

The Linxian Cataract Studies

Two Nutrition Intervention Trials

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Objective: To determine whether the vitamin/mineral supplements used in two cancer intervention trials affected the risk of developing age-related cataracts.

Design: Two randomized, double-masked trials with a duration of 5 to 6 years and end-of-trial eye examinations.

Setting: Rural communes in Linxian, China.

Participants: In trial 1, 2141 participants aged 45 to 74 years, and, in trial 2, 3249 participants aged 45 to 74 years.

Interventions: Multivitamin/mineral supplement or matching placebo in trial 1; factorial design to test the effect of four different vitamin/mineral combinations in trial 2 (retinol/zinc, riboflavin/niacin, ascorbic acid/molybdenum, and selenium/alpha-tocopherol/beta carotene).

Main Outcome Measures: Prevalence of nuclear, cortical, and posterior subcapsular cataracts in treatment groups at end of trials.

Results: In the first trial, there was a statistically significant 36% reduction in the prevalence of nuclear cataract for persons aged 65 to 74 years who received the supplements. In the second trial, the prevalence of nuclear cataract was significantly lower in persons receiving riboflavin/niacin compared with persons not receiving these vitamins. Again, persons in the oldest group, 65 to 74 years, benefited the most (44% reduction in prevalence). No treatment effect was noted for cortical cataract in either trial. Although the number of posterior subcapsular cataracts was very small, there was a statistically significant deleterious effect of treatment with riboflavin/niacin.

Conclusions: Findings from the two trials suggest that vitamin/mineral supplements may decrease the risk of nuclear cataract. Additional research is needed in less nutritionally deprived populations before these findings can be translated into general nutritional recommendations.

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INITIAL SUGGESTIONS that nutritional status might affect lens clarity came from studies in which nutrients were withheld from the diet of experimental animals. Such dietary restriction studies and in vitro experiments have implicated a diverse group of nutrients in cataract formation, including protein, amino acids (most notably tryptophan), riboflavin, vitamin C, vitamin E, selenium, calcium, zinc, and others.¹⁻³ The relevance of these findings for human cataract is unclear because nutrient deprivation has been extreme in the animal studies, lens changes have not been recorded as responses to either acute or chronic malnutrition in humans, and

there is considerable variation between species in the utilization of various exogenous nutrients.

In recent years, recognition of the importance of oxidative damage in cataract formation and suggestions that micronutrients with antioxidant capabilities may help protect the lens from oxidative damage have stimulated renewed interest in the micronutrient/ataract relationship.^{1,4,5} However, a series of observational studies have

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METHODS

STUDY POPULATION

Two groups of subjects, aged 40 to 69 years, were recruited from Linxian, a county in north central China, whose population is affected by chronic deficiencies of multiple nutrients and extraordinarily high rates of esophageal cancer.⁹⁻¹¹ Pretrial recruitment and screening identified subjects with no history of cancer, including 3318 with cytologically demonstrated esophageal dysplasia (a high-risk characteristic for esophageal cancer) and 29 584 subjects from the area's general population who met the eligibility requirements and agreed to participate in randomized nutritional intervention trials.¹¹

RANDOMIZATION SCHEME

In one study, the dysplasia trial, subjects with esophageal dysplasia from three communes were randomly assigned to daily use of either two multiple vitamin/mineral tablets (Centrum, Lederle Laboratories Inc, Pearl River, NY) and one 15-mg beta carotene capsule (Solatene, Hoffmann-LaRoche Inc, Nutley, NJ) or matching placebos (**Table 1**).

Nutrient dosages of approximately 1.5 to three times the US recommended daily allowance were selected in an attempt to shift the mean nutrient status of the nutritionally deficient population of Linxian to approximately that of the upper 10% or 20% of the US population.⁹ All micronutrients of potential interest for cataract were included in the supplement. Distribution of the tablets/capsules began in May 1985 and continued through April 1991.

In the general population trial, begun in March 1986, an attempt was made to separate the possible effects associated with various micronutrients. Nine micronutrients (which included those with the greatest potential for affecting cataract risk) were of special interest in the cancer trial because there was a strong suspicion (usually based on biochemical evidence) that the Linxian population was deficient in these nutrients, and there was laboratory evidence suggesting that each of these nutrients lowered the risk of chemically induced cancer in experimental animals.

A factorial design evaluating each of the nine nutrients was impractical, but there was a reluctance to eliminate any of the nine from consideration. Therefore, the nutrients were first clustered in the following four vitamin/mineral combinations: retinol/zinc (factor A), riboflavin/niacin (factor B), ascorbic acid/molybdenum (factor C), and selenium/alpha-tocopherol/beta carotene (factor D) (**Table 2**). An eight-group fractional factorial design, a one-half replication of a 2⁴ factorial, was then used. The eight treatment groups represent the following combinations of the factors: placebo, AB, AC, AD, BC, BD, CD, and ABCD. As can be seen, one half of the participants received supplementation with each of the four vitamin/mineral combinations, so that randomized contrasts between the presence and absence of each of the factors were possible. Although considerations in the

cancer component of the study determined the groupings of nutrients, each group contained one or more nutrients of interest for cataract, based on findings from earlier observational studies.^{6,7} The supplements were taken daily.

TABLET/CAPSULE DELIVERY SYSTEM

An elaborate tablet delivery system with numerous quality control checks was used.¹¹ After participants had been identified during the screening examination, randomized intervention assignments were made at a data management center in the United States and masked tablet distribution logs were sent to Linxian. The log indicated which of the specially prepared and labeled bottles available at a central distribution center in Linxian were to be assigned to subjects. At the start of the study and each month thereafter, when village medical personnel collected a new supply of tablets/capsules for distribution, one tab was removed from a participant's assigned bottle and affixed to the distribution log at the central distribution site. A second tab was removed from the bottle at the time of monthly delivery of tablets/capsules to participants and affixed to a second distribution log. When new supplies were delivered, the number of tablets/capsules remaining in previously dispensed bottles was counted and recorded.

COMPLIANCE MONITORING

Compliance was monitored by the monthly tablet/capsule counts on all subjects and by quarterly biochemical assessments of blood samples taken from random samples of approximately 100 study subjects. Tablet/capsule counts showed that more than 86% of subjects were taking more than 90% of their tablets/capsules. Fewer than 5% of subjects were poor compliers (ie, took <50% of their tablets/capsules). Blood biochemical assessments showed marked differences in mean values of several nutrients between those receiving and not receiving interventions with the nutrient. The most marked differences were for serum beta carotene. Mean (\pm SD) serum values in the general population trial were 12.0 \pm 0.7 μ g/dL and 83.6 \pm 3.7 μ g/dL for those receiving and not receiving capsules with beta carotene, respectively.

EXAMINATION PROTOCOL

Special end-of-trial examinations were conducted in March and April 1991. All eligible persons in the dysplasia trial who were still living and a subset of persons in the general population trial who lived in selected villages in one of the communes were invited to participate. For the general population sample, villages were selected by the data management center based on village size, village location, and number of residents also in the dysplasia trial. Village selection was not random, but since Linxian County's population is so homogeneous, it seems likely that the selected persons were representative of persons in the larger general popu-

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lation cohort. The targeted population included 2749 persons in the dysplasia trial and 4656 persons in the general population trial who were between the ages of 45 and 74 years at the time of examination.

Eye examinations, sponsored by the National Eye Institute, were conducted by investigators from the Peking Union Medical College Hospital, Beijing, China. Both pupils were dilated with 2.5% phenylephrine hydrochloride until a minimal pupillary diameter of 6 mm was achieved. The Lens Opacities Classification System II, which uses photographic standards for grading cataract type and severity, was used to evaluate lens status at the slit lamp.¹² The system provides ordinal scores for separately grading nuclear (NO, NI, NII, NIII, or NIV), cortical (CO, Ctr, CI, CII, CIII, CIV, or CV), and posterior subcapsular (PO, PI, PII, PIII, or PIV) opacities. A person was judged to have a nuclear cataract if either eye had a grade of NII or greater, a cortical cataract if either eye had a grade of CII or greater, and a posterior subcapsular cataract if either eye had a grade of PI or greater. The remaining lens was used to classify persons with unilateral aphakia.

The lens examinations were conducted by three senior ophthalmologists. Two of the examiners had used the Lens Opacities Classification System I,¹³ a forerunner of the Lens Opacities Classification System II, in an earlier population study. The examiners attended training sessions on use of the grading system and were certified before the start of data collection.

STATISTICAL ANALYSIS

Treatment effect on prevalence was analyzed separately for the three types of cataract. Persons were considered to have a specific type of cataract when that type of cataract was present in either eye, regardless of the presence or absence of other types of cataract. Analysis was restricted to persons aged 45 to 74 years at the time of examination. Analysis of treatment effect in the dysplasia trial was done by assessment of the prevalence odds ratio (OR) for pooled and age-stratified data. For the general population trial, we used logistic regression analysis following the approach of Dyke and Patterson¹⁴ and recommended by Cox and Snell.¹⁵ The logistic model allows for inclusion of covariates, such as age, and for assessment of the significance of interactions. Analysis was done using BMDP program PLR (University of California Press, Berkeley).¹⁶ In this fractional factorial design, two-factor interactions are aliased, that is, the estimate of the interaction of factors A and B includes and cannot be separated from the interaction of factors C and D.¹⁷ The three two-factor interactions in this design so interpreted can be estimated and tested.

Table 1. Daily Dosage of the Micronutrients in the Supplements in the Dysplasia Trial

Beta carotene (15 mg)	Calcium (324 mg)
Retinol (10 000 IU)	Phosphorus (250 mg)
Alpha-tocopherol (60 IU)	Iodine (300 µg)
Ascorbic acid (180 mg)	Iron (54 mg)
Folic acid (800 µg)	Magnesium (200 mg)
Thiamin (4.5 mg)	Copper (6 mg)
Riboflavin (5.2 mg)	Manganese (15 mg)
Niacin (40 mg)	Potassium (15 mg)
Vitamin B ₆ (6 mg)	Chloride (14 mg)
Vitamin B ₁₂ (18 µg)	Chromium (30 µg)
Vitamin D (800 IU)	Molybdenum (30 µg)
Biotin (90 µg)	Selenium (50 µg)
Pantothenic acid (20 mg)	Zinc (45 mg)

Table 2. Treatment Factors and Groups, General Population Trial*

Treatment Factor	Nutrients
A	Retinol (5000 IU), zinc (22 mg)
B	Riboflavin (3 mg), niacin (40 mg)
C	Ascorbic acid (120 mg), molybdenum (30 µg)
D	Selenium (50 µg), alpha-tocopherol (30 mg), and beta carotene (15 mg)

*Treatment groups were placebo, AB, AC, AD, BC, BD, CD, and ABCD.

provided no conclusive data. Some,^{6,7} but not all,⁸ case-control studies have reported a decreased risk of cataract with a higher intake or higher blood levels of a number of micronutrients, including those with antioxidant capabilities. While the findings from the observational studies provide some support for the hypothesis of a link between nutritional status and risk of cataract, problems inherent in observational studies have made it difficult to reach conclusions about whether dietary modifications can influence the risk of cataract. Of special concern in such nonrandomized studies of nutrition and cataract are questions about the possibility of unadjusted confounding. Do persons who take vitamin/mineral supplements or who eat better diets differ from others in important but unrecognized ways that explain the apparent decreased risk of cataract? Unadjusted confounding and many of the potential biases that can affect observational studies are of less concern in a randomized clinical trial.

The National Cancer Institute, in collaboration with the Cancer Institute of the Chinese Academy of Medical Sciences, has been conducting two double-masked, randomized, nutrition intervention trials in Linxian, China, since 1986 to determine whether supplementation of the diet with multiple vitamin/mineral preparations can reduce the risk of esophageal/gastric cardia cancer.⁹ Included in the supplements under investigation are vitamins and minerals with the greatest potential for affecting

age-related cataracts. In March and April 1991, participants in both trials were recalled for examination. An eye examination, which included detailed lens evaluations, was included in the extensive reexamination protocol. The purpose of this article is to report whether use of the supplements had affected the risk of developing age-related cataracts among participants in the two trials.

RESULTS

Eye examinations were done on 2141 persons (78% of those targeted) in the dysplasia trial and 3249 persons (70% of those targeted) in the general population trial who were aged 45 to 74 years. Persons examined in the dysplasia trial were slightly older and more frequently female than those in the general population trial (Table 3). Persons in the dysplasia trial also weighed less, tended to have higher systolic blood pressure, and were more frequently in poor health. Within each trial, persons were very similar across treatment groups with respect to a number of characteristics measured at baseline (Table 3).

The prevalence of cataract type by treatment group, is given for both trials in Table 4. Most persons with cataracts had a single type of cataract. Only about 15% of persons with cataract in each trial had mixed opacities. Cortical cataracts were by far the most common of the cataract types.

Table 5 presents the treatment effect on the prevalence of any nuclear, any cortical, and any posterior subcapsular cataract. Nuclear cataract was uncommon in persons aged 45 to 64 years, and posterior subcapsular cataract was uncommon at all ages. The prevalence of cortical and posterior subcapsular cataract showed no significant association with treatment. There was a modest, but non-significant, beneficial treatment effect on the prevalence

of nuclear cataract (prevalence OR, 0.80; 95% confidence interval (CI), 0.57 to 1.12). However, treatment effect differed significantly by age (homogeneity χ^2 , 5.49; $P=.02$). No significant effect was found among persons aged 45 to 64 years, while a significant protective effect yielding a prevalence OR of 0.57 (95% CI, 0.36 to 0.90) was found among persons aged 65 to 74 years.

In the general population trial, as in the dysplasia trial, nuclear cataract was rare in patients younger than age 55 years, and posterior subcapsular cataract was rare at all ages (Table 6). Analysis of treatment and nuclear

Table 3. Baseline Characteristics of Subjects Aged 45 to 74 Years at Time of Examination, by Trial and Treatment Group*

Characteristic	Dysplasia Trial		General Population Trial†
	P	M	
No. of subjects	1083	1058	382-428
Mean age, y	59	59	56-57
Female subjects	57	58	48-52
Mean height, cm	158	157	158-159
Mean weight, kg	51	51	55-56
Mean systolic blood pressure, mm Hg	130	130	126-129
Ill, could not work	11	11	9-11
Took medicine regularly	9	7	5-7
Smoked cigarettes regularly for 6 mo	26	28	33-39
Ever diagnosed as being hypertensive	8	7	5-9
No formal schooling	41	43	41-46

*P indicates placebo; M, multivitamin/mineral. Unless otherwise indicated, data are percent of subjects.

†Range over general population trial treatment groups as shown in Table 2.

Table 4. Frequency of Cataract by Type, Trial, and Treatment Group*

Trial and Treatment Group	Cataract Type								Total No. of Subjects
	None	Pure			Mixed				
		C	N	P	CN	PC	PN	PNC	
Dysplasia trial									
Placebo	659	317	48	4	40	14	1	0	1083
Multivitamin/mineral	647	317	35	1	33	22	0	3	1058
General population trial†									
Placebo	263	106	22	1	22	0	0	0	414
AD	264	100	20	0	24	2	0	2	412
BD	258	93	12	2	10	3	1	3	382
AB	247	113	13	1	11	1	0	1	387
CD	267	87	16	1	23	2	1	0	397
AC	279	98	9	1	15	1	0	0	403
BC	283	107	15	3	13	5	1	1	428
ABCD	282	116	9	0	13	4	1	1	426

*Data are number of subjects. C indicates cortical; N, nuclear; and P, posterior subcapsular.

†A indicates retinol and zinc; B, riboflavin and niacin; C, ascorbic acid and molybdenum; and D, selenium, alpha-tocopherol, and beta carotene.

Table 5. Treatment Effect on Prevalence of Nuclear, Cortical, or Posterior Subcapsular Cataract Among Persons Aged 45 to 74 Years, Dysplasia Trial*

Cataract Type	Treatment	No. of Subjects	No. (%) of Subjects With Cataract	Prevalence Odds Ratio (95% CI)
Nuclear†	M	1058	71 (6.7)	0.80 (0.57-1.12)
	P	1083	89 (8.2)	
	M	800	31 (3.9)	1.28 (0.76-2.14)
	P	821	25 (3.0)	
Subjects aged 65-74 y	M	258	40 (15.5)	0.57‡ (0.36-0.90)
	P	262	64 (24.4)	
Cortical	M	1058	375 (35.4)	1.05 (0.88-1.26)
	P	1083	371 (34.3)	
Posterior subcapsular	M	1058	26 (2.5)	1.41 (0.75-2.67)
	P	1083	19 (1.8)	

*CI indicates confidence interval; M, multivitamin/mineral; and P, placebo.

†Significant heterogeneity of effect by age: $\chi^2=5.49$ (1 df); $P=.02$. Age-stratified analysis also presented.

‡ $P=.01$.

cataract was restricted to persons aged 55 to 74 years since there were only seven persons (0.5%) with nuclear cataract in the younger group. A logistic regression model that included age, main effects, and two-factor interactions was reduced without significant change in deviance to a simpler model containing age and the four main treatment effects (A, B, C, and D).

The effect of treatment B was highly significant and protective, with a prevalence OR of 0.59 ($P<.001$; 95% CI, 0.45 to 0.79) (**Table 7**). Treatment effects for A, C, and D were not significant ($P\geq.05$), although treatments A and C showed similar protective effects (prevalence ORs, 0.77 and 0.78, respectively), and 95% CIs barely included unity.

The inclusion of an age/treatment B interaction term significantly improved the fit of the logistic regression model (deviance χ^2 , 7.0; 1 df; $P<.01$), with no further significant improvement seen by including interactions of other treatments with age. There was no effect in the younger group (ages 55 to 64 years), but there was a significant protective effect for treatment B (riboflavin/niacin) among those aged 65 to 74 years (prevalence OR, 0.45; 95% CI, 0.31 to 0.64).

In the general population trial, analysis of cortical cataract showed no significant treatment effect (**Table 8**) on cataract prevalence. For posterior subcapsular cataract (Table 8), no significant effect was seen for treatments A, C, and D, but the low prevalence of this cataract type may reduce the ability to detect an effect. Treatment B showed a significant deleterious effect (prevalence OR, 2.64; 95% CI, 1.31 to 5.35).

COMMENT

Results from the two randomized trials suggest a beneficial effect of nutritional supplements on risk of nu-

clear cataract. The beneficial effect noted for nuclear cataract in the dysplasia trial was related to age. For the age group most affected by nuclear cataract (65 to 74 years), there was a statistically significant 36% reduction in prevalence of nuclear cataract for those who received the supplements. In the general population trial, there was a significant protective effect for nuclear cataract in persons receiving riboflavin/niacin compared with persons not receiving these vitamins. Again, the oldest subgroup, those aged 65 to 74 years, benefited the most from treatment (44% reduction in prevalence). Beneficial treatment effects for two of the other three vitamin/mineral combinations (vitamin C/molybdenum and vitamin A/zinc) approached statistical significance for nuclear cataract.

We found no effect of the nutritional supplements on prevalence of cortical cataract in either trial. However, in the general population trial, although the number of posterior subcapsular cataracts was very small, there was a statistically significant deleterious effect of treatment with riboflavin/niacin. No statistically significant effect on posterior subcapsular cataract was noted in the dysplasia trial, but the effect was in a deleterious direction.

Suggestions of how micronutrients might affect cataract development have come from laboratory observations. The lens is under constant oxidative stress from highly reactive forms of oxygen produced by a variety of external insults, such as exposure to near UV light, or as products of normal metabolism. These activated forms of oxygen can damage lens epithelial and fiber-cell membranes as well as lens enzymes important for energy production and the maintenance of electrolyte balance within lens fibers. Enzymatic and nonenzymatic defenses capable of deactivating the oxygen-containing molecular species are present in the lens but are thought to erode with aging. Naturally occurring antioxidants of potential im-

Table 6. Prevalence of Cataract in the General Population Trial, by Type of Cataract, Treatment Group, and Age

Treatment Group*	Age, y							
	45-74		45-54		55-64		65-74	
	No. of Subjects	No. (%) of Subjects With Cataract	No. of Subjects	No. (%) of Subjects With Cataract	No. of Subjects	No. (%) of Subjects With Cataract	No. of Subjects	No. (%) of Subjects With Cataract
Nuclear Cataract								
Placebo	414	44 (10.6)	178	1 (0.6)	161	16 (9.9)	75	27 (36.0)
AD	412	46 (11.2)	173	0	155	10 (6.4)	84	36 (42.9)
BD	382	26 (6.8)	174	1 (0.6)	142	5 (3.5)	66	20 (30.3)
AB	387	25 (6.5)	173	2 (1.2)	137	6 (4.4)	77	17 (22.1)
CD	397	40 (10.8)	159	0	166	9 (5.4)	72	31 (43.1)
AC	403	24 (6.0)	172	1 (0.6)	163	3 (1.8)	68	20 (29.4)
BC	428	30 (7.0)	184	1 (0.5)	159	13 (8.2)	85	16 (18.8)
ABCD	426	24 (5.6)	185	1 (0.5)	163	11 (6.8)	78	12 (15.4)
Cortical Cataract								
Placebo	414	128 (31.1)	178	26 (14.6)	161	56 (34.8)	75	46 (61.3)
AD	412	128 (31.1)	173	20 (11.7)	155	56 (36.1)	84	52 (61.9)
BD	382	109 (32.6)	174	19 (10.9)	142	49 (34.5)	66	41 (62.1)
AB	387	126 (29.4)	173	24 (13.9)	137	55 (40.2)	77	47 (61.0)
CD	397	112 (28.2)	159	17 (10.7)	166	52 (31.3)	72	43 (59.7)
AC	403	114 (28.3)	172	20 (11.6)	163	57 (35.0)	68	37 (54.4)
BC	428	126 (31.4)	184	24 (13.0)	159	51 (32.1)	85	51 (60.0)
ABCD	426	134 (30.9)	185	30 (16.2)	163	60 (36.8)	78	44 (56.4)
Posterior Subcapsular Cataract								
Placebo	414	1 (0.2)	178	0	161	1 (0.6)	75	0
AD	412	4 (1.0)	173	0	155	1 (0.7)	84	3 (3.6)
BD	382	9 (2.4)	174	2 (1.1)	142	4 (2.8)	66	3 (4.6)
AB	387	3 (0.8)	173	0	137	1 (0.7)	77	2 (2.6)
CD	397	4 (1.0)	159	1 (0.6)	166	0	72	3 (4.2)
AC	403	2 (0.5)	172	1 (0.6)	163	0	68	1 (1.5)
BC	428	10 (2.3)	184	3 (1.6)	159	2 (1.3)	85	5 (5.9)
ABCD	426	6 (1.4)	185	1 (0.5)	163	3 (1.8)	78	2 (2.6)

*A indicates retinol and zinc; B, riboflavin and niacin; C, ascorbic acid and molybdenum; and D, selenium, alpha-tocopherol, and beta carotene.

portance include glutathione, vitamin C, vitamin E, and the carotenoids.

Theoretical explanations of how oxidative damage might lead to cataract formation, combined with observations that oxidative damage is indeed an important feature of both nuclear and cortical cataract, have led to suggestions that dietary intake of micronutrients with antioxidant capabilities might influence the risk of cataract. Micronutrients with the greatest potential for influencing antioxidant status were used in both the dysplasia trial and in the general population trial. Of particular interest were vitamin C, vitamin E, the carotenoids, and riboflavin. The first three are naturally occurring antioxidants; riboflavin was of interest because its biologically active derivative is the cofactor for the enzyme glutathione reductase, which is important in maintaining the cellular pool of reduced glutathione.

While the antioxidant hypothesis may explain a beneficial effect of the supplements, we have no biological explanation for the possible increased risk of posterior subcapsular cataract with use of riboflavin/niacin. It is pos-

sible that the finding for posterior subcapsular cataract was a chance finding, given the number of statistical tests that were done and the small number of prevalent posterior subcapsular cataracts.

Observational epidemiologic studies have previously suggested a link between nutritional status and risk of cataract. A study done in India found a decreased risk of nuclear, mixed, and posterior subcapsular, but not cortical, cataracts in better nourished persons.⁶ In that study, the findings for cortical cataract were significantly different from those for the other types of cataract. Another case-control study done in the United States found that high values of an antioxidant index (determined by the dietary intake of riboflavin, vitamin C, vitamin E, and carotene) were associated with a greater than 50% reduction in the risk of cortical, nuclear, and mixed cataracts.⁷ Unlike the other two case-control studies, a third case-control study failed to find any association between cataract and individual nutrient variables obtained from dietary interviews or biochemical testing of blood specimens.⁸

Table 7. Treatment Effect on Prevalence of Nuclear Cataract Among Persons Aged 55 to 74 Years, General Population Trial, Using Logistic Regression (N=1851)*

Treatment†	Estimated Proportion of Subjects With Cataract		Prevalence Odds Ratio (95% CI)
	Treatment Present	Treatment Absent	
	A	0.120	
B	0.107	0.169	0.59‡ (0.45-0.79)
Aged 55-64 y§	0.0577	0.0581	0.99 (0.62-1.59)
Aged 65-74 y§	0.213	0.378	0.45‡ (0.31-0.64)
C	0.121	0.150	0.78 (0.59-1.04)
D	0.146	0.125	1.19 (0.90-1.59)

*Subjects aged 45 to 54 years were omitted since the prevalence of nuclear cataract in this age group was only 0.5% (seven of 1398). CI indicates confidence interval.

†A indicates retinol and zinc; B, riboflavin and niacin; C, ascorbic acid and molybdenum; and D, selenium, alpha-tocopherol, and beta carotene.

‡P<.001.

§Significant age and treatment B interaction in logistic regression analysis; age-stratified results are also presented.

Table 8. Treatment Effect on Prevalence of Cortical and Posterior Subcapsular Cataract Among Persons Aged 45 to 74 Years, General Population Trial, Using Logistic Regression

Treatment*	Estimated Proportion of Subjects With Cataract		Prevalence Odds Ratio (95% Confidence Interval)
	Treatment Present	Treatment Absent	
	Cortical		
A	0.342	0.325	1.08 (0.92-1.27)
B	0.342	0.325	1.08 (0.92-1.27)
C	0.325	0.342	0.92 (0.79-1.09)
D	0.330	0.338	0.96 (0.82-1.13)
Posterior Subcapsular			
A	0.008	0.013	0.59 (0.31-1.14)
B	0.016	0.006	2.64† (1.31-5.35)
C	0.011	0.009	1.25 (0.65-2.38)
D	0.013	0.008	1.56 (0.81-3.00)

*A indicates retinol and zinc; B, riboflavin and niacin; C, ascorbic acid and molybdenum; and D, selenium, alpha-tocopherol, and beta carotene.

†P=.007.

A major strength of our study was the randomized, double-masked design. Randomization resulted in a balance of the treatment groups with respect to a variety of known factors. Given the large sample size, the randomization should also have resulted in balance between treatment groups for other unrecognized, and therefore unmeasured, potential confounding variables and for baseline prevalence of cataract. Masking of study participants and study personnel about treatment assignments further minimized the potential for bias.

Table 9. Baseline Characteristics of Persons Examined and Not Examined, by Trial

Baseline Characteristic	Dysplasia Trial		General Population Trial	
	Examined	Not Examined	Examined	Not Examined
Mean age, y	59	60	57	58
Female subjects, %	58	60	49	58
Ill, could not work, % of subjects	11	14	10	13
No formal schooling, % of subjects	42	49	43	51

An unusual additional advantage of the study was our ability to compare treatment effects observed in two separate trials. The similarity of findings across the two studies strengthens the likelihood that the treatment effects are real.

Adherence to treatment assignments was excellent as monitored by pill counts and biochemical monitoring. Random periodic blood collections showed clear separation in the distributions of serum beta carotene between those receiving and those not receiving the nutrient. Beta carotene was a particularly appropriate marker for compliance because baseline levels of this nutrient are low in the Linxian population.

Interpretation of the results also requires recognition of the study's limitations. The study was done in a population with chronic deficiencies of multiple nutrients.⁹ While such a population might afford the best chance of demonstrating a treatment effect, if use of any of the supplements had an effect, the results might not be generalizable to better nourished populations. Another potential problem is that only about 70% of the participants who were targeted for examinations had eye examinations. The numbers not examined did not vary by treatment assignment in either of the trials, but, as a group, those subjects not examined tended to be slightly older than those subjects examined and were more likely to be female, to not have attended school, and to not work because of illness (**Table 9**).

If treatment effects were different for examined and nonexamined participants, the results could have been affected. Also, since eye examinations were conducted only at the end-of-study examination, we have no way of knowing the prevalence of cataract in the population at the start of the study. Thus, the results could have been affected by a failure of the randomization process to balance the prevalence of cataract across treatment groups at the time of randomization. Finally, the intervention may have come too late in the disease process or may have been applied for too short a period to have demonstrated an effect on risk of cortical or posterior subcapsular cataract.

The totality of evidence from the two trials suggests that use of the vitamin/mineral supplements decreased the risk of nuclear cataract. However, until the results from other studies in less nutritionally deprived populations are available, it would be premature to translate these findings into nutritional recommendations for the US population.

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