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Lowered Risks of Hypertension and Cerebrovascular Disease after Vitamin/Mineral Supplementation

The Linxian Nutrition Intervention Trial

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A total of 3,318 men and women from a region in rural China were randomized to receive daily either a multiple vitamin/mineral supplement or a placebo. Deaths that occurred in the participants were ascertained and classified according to cause over the 6-year period from 1985 to 1991. At the end of supplementation, blood pressure readings were taken, and the prevalence of hypertension was determined. There was a slight reduction in overall mortality in the supplement group (relative risk (RR) = 0.93, 95% confidence interval (CI) 0.75–1.16), with the decreased relative risk most pronounced for cerebrovascular disease deaths (RR = 0.63, 95% CI 0.37–1.07). This benefit was greater for men (RR = 0.42, 95% CI 0.19–0.93) than for women (RR = 0.93, 95% CI 0.44–1.98). Among the survivors, the presence of elevations in both systolic and diastolic blood pressures was less common in those who received the supplement (RR for men = 0.43, 95% CI 0.28–0.65; RR for women = 0.92, 95% CI 0.68–1.24). This study indicates that supplementation with a multivitamin/mineral combination may have reduced mortality from cerebrovascular disease and the prevalence of hypertension in this rural population with a micronutrient-poor diet. *Am J Epidemiol* 1996;143:658–64.

antioxidants; cerebrovascular disorders; hypertension; minerals; nutrition; randomized controlled trials; stroke; vitamins

Cerebrovascular disease is the second leading cause of death in Linxian, a county in north-central China with one of the world's highest rates of esophageal/gastric cardia cancer (1). The determinants of cerebrovascular disease in Linxian and other parts of China are not well-known, but dietary factors, including low vitamin and mineral intake, may be involved. As part of a randomized trial to evaluate the effectiveness of supplementation with multiple vitamins and minerals in reducing the high incidence of cancer among adults with cytologic evidence of esophageal dysplasia in Linxian, information on all deaths, including those from cerebrovascular disease, was ascertained. In addition, measurements of blood pressure were taken prior to and after the vitamin/mineral intervention. We previously reported finding no significant benefit of the supplement on either overall mortality or cancer mortality (2) among individuals with esophageal dysplasia. There was, however, a significantly increased prevalence of reversion to nondysplastic cytology among individuals who received the supplement (3). Herein, we report the effects of the supplements on the prevalence of hypertension and mortality from cerebrovascular disease.

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MATERIALS AND METHODS

The design, methods of conduct, and primary endpoint analyses of the trial have been described in detail elsewhere (2–4). In brief, 3,318 adults aged 40–69 years who were cytologically diagnosed prior to the start of the trial with esophageal dysplasia were randomly assigned to receive daily supplementation with 26 vitamins and minerals (table 1) or look-alike placebos during the period of May 1985 to April 1991. Doses of the supplement were typically two to three times (range, 20–700 percent) the US Recommended Dietary Allowance. The supplements were delivered monthly, with compliance assessed by counting unused pills and by assaying nutrient levels in blood collected from random samples of participants every 3 months. Individuals with a history of cancer or debilitating diseases were excluded.

Deaths that occurred among trial participants were ascertained through close surveillance of the study population by village doctors responsible for health

TABLE 1. Daily doses and types of micronutrients in the supplements*, Linxian, China, 1985–1991

Vitamin/mineral	Compound	Dose
Beta-carotene		15 mg
Vitamin A	Acetate	10,000 IU
Vitamin E	dl-Alpha-tocopherol acetate	60 IU
Vitamin C	Ascorbic acid	180 mg
Folic acid		800 μg
Vitamin B_1	Thiamine mononitrate	5 mg
Vitamin B_2	Riboflavin	5.2 mg
Niacinamide		40 mg
Vitamin B_6	Pyridoxine HCl	6 mg
Vitamin B_{12}	Cyanocobalamin	18 μg
Vitamin D		800 IU
Biotin		90 μg
Pantothenic acid	Calcium pantothenate	20 mg
Calcium	Dibasic calcium phosphate	324 mg
Phosphorus	Dibasic calcium phosphate	250 mg
Iodine	Potassium iodide	300 μg
Iron	Ferrous fumarate	54 mg
Magnesium	Magnesium oxide	200 mg
Copper	Cupric oxide	6 mg
Manganese	Manganese sulfate	15 mg
Potassium	Potassium chloride	15.6 mg
Chloride	Potassium chloride	14 mg
Chromium	Chromium chloride	30 μg
Molybdenum	Sodium molybdate	30 μg
Selenium	Sodium selenite	50 μg
Zinc	Zinc sulfate	45 mg

*Participants received two multivitamin/mineral tablets (Centrum, Lederle Laboratories, Wayne, New Jersey) and one beta-carotene capsule (Solatene, Hoffman-La Roche, Nutley, New Jersey) or matching placebo daily.

care. The causes of noncancer deaths, one category of which was cerebrovascular disease, were determined by local physicians and reviewed by experienced senior Chinese clinicians involved in this study. Deaths attributed to cancer were reviewed by a panel of Chinese and American experts in gastroenterology, pathology, radiology, and clinical medicine. At baseline (prior to randomization) in 1984 and again in the spring of 1991, questionnaires were administered, and brief physical examinations were conducted. The baseline questionnaire included information on age, sex, cigarette smoking, and alcohol drinking. Physical examinations included standard mercury sphygmomanometer measurement of systolic and diastolic blood pressures and measurement of weight and height (subjects wore indoor clothing, but no shoes). In 1991, blood pressure was measured by using an electronic digital sphygmomanometer, and readings were taken by field staff blinded to intervention group status. At both the baseline and end-of-trial examinations, the blood pressures were taken once at the beginning of the physical examination with the subject seated. At the end of the trial, participants could be classified as either "healthy" or in one of six mutually exclusive disease categories: 1) deceased from cerebrovascular disease (stroke); 2) deceased from other causes; 3) alive with cancer; 4) alive, cancer free, with systolic (systolic pressure $\geq$ 160 mmHg), but not diastolic, hypertension; 5) alive, cancer free, with diastolic (diastolic pressure $\geq$ 95 mmHg), but not systolic, hypertension; 6) alive, cancer free, with both systolic and diastolic hypertension. The cutoff values for systolic and diastolic pressures follow World Health Organization criteria (5).

Relative risks and corresponding 95 percent confidence intervals for stroke mortality were calculated for treatment group and for baseline risk factors by using proportional hazards models (6). The proportionality assumption was examined graphically and by using time-dependent models to test for variation of the relative risk over time. The effect of the treatment group on 1991 systolic and diastolic pressures was estimated by linear regression. Polytomous logistic regression (7) was used to compare the odds in the treated versus the nontreated group for each of the six possible disease categories. Confidence intervals for the relative risks from the proportional hazards models were likelihood based (8), while for the logistic and linear regressions Wald intervals were used. Significance tests were two-sided and were calculated by using the likelihood ratio test (proportional hazards models and logistic regression) or the F test (linear regression). Cumulative incidence curves were estimated by the method of Kaplan and Meier (9).

RESULTS

Characteristics of the participants at the beginning of the trial are shown in table 2. The median age was 54 years, and 56 percent were female. About two thirds of the men, but few women, smoked cigarettes (i.e., lifetime use for 6 months or more). Less than 20 percent of the participants reported ever drinking alcohol in the previous year (33 percent male and 8 percent female), typically infrequently and in small amounts. There were no appreciable differences for any of these characteristics between subjects in the supplemented versus the placebo groups. The distributions of body mass index (weight (kg)/height (m^2)), systolic pressure, and diastolic pressure were similar between the groups at the start of the trial. Data on serum nutrients from samples of trial participants and from surveys prior to the start of the trial indicate that the Linxian region has poor overall nutrition. Dietary surveys conducted in this area have indicated that as many as 90 percent of the adults in the Linxian population have less than two thirds of the Chinese or US recommended intake of vitamin A, riboflavin, and calcium (10). Plasma levels of vitamin A, many of the

TABLE 2. Baseline characteristics of trial participants by treatment group, Linxian, China, 1985–1991

Characteristic	Placebo		Supplement	
	No.*	%	No.*	%
Age (years)				
<50	537	32	545	33
50–59	743	45	717	43
≥60	381	23	395	24
Sex				
Male	731	44	730	44
Female	930	56	927	56
Ever smoked tobacco				
No	1,176	71	1,172	71
Yes	477	29	477	29
Ever drank				
No	1,359	82	1,328	81
Yes	294	18	321	19

	No.	Mean ± SE†	No.	Mean ± SE
Height (cm)	1,653	157.8 ± 0.2	1,649	157.7 ± 0.2
Weight (kg)	1,653	50.8 ± 0.2	1,649	50.7 ± 0.2
Diastolic pressure (mmHg)	1,653	80.1 ± 0.3	1,649	79.9 ± 0.3
Systolic pressure (mmHg)	1,653	131.8 ± 0.6	1,649	131.8 ± 0.6

*Numbers may not add to 1,661 for the placebo group and 1,657 for the supplement group because of missing data.
†SE, standard error.

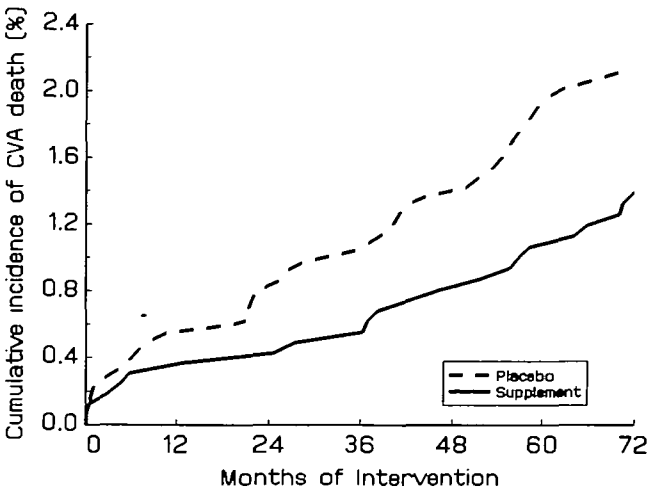

FIGURE 1. Cumulative incidence of death from cerebrovascular accidents (CVA) by treatment group, Linxian, China, 1985–1991.

carotenoids, vitamin E, vitamin C, riboflavin, and zinc have also been found to be low and/or deficient compared with levels in and standards for the US population (4, 11, 12).

During the 6-year course of the trial, 167 deaths occurred among those who received placebos versus 157 among those who received supplements (table 3). The reduction was primarily due to lower mortality from cerebrovascular disease, with 35 versus 22 deaths in the placebo and supplemented groups, respectively (RR = 0.63, 95 percent CI 0.37–1.07, p = 0.08). Figure 1 displays the cumulative stroke mortality curve, with the advantage for the supplemented group appearing within the first year of the trial. Formal testing showed no evidence of a latency period: The relative risk in the first 2 years did not differ from the subsequent relative risk (p = 0.40).

Overall, men experienced higher death rates for stroke than did women (RR = 1.5, 95 percent CI 0.87–2.40, p = 0.15). Sex also was an important modifier of the effect of treatment group (figure 2). Whereas stroke mortality for women was not greatly affected by treatment group (RR = 0.93, 95 percent CI 0.44–1.98, p = 0.85), the death rate for men was significantly lower in the supplement group than in the placebo group (RR = 0.42, 95 percent CI 0.20–0.93, p = 0.02).

Table 4 lists the relative risks of stroke mortality according to the other baseline covariates. The strongest predictors of stroke mortality, and the only ones that remain significant when jointly entered into the model, were baseline systolic pressure and age. For every 5-mmHg increase in systolic pressure, the relative risk of an individual increased by a factor of 1.2; for every 5-year increase in age, the relative risk increased by a factor of 1.9. Drinkers had less than half the risk of stroke than did nondrinkers. When age and systolic pressure were controlled for, the point estimate of the relative risk for drinking remained largely

TABLE 3. Cause-specific mortality rates by treatment group, Linxian, China, 1985–1991

Cause of death	Placebo		Supplement		RR†	95% CI†
	No.	Rate*	No.	Rate*		
Cancer	89	9.3	87	9.0	0.96	0.71–1.29
Cerebrovascular	35	3.6	22	2.3	0.63	0.37–1.07
Other	43	4.5	48	5.0	1.12	0.74–1.69
Total	167	17.4	157	16.3	0.93	0.75–1.16

*Deaths per 1,000 person-years.
†RR, relative risk; CI, confidence interval.

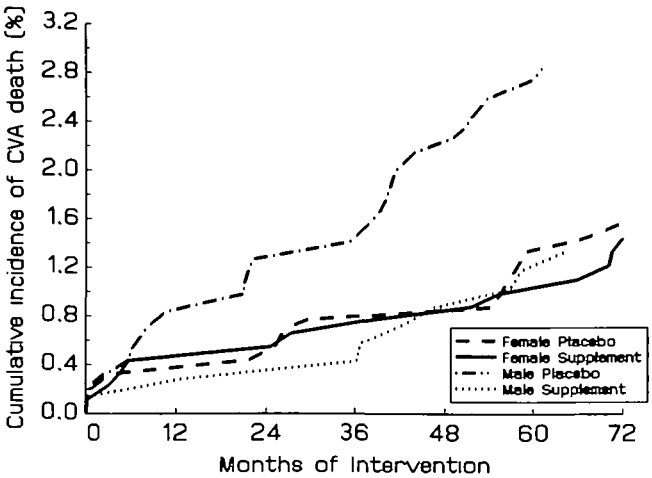

FIGURE 2. Cumulative incidence of death from cerebrovascular accidents (CVA) by treatment group and sex, Linxian, China, 1985–1991.

TABLE 4. Relative risks* of stroke associated with pretreatment variables, Linxian, China, 1985–1991

	RR†	95% CI†	*p* value
Systolic pressure per 5 mmHg	1.21	1.15–1.24	0.00
Diastolic pressure per 5 mmHg	1.25	1.16–1.32	0.00
Age per 5 years	1.90	1.55–2.34	0.00
Body mass index	1.00	0.88–1.11	0.94
Drink	0.43	0.16–0.94	0.03
Smoke	1.00	0.48–2.12	0.99

*Estimates when each pretreatment variable is entered separately into a Cox model stratified on sex and treatment group.
†RR, relative risk; CI, confidence interval.

unchanged (RR = 0.56), although the confidence interval expanded to include the null value of 1 (95 percent CI 0.24–1.27). Baseline diastolic pressure added little information to stroke risk once systolic pressure and age were in the model (RR = 1.002, p = 0.98).

The difference between the effect of treatment group on stroke mortality in men versus women was not explained by the higher prevalence of smoking and drinking in men. Tests for an interaction of treatment with smoking (p = 0.94) and drinking (p = 0.93) were not significant.

Individuals aged 60 years or more with systolic hypertension (systolic pressure ≥ 160 mmHg) at baseline accounted for about 6 percent of the study population, but experienced nearly 30 percent of the stroke deaths. There was no evidence, however, that the effect of treatment was different in this high-risk population than in those without these two risk factors (p = 0.29).

Among surviving participants, 2,384 (80 percent) had blood pressure measurements taken during the end-of-trial examinations in March-April 1991, with no significant difference between the treatment groups in the percentage with measurements (p = 0.50). Among women, however, higher age and higher baseline blood pressure lessened the probability of repeat measurement in 1991. To account for these differences, we estimated the effect of treatment group on systolic and diastolic pressures separately by sex with models that included age, baseline systolic and diastolic pressures, smoking, drinking, and body mass index. For men, the average 1991 diastolic pressure was 2.02 mmHg lower in the treated group than the control group (p = 0.009), and the average systolic pressure was 1.33 mmHg lower (p = 0.32). For women, the differences in blood pressure between the two groups at the end-of-trial examinations were small. The treated group had an average diastolic pressure 0.41 mmHg lower than that of the control group (p = 0.58) and an average systolic pressure 0.74 lower (p = 0.53).

The overall (6 degrees of freedom) test of whether treatment group had an effect on outcome was statistically significant (p = 0.05). The reference category was individuals who were alive and healthy at the end of the trial. The six possible disease categories are listed in table 5. Since the interaction of sex and treatment effect was also significant (p = 0.03), results are presented separately for men and women. In men, the overall effect of treatment group (p = 0.001) was largely due to the treated men having less than half the risk of both high systolic and high diastolic pressures and approximately one third of the risk of dying from stroke. The prevalence of jointly elevated systolic and diastolic pressures in the male placebo group was 14 percent, so that this reduction in relative risk translates into a risk difference of approximately 7 percent. In women, neither the overall test (p = 0.86) nor any of the individual outcomes differed significantly between the supplement and placebo groups.

DISCUSSION

Although hypertension is a key risk factor for cerebrovascular disease, both conditions have complex etiologies that remain to be clarified. The importance of diet in these diseases has been suggested by ecologic studies (12–18), migrant studies (19), observational analyses of assembled cohorts (12, 13, 20–22), and, for hypertension, intervention trials (13, 20, 23).

Dietary sodium is generally believed to increase blood pressure, and there is suggestive evidence that potassium, calcium, and possibly magnesium may lower blood pressure (12, 13, 22–25). Evidence for an

TABLE 5. Odds ratios† for effect of supplements on end-of-trial outcomes, Linxian, China, 1985–1991

Sex and outcome	Prevalence placebo group	Prevalence supplement group	OR‡	95% CI‡	p value
Men*					
High systolic pressure	4.1	6.1	1.22	0.71–2.09	0.46
High diastolic pressure	5.7	4.8	0.74	0.44–1.23	0.25
Both high	14.3	7.2	0.43	0.28–0.65	0.02
Alive with cancer	10.7	11.9	0.96	0.67–1.40	0.84
Stroke death	3.2	1.4	0.36	0.16–0.83	0.02
Other death	13.0	13.5	0.89	0.62–1.27	0.52
Women**					
High systolic pressure	10.0	9.0	0.89	0.62–1.29	0.55
High diastolic pressure	5.0	6.3	1.28	0.82–2.01	0.28
Both high	19.1	18.6	0.92	0.68–1.24	0.57
Alive with cancer	8.3	8.5	1.02	0.70–1.50	0.90
Stroke death	1.7	1.6	0.74	0.31–1.74	0.49
Other death	6.4	6.5	1.00	0.65–1.53	1.00

* $p = 0.001$ for overall test of significance of treatment group.
** $p = 0.86$ for overall test of significance of treatment group.
† Model includes terms for age, baseline systolic pressure, baseline diastolic pressure, and body mass index. The reference group is people who are alive and free of cancer, systolic hypertension, and diastolic hypertension at the end of the trial.
‡ OR, odds ratio; CI, confidence interval.

effect of other minerals or vitamins on blood pressure is less clear. Observational and intervention studies indicate that vegetarian and vegetarian-like diets that are low in saturated fat and high in fiber, fruits, and vegetables (20) may lower blood pressure in excess of what would be predicted from differences in cation consumption. Cross-sectional studies suggest that low dietary and blood levels of vitamin C (26–31) and low serum levels of selenium (27, 31) are associated with increased blood pressure. Two small, randomized trials found decreases in blood pressure after 4 and 6 weeks of daily vitamin C supplementation (32, 33).

Stroke mortality has decreased steadily in most countries coincident with improvements in nutritional patterns (14–17), and several correlational studies have reported inverse associations with consumption of fruits, vegetables, potassium, and vitamin C (15, 18). Only a few analytic studies, however, have evaluated risk of stroke in relation to dietary nutrients. In a follow-up of 859 men and women in California, dietary potassium, which was highly correlated with fruit and vegetable intake, was inversely associated with stroke mortality (23). In Norway (34), stroke mortality was lower among those with high vitamin C intake, although no protective effect was observed in a cohort of women in Sweden (35) or in a British case-control study of stroke patients (36). In Finland and the Netherlands, serum selenium levels were lower in men who subsequently died of stroke (37, 38). The Basel Prospective Study (39) found that the risk of stroke death was increased among individuals with low baseline levels of vitamin C or beta-carotene; the effect of having low levels of both nutrients appeared multiplicative. A study of patients hospitalized for stroke (40) found that higher serum concentrations of vitamins A and E were predictive of lower mortality.

Besides the present trial, only two randomized studies of vitamin intervention have reported stroke mortality as a separate category: the Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (41) and the Linxian General Population Trial (42). The study in Finland of middle-aged male cigarette smokers observed slightly higher rates of stroke mortality in both the vitamin E and the beta-carotene groups than in the controls. Combining the reported categories of hemorrhagic and ischemic stroke and assuming that the number of deaths follows a Poisson distribution, the relative risks of stroke mortality are 1.10 (95 percent CI 0.85–1.42) for the vitamin E recipients and 1.21 (95 percent CI 0.93–1.56) for the beta-carotene recipients. No measures of blood pressure were reported. In the Linxian General Population Trial, four separate combinations of micronutrients were studied. The relative risks of stroke mortality were 0.99 (95 percent CI 0.84–1.18) for retinol and zinc; 0.93 (95 percent CI 0.79–1.11) for riboflavin and niacin; 1.04 (95 percent CI 0.88–1.24) for vitamin C and molybdenum; and 0.90 (95 percent CI 0.76–1.07) for beta-carotene, vitamin E, and selenium. A more detailed analysis of stroke mortality, as well as an analysis of blood pressure measurements made on participants in the Linxian General Population Trial, is currently under way. In totality, the epidemiologic evidence re-

garding vitamin and mineral supplementation and risk of stroke and hypertension has not been conclusive.

Our trial in Linxian revealed a lower prevalence of end-of-study hypertension and a lower incidence of stroke mortality in the group supplemented with a multivitamin/mineral combination. For both of these endpoints, the beneficial effect was greater in men than in women. The design and execution of this study make it unlikely that these results are due to bias. The randomization process assures that there is no self-selection of low-risk individuals into the supplemented group. Although the classification of noncancer deaths was not confirmed by expert review, the prospective nature of the data gathering and the fact that study participants and data collectors were unaware of the treatment status prevents information bias. The most likely effect of misclassification is underestimating the effect of the intervention in men, in women, or in both. Exposure (treatment group) is known for all participants, and excellent pill compliance (4) and the demonstration that the supplement raises serum levels of nutrients (10, 11) suggest that treatment group is a good indicator for actual increased concentration of nutrients in the blood.

Although stroke is the major cause of mortality in China (43), with approximately one-third attributable to intracerebral hemorrhage, stroke deaths and hypertension were not the primary endpoints of the study. Therefore, the p values and confidence intervals we cite in this paper, while still meaningful in terms of a measure of the strength of association and the precision of the estimate, lose the pristine interpretability accorded a single main outcome.

The complex nature of the vitamin/mineral supplement makes it impossible to implicate one nutrient, or even one class of nutrients, as the likely cause of the lowered risk of stroke and hypertension in our study. In any case, such an attempt may be misguided since for the antioxidants, and perhaps even for some combination of cations and micronutrients, it is possible that synergism is important to the biologic effect (44, 45), particularly in an area such as Linxian with low dietary intake of multiple nutrients. Although in terms of etiologic consistency it is encouraging to find that stroke mortality as well as the strong risk factor of hypertension were both decreased, the decline in the former may not necessarily be entirely due to the decline in the latter. Before the advent of hypertension therapy, the incidence of intracerebral hemorrhage in North America was considerably lower than that found in China today, even though the prevalence of hypertension in North America then was significantly higher than that in China today (43). This pattern suggests that in China some nonhypertension risk factors contribute to the high incidence of stroke mortality by a mechanism that may be impeded by nutritional supplements. For example, folate and the B vitamins may reduce the risk of stroke by lowering homocysteine levels (46), while antioxidants may slow the progression of cerebral atherosclerosis by inhibiting oxidation of low density lipoprotein (47) or perhaps limit ischemic neuronal damage. The rapid separation of curves by treatment suggests that at least the initial benefit is attributable to a mechanism unrelated to retarding atherosclerosis. Given the significant morbidity and mortality attributable to stroke and hypertension throughout the world, the small doses of nutrients in this supplement, the unobtrusive nature of the intervention, and the plausible mediating mechanisms, it is important to seek confirmation of these results both in nutritionally deprived populations and in Western populations in which diets are generally sufficient in natural antioxidants and other nutrients.

In summary, the results of this randomized trial suggest that dietary supplementation with multivitamins and minerals may lower the risk of both cerebrovascular disease and hypertension, particularly among men. The findings should stimulate further research into the potential benefits of micronutrient supplements on hypertension and cerebrovascular disease.

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