS more than half of the participants already were taking dietary supplements of a multivitamin or at least one of the ingredients in the AREDS formulation. To standardize the usage of nonstudy supplements and to accommodate AREDS participants who wanted to continue or start taking a multivitamin supplement, participants were offered a widely available broad-spectrum multivitamin/mineral supplement containing recommended daily allowance (RDA)-level dosages (Centrum without lutein). The objective of this report is to evaluate the effect of Centrum on the development and progression of age-related lens opacities in the AREDS cohort using a propensity score approach. This approach provides a means for adjusting for selection bias that may have occurred with the elective use of Centrum.

## Materials and Methods

### The Age-Related Eye Disease Study

The Age-Related Eye Disease Study<sup>9</sup> enrolled its first participant in 1992 to study the effect of high-dose antioxidants (vitamin C, 500 mg; vitamin E, 400 IU; and beta carotene, 15 mg) and zinc (80 mg; with copper, 2 mg) supplements on the development of advanced age-related macular degeneration (AMD) and age-related cataract. Zinc was included because of a possible beneficial effect on the development of AMD. There were 4596 participants analyzed in the cataract trial, with half randomly assigned to antioxidants and half to no antioxidants. The AMD and cataract trials ended in 2001, when it was announced that there was no difference in a primary outcome, development or progression of any lens event in the antioxidant and no antioxidant groups.

Film slit-lamp camera and retroillumination camera (Neitz Instruments Co., Ltd., Tokyo, Japan) lens photographs were graded at a reading center at baseline and annually starting with the second annual visit.<sup>10</sup> Nuclear opacities were graded on a decimal scale ranging from 0.9 to 6.1 with respect to cutoff points set by a series of standard slit-lamp photographs. Cortical

and posterior subcapsular opacities were graded by estimating on retroillumination photographs the area of lens involvement in the central 5-mm area of the lens. An “any” lens opacity event was defined as the occurrence of change from baseline of specified amounts of nuclear, cortical, or posterior subcapsular opacity, or the performance of cataract surgery.<sup>10</sup> Each type-specific event was defined irrespective of the other type-specific events. Participants without a type-specific event before cataract surgery were excluded from our analyses for that type of cataract. Baseline lens status was not a factor in study eligibility or treatment assignment, except that the lens had to be sufficiently clear to permit good retinal photographs that would permit identification and quantification of small drusen. Thus, persons with severe or late-stage lens opacities, perhaps least likely to respond to nutritional intervention, are not represented in this study.

At baseline, 15% of participants had at least nuclear grade 4 in at least one eye, and 11% (2.5%) had at least 5% area involved in cortical (posterior subcapsular) opacity in at least one eye. The probability of a lens event of any type in at least one eye by 5 years was 30%. Lens events are defined as nuclear (a change from baseline of >1.5 steps on the nuclear scale), cortical (absolute change of >10% involvement of the central 5-mm circle of the lens), and posterior subcapsular (absolute change of >5% involvement of the central 5-mm circle of the lens).

Examples of lens opacities and grades from lens photographs, comparing photographs at baseline and 5 to 6 years’ follow-up, are shown in Figure 1. Figure 1A, B is a nuclear event example: grades 2 to 3.9. Figure 1C, D is a cortical event: 6% to 40%. Figure 1E, F is a posterior subcapsular event: 6% to 22%. There were no statistically significant differences in the progression of any specific type of lens event or the “any” lens event outcome in the AREDS cataract trial of high-dose antioxidants.<sup>4</sup>

Demographic information, history of smoking and sunlight exposure, medical history, history of specific prescription drug and nonprescription medication use, and history of vitamin and mineral use were obtained at baseline.

### Centrum Use in the Age-Related Eye Disease Study

Over half of AREDS participants were supplementing their diets with some antioxidant vitamins or zinc at enrollment. To standardize the usage of nonstudy supplements and to accommodate AREDS participants who wanted to take a multivitamin, those participants were asked to refrain from using other supplements and were provided at baseline and regularly throughout the trial with a multivitamin/mineral supplement containing RDA-level dosages (Centrum without lutein) (Table 1). Because the amount of the study nutrients in Centrum is small compared with the 5- to 15-fold higher levels in the study formulation, the primary treatment contrast between very high and lower doses of the antioxidant vitamins, which are part of the normal diet, was maintained. Two thirds of AREDS participants elected to supplement with Centrum. No formal compliance procedures were implemented for Centrum use, and analyses of Centrum’s effect in this study are intent-to-treat. Because Centrum use was not randomized, we developed a propensity score for Centrum use to adjust for possible selection bias and confounding<sup>11,12</sup> for analyses of Centrum’s effect on lens events.

### Propensity Scores

In this setting, a propensity score for a person is the probability of being treated (taking Centrum), conditional on the person’s covariates. We developed a scalar summary of the covariate information using a logistic regression model. Use of the propensity score tends to produce unbiased estimates of treatment effects, when the choice to take the treatment and the response variable are conditionally independent, given the covariates. It tends to reduce bias by balancing the covariates between treatment groups, in contrast to a randomized trial in which

one depends on the randomization to achieve balance. This creates a quasi-randomized experiment.<sup>13</sup>

We determined the probability of taking Centrum, without regard to lens event outcomes, using logistic regression with 16 baseline characteristics as covariates, which included general indicators of health and some thought or known to be associated with lens opacity (Table 2). A strength of this approach to modeling the likelihood of taking Centrum is that it allows use of many covariates and, if needed, complex relationships of these covariates, to determine the propensity scores. This then simplifies the modeling of treatment effect on outcome.

One criterion for assessing the effectiveness of the computed propensity score is to compare covariate values for treated and untreated groups (Centrum and no Centrum), before and after stratification by propensity score. We used 5 propensity strata, defined by the 4 quintiles of propensity scores. All but one of the instances of significant observed covariate imbalance before stratification were remedied by the stratification—that is, large significant  $\chi^2$  statistics became nonsignificant and mostly near zero (Table 2).

We used repeated-measures logistic regression (Procedure GENMOD, SAS Institute, Cary, NC) to assess the relationship of Centrum use to lens events: unadjusted, adjusted for propensity score quintile group (i.e., with propensity score stratum as a covariate), and with further adjustment for baseline covariates. Risk of progression to a lens event was assessed by odds ratios (ORs) with 95% confidence intervals (CIs).

## Results

Median follow-up for lens events was 6.3 years on 4590 participants with complete covariate data. Six participants with incomplete covariate data were excluded from analysis. The discriminatory power of the logistic regression in predicting use of Centrum is good, according to the 0.87 c-statistic or area under the response operating characteristic curve. In this analysis, the unadjusted risk of development of or progression to “any” lens opacity is decreased by Centrum use (OR = 0.88, 95% CI = 0.79–0.98; Table 3). With adjustment for propensity score—the quasi-randomized experiment result—the risk decreases (OR = 0.82, 95% CI = 0.71–0.95). After further adjustment by baseline covariates, OR = 0.84 (95% CI = 0.72–0.98). These ORs are statistically significant ( $P < 0.01$ ).

Looking at type-specific analyses, when adjusting for propensity score and after further adjustment by baseline covariates—the quasi-randomized experiment result—the risk decreases for nuclear opacity events (OR = 0.75,  $P = 0.006$ ; Table 3). No beneficial effect is seen for cortical and posterior subcapsular opacities.

## Discussion

Prospective observational data from the AREDS, a large multicenter study of cataracts and AMD, showed fewer lens events in participants who elected to use a multivitamin/mineral supplement (Centrum) containing RDA-level doses after a median follow-up time of 6.3 years. Nuclear opacity events were significantly less common in users of the supplement, and although not significant, there was a similar reduction in risk of cortical lens events. No effect was noted for posterior subcapsular opacities.

The AREDS included a clinical trial to test whether a high-dosage supplement of vitamin C, vitamin E, and  $\beta$ -carotene affected cataract development and progression. Fifty-five percent of participants were supplementing their diets with antioxidant vitamins or zinc before joining the study. These participants were asked to stop using their supplements and were offered Centrum for the duration of the study. Almost this entire group chose to take Centrum. An

additional 13% of participants who were not using supplements before the study chose to take Centrum, which the study provided.

Other observational studies have reported association between multivitamin use and risk of cataract. The Physicians' Health Study noted significantly fewer self-reports of cataract or cataract surgery confirmed by medical record review during 60 months' follow-up in users of multivita-mins.<sup>1</sup> The Longitudinal Study of Cataract found that the risk of nuclear opacification was reduced significantly by one third in regular users of multivitamins.<sup>2</sup> The Beaver Dam Eye Study found that taking multivitamins for >10 years lowered the risk of nuclear and cortical but not posterior subcapsular cataracts (PSCs).<sup>3</sup> Use of supplements for shorter periods was not associated with risk of cataract. However, the Nurses' Health Study found no association between long-term multivitamin use and incidence of cataract extraction.<sup>12</sup>

The Linxian cataract studies, conducted in a nutritionally deficient population in China, examined whether the vitamin/mineral supplements used in 2 cancer intervention trials affected the risk of developing age-related cataracts.<sup>8</sup> One of 2 cataract trials examined the effect of 2 Centrum tablets plus a 15-mg  $\beta$ -carotene capsule. It found that after 5 to 6 years of treatment there was a significant 36% reduction in the prevalence of nuclear cataract among 520 persons 65 to 74 years old assigned to daily use of the supplements, compared with those receiving matching placebos. No treatment effect was noted for cortical cataracts or PSCs.

Although observational studies suggest associations between the dietary intake or blood levels of various nutrients and risk of cataract, there is no consensus about the role of any specific nutrient in cataract prevention. Theoretical considerations about the role of oxidative damage in cataract formation and the results from some epidemiological studies have focused attention on nutrients with antioxidant capabilities, particularly vitamin C, vitamin E, and the carotenoids. Trials conducted to date have tested high-dose formulations of one or more of these nutrients<sup>4-7,14</sup> and, with one exception,<sup>14</sup> have not reported protective associations. Only one 3-year trial, which used a mixture of the 3 nutrients, reported a "small deceleration in progression of age related cataract," as measured with image analysis of retroillumination photographs.<sup>14</sup> Interpreting the largely negative findings from the trials, which have used vitamin C, vitamin E, or  $\beta$ -carotene, requires consideration of the underlying nature of the study populations. All were conducted in older well-nourished populations. Whether earlier intervention or inclusion of more nutritionally deprived populations would have altered the results cannot be determined. It is also possible that other nutrients may be important. Though containing only RDA-level doses of nutrients, Centrum, especially when combined with the individual's diet, includes a broad spectrum of vitamins and minerals of potential interest in cataract development. These include B vitamins and some of the trace minerals found in Centrum.

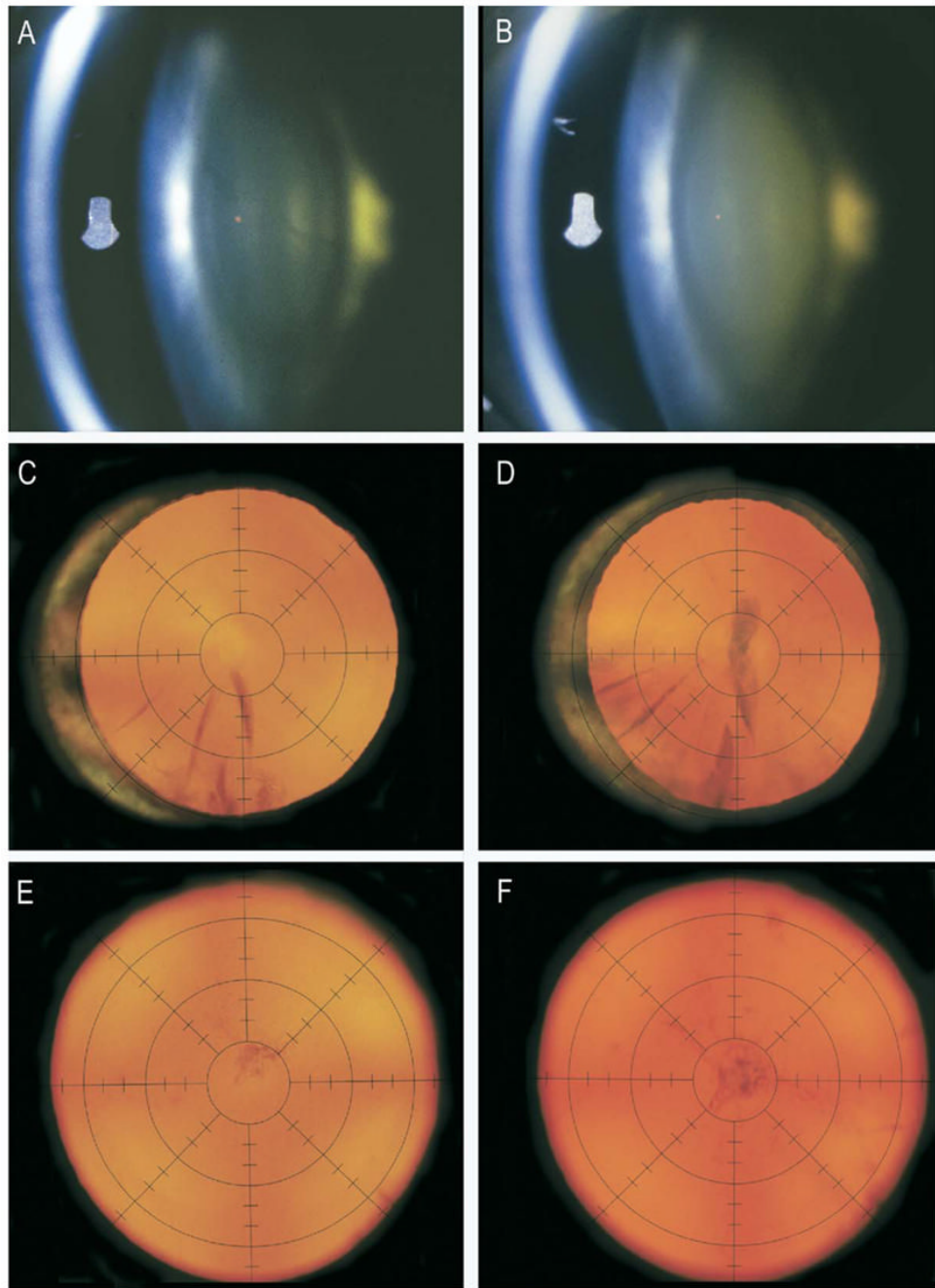
Our study, like previous observational studies of multi-vitamin use and cataract development, is subject to potential selection bias and uncontrolled confounding. Could participants who elected to take Centrum have differed from those who did not take Centrum in important ways that could have affected their risk of cataract? We attempted to address this concern by using a propensity score for Centrum use in the analysis. This technique is designed to reduce bias by balancing the covariates between those choosing and not choosing to take Centrum. Note that in a well-designed randomized trial the randomization is assumed to achieve balancing of covariates. If adequately controlled for inherent bias, observational studies can achieve estimates of the effects of therapeutic interventions that are remarkably similar to those of controlled randomized trials.<sup>15,16</sup> The propensity score is one way of controlling for this bias. The propensity technique can adjust only for factors that were measured in the AREDS. Whether other unknown important covariates exist that affect the decision to take Centrum

cannot be determined. Therefore, we cannot exclude the possibility that unadjusted confounding partially or fully explains our findings.

Unadjusted confounding and selection bias are less likely to influence findings in clinical trials. The National Eye Institute is currently supporting a randomized placebo-controlled clinical trial at the University of Parma in Italy to assess the effect of Centrum use on development and progression of lens opacities.<sup>17</sup> The study has 1020 participants and follows the AREDS protocol for assessing lens opacities. Median follow-up is now almost 7 years, with completion expected in 2007.

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**Figure 1.**

Examples of lens opacity progression in Age-Related Eye Disease Study (AREDS) participants. Nuclear opacity graded from slit-lamp photographs (model SL-6E, Topcon Corp., Tokyo, Japan) increased from 2.0 U (equal to AREDS standard photograph 3) at baseline (A) to 3.9 U (approaching standard photograph 5) at the 5-year visit (B). Cortical opacity within 5 mm of the lens center graded from retroillumination photographs (Neitz Instruments Co., Ltd., Tokyo, Japan) increased from 6% at baseline (C) to 45% at the 6-year visit (D). Posterior subcapsular opacity within 5 mm of the lens center increased from 6% at baseline (E) to 22% at the 5-year visit (F). Reproduced with permission from *Archives of Ophthalmology* (2001;119:1444). Copyright © 2001, American Medical Association. All rights reserved.

**Table 1**

## Composition of Centrum

Substances	Amount	U.S. RDA*
Vitamin A	5000 IU	100%
Vitamin E	30 IU	100%
Vitamin C	60 mg	100%
Folic acid	400 $\mu$ g	100%
Vitamin B <sub>1</sub>	1.5 mg	100%
Vitamin B <sub>2</sub>	1.7 mg	100%
Niacinamide	20 mg	100%
Vitamin B <sub>6</sub>	2 mg	100%
Vitamin B <sub>12</sub>	6 $\mu$ g	100%
Vitamin D	400 IU	100%
Biotin	30 $\mu$ g	10%
Pantothenic acid	10 mg	100%
Calcium	162 mg	16%
Phosphorus	125 mg	13%
Iodine	150 $\mu$ g	100%
Iron	18 mg	100%
Magnesium	100 mg	25%
Copper	2 mg	100%
Zinc	15 mg	100%

RDA = recommended daily allowance.

The tablet also contains trace amounts of the following substances for which no U.S. RDA doses have been established: manganese, potassium, chlorine, chromium, molybdenum, selenium, vitamin K<sub>1</sub>, nickel, tin, silicon, vanadium, and boron.

\* In 1993.

**Table 2**  
Effect of Stratification by Propensity Score: Centrum Use Versus No Centrum Use

Baseline Characteristic	No Centrum Use [n (%)]	Centrum Use [n (%)]	$\chi^2$ Statistic before Stratification	$\chi^2$ Statistic after Stratification
Age category (yrs)			0.41	0.82
<65	357 (23)	708 (23)		
65–69	546 (35)	1010 (33)		
≥70	650 (42)	1319 (43)		
Gender			34.26*	5.79 <sup>†</sup>
Female	773 (50)	1787 (59)		
Male	780 (50)	1250 (41)		
AMD category			11.19*	0.79
1	410 (26)	699 (23)		
2	380 (24)	671 (22)		
3	481 (31)	1058 (35)		
4	282 (18)	609 (20)		
Race			7.01*	0.50
White	1468 (95)	2922 (96)		
Other	85 (5)	115 (4)		
Education			10.24*	0.90
High school or less	603 (39)	1017 (33)		
Some college	441 (28)	937 (31)		
College graduate or more	509 (33)	1083 (36)		
Marital status			4.98 <sup>†</sup>	0.00
Married	1146 (74)	2143 (71)		
Divorced/separated	102 (7)	227 (7)		
Widowed	237 (15)	525 (17)		
Never married	68 (4)	142 (5)		
Arthritis			12.53*	0.00
No	901 (58)	1595 (53)		
Yes	652 (42)	1442 (47)		
Diabetes			4.01 <sup>†</sup>	0.59
No	1447 (93)	2874 (95)		
Yes	106 (7)	163 (5)		
Aspirin use			1.37	2.68
No	1401 (90)	2706 (89)		
Yes	152 (10)	331 (11)		
Cancer			6.69*	0.03
No	1309 (84)	2467 (81)		
Yes	244 (16)	570 (19)		
Body mass index (kg/m <sup>2</sup> )			3.03	1.79
≤22	134 (9)	285 (9)		
>22, <30	997 (64)	2015 (66)		
≥30	422 (27)	737 (24)		
High blood pressure			0.07	0.26
No	937 (60)	1847 (61)		
Controlled	391 (25)	742 (24)		
Uncontrolled	104 (7)	222 (7)		
Yes/no medication	121 (8)	226 (7)		
Previous vitamin usage			1683.6*	0.00
No	1200 (77)	362 (12)		
Yes, <1 tablet/wk	112 (7)	131 (4)		
Yes, ≥1 tablets/wk	241 (16)	2544 (84)		
Current smoker			0.12	2.03
No	1434 (92)	2796 (92)		
Yes	119 (8)	241 (8)		
Run-in compliance			4.27 <sup>†</sup>	0.01
Quartile 1	375 (24)	652 (21)		
Quartiles 2, 3, and 4	1178 (76)	2385 (79)		
Antiinflammatory drug use			1.09	0.13
No	1381 (89)	2670 (88)		
Yes	172 (11)	367 (12)		

AMD = age-related macular degeneration.

\*  $P < 0.01$ .

<sup>†</sup>  $P < 0.05$ .

Table 3

Risk of Progression of Lens Opacity with Centrum Use

	Any Opacity		Nuclear Opacity		Cortical Opacity		Posterior Subcapsular Opacity	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Unadjusted	0.88	0.79–0.98 <sup>*</sup>	0.78	0.68–0.89 <sup>*</sup>	0.94	0.77–1.14	1.03	0.82–1.28
Adjusted <sup>†</sup>	0.82	0.71–0.95 <sup>*</sup>	0.78	0.64–0.95 <sup>*</sup>	0.82	0.64–1.06	1.11	0.84–1.47
Adjusted <sup>‡</sup>	0.84	0.72–0.98 <sup>*</sup>	0.75	0.61–0.91 <sup>*</sup>	0.91	0.68–1.22	1.02	0.77–1.36

CI = confidence interval; OR = odds ratio.

<sup>\*</sup>  $P < 0.01$ .

<sup>†</sup> Adjusted for propensity score (5 strata).

<sup>‡</sup> Adjusted for propensity score, age (<65, 65–69, ≥70 yrs), gender, race (white, other), smoking status (never/former smoker, current smoker), education (high school or less, some college, college graduate), lens status (present [nuclear ≥ grade 4.0, cortical ≥5%, or posterior subcapsular ≥5% in at least one eye], absent), Age-Related Eye Disease Study treatment (antioxidants, no antioxidants), antiinflammatory drug use, and run-in compliance (quartiles 2, 3, 4 vs. quartile 1). Type-specific analyses are adjusted for type-specific baseline lens opacity status.