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26 Year Follow-up of the Randomized Linxian Dysplasia Nutrition Intervention Trial: No Effect of Multivitamin Supplementation on Mortality

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Although substantial numbers of people worldwide take multivitamin supplements, including an estimated 40% or more of US adults, their effectiveness remains unclear. Recent reports from the Physicians' Health Study (PHS) II, a randomized trial of daily multivitamins, found fewer total cancers in multivitamin recipients, but no effect on overall

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Conflict of Interest Disclosures:
All authors declare no conflicts of interest.

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Trial registration The trial is registered with ClinicalTrials.gov, NCT00342654. The trial registry name is Nutrition Intervention Trials in Linxian Follow-up Study, and the URL for the registry is http://www.clinicaltrials.gov/ct2/show/NCT00342654?term=NCT00342654&rank=1.

or cause-specific mortality [1, 2] in a Western population that was well nourished. However, few multivitamin trials have been conducted in under-nourished populations where the potential for benefit is most likely.

In 1985, we initiated the Linxian Dysplasia Nutrition Intervention Trial (NIT) to evaluate the effect of multivitamin supplements on cancer incidence and mortality in Linxian, China, a region with extremely high rates of esophageal and gastric cardia cancer and multiple vitamin and mineral deficiencies. Individuals with a previous cytological diagnosis of esophageal squamous dysplasia were randomized to receive multivitamin supplementation or placebo for six years.[3] Results after the six-year intervention period showed no statistically significant benefit on mortality.[4] However, an additional 20 years of active follow-up after cessation of the intervention gave us the opportunity to examine the long-term effects of supplementation.

The purpose of this report is to update results of the Linxian Dysplasia NIT after 26 years of follow-up to provide data informative on the effect of multivitamin supplementation on mortality in an under-nourished population. Our findings should be helpful for clinical practice and public health recommendations.

Methods

The Linxian Dysplasia NIT was a randomized, double-blind, placebo-controlled trial of multivitamins conducted in 1985-1991 in northern China in an under-nourished population of 3318 persons aged 40-69 years who had a previous cytologic diagnosis of esophageal squamous dysplasia. Participants were followed for 20 additional years after cessation of supplementation. Methods [3] and results [4] for the intervention phase of this trial were previously published and are further detailed in **eMethods, eFigure 1, and eTable 1**.

Results

Baseline characteristics are summarized in **eTable 2**. Participant characteristics, including age, sex, smoking, drinking, family history of esophageal and gastric cancers, and body mass index were similar between the supplementation and placebo groups.

A total of 2239 deaths occurred during follow-up (1985-2010), including 42% from cancer, 21% from heart disease, 25% from cerebrovascular disease, and 12% due to other causes. Cumulative mortality for all causes, cancer, heart disease, and cerebrovascular disease for all participants is shown in **eFigure 2**. Results from Cox models were similar to the cumulative mortality graphs (**Table**). Overall, multivitamin supplements had no effect on total mortality or mortality from any of the specific causes of death examined (including cancer mortality) among all participants.

When results were examined by subgroups defined by gender and age (**Table**), heart disease deaths were reduced in supplemented men (HR=0.73, 95% CI=0.56-0.96) and cerebrovascular disease deaths were increased in supplemented women (HR=1.25, 95% CI=1.00-1.56, P=0.047). Heart disease deaths were also decreased in older supplemented

participants (HR=0.79, 95% CI=0.64-0.98) and cerebrovascular disease deaths were increased in younger supplemented participants (HR=1.42, 95% CI=1.07-1.88).

Comment

In the Linxian Dysplasia NIT, after six years of supplementation and nearly 20 years of additional follow-up, multivitamin supplementation had no effect on total or cause-specific mortality. Both beneficial and adverse effects on heart disease and stroke mortality were observed among subgroups defined by gender and age.

Most prior micronutrient intervention trials tested only one or two supplements. Among those that tested three or more vitamins/minerals, supplements reduced total mortality in two trials.[5, 6] However, only one previously-reported micronutrient trial was truly comparable to the Linxian Dysplasia NIT in terms of testing an existing commercially available multivitamin and mineral supplement formulation: the PHS II supplemented with Centrum Silver (31 vitamins/minerals), whereas the Linxian Dysplasia NIT supplemented with two Centrum tablets (26 vitamins/minerals). Poorly-nourished populations should benefit most from multivitamin supplementation, making the current study a strong test of their potential beneficial effects. However, like the well-nourished PHS II population, no benefit of multivitamins for total mortality was observed in our study.

Our results show differences in the effect of supplementation on heart disease and stroke mortality in men and women. Multivitamin trials in well-nourished Western populations have not shown reduced heart disease in supplemented men or women. For stroke, Western trials in women either showed no effect [6-8] or suggested a benefit. [9] For heart disease in men, PHS II indicated no effect.[2] The different cardiovascular disease results observed in Linxian compared to other multivitamin trials may be due to differences in nutritional status, trial design, or chance.

In summary, during six years of multivitamin supplementation and 20 years of post-intervention follow-up, we observed no effect of multivitamins on total or cause-specific mortality in a nutrient-deficient population. Together with data from previous trials, these results demonstrate little benefit of multivitamin supplementation on mortality in either well- or poorly-nourished populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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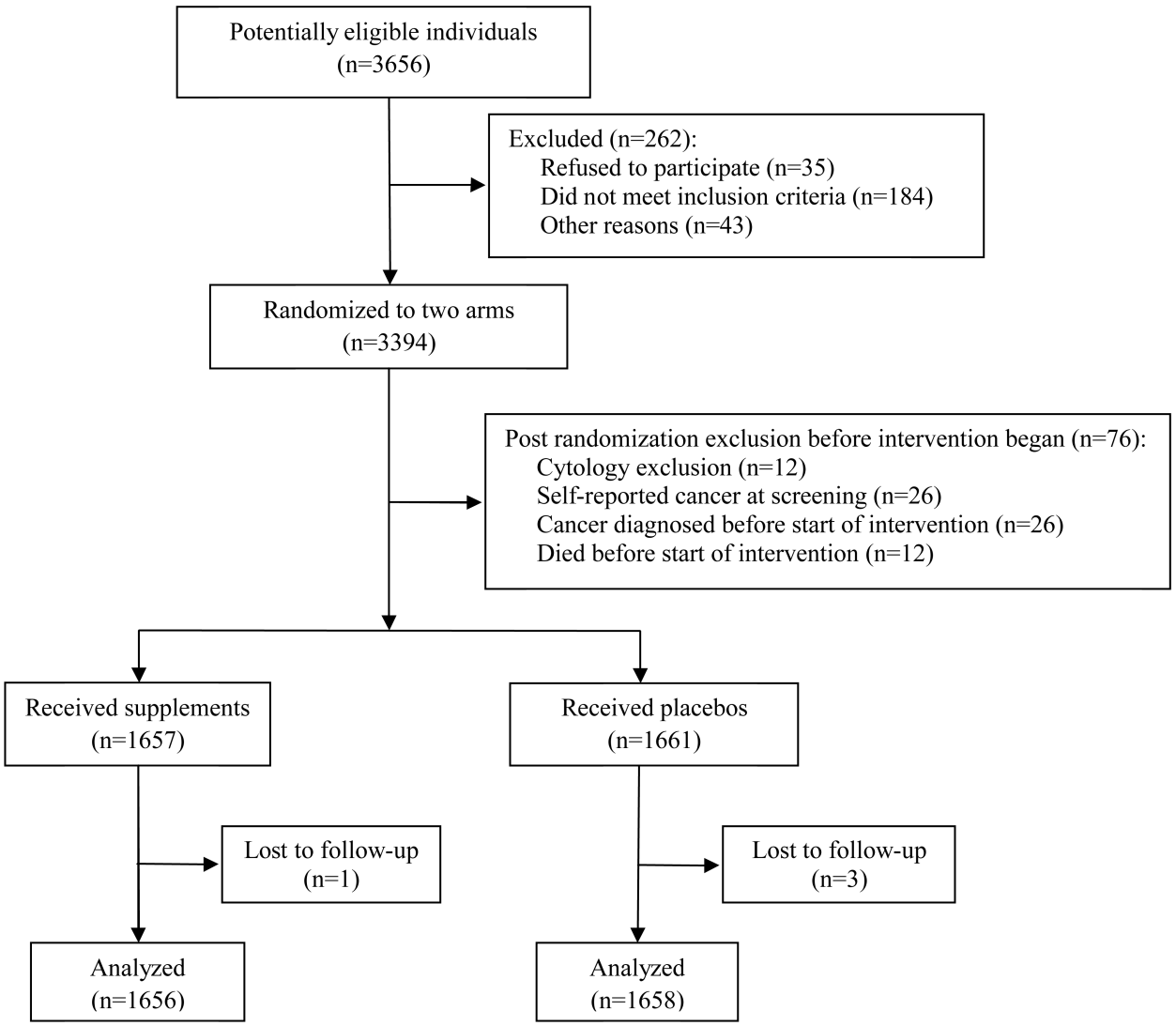
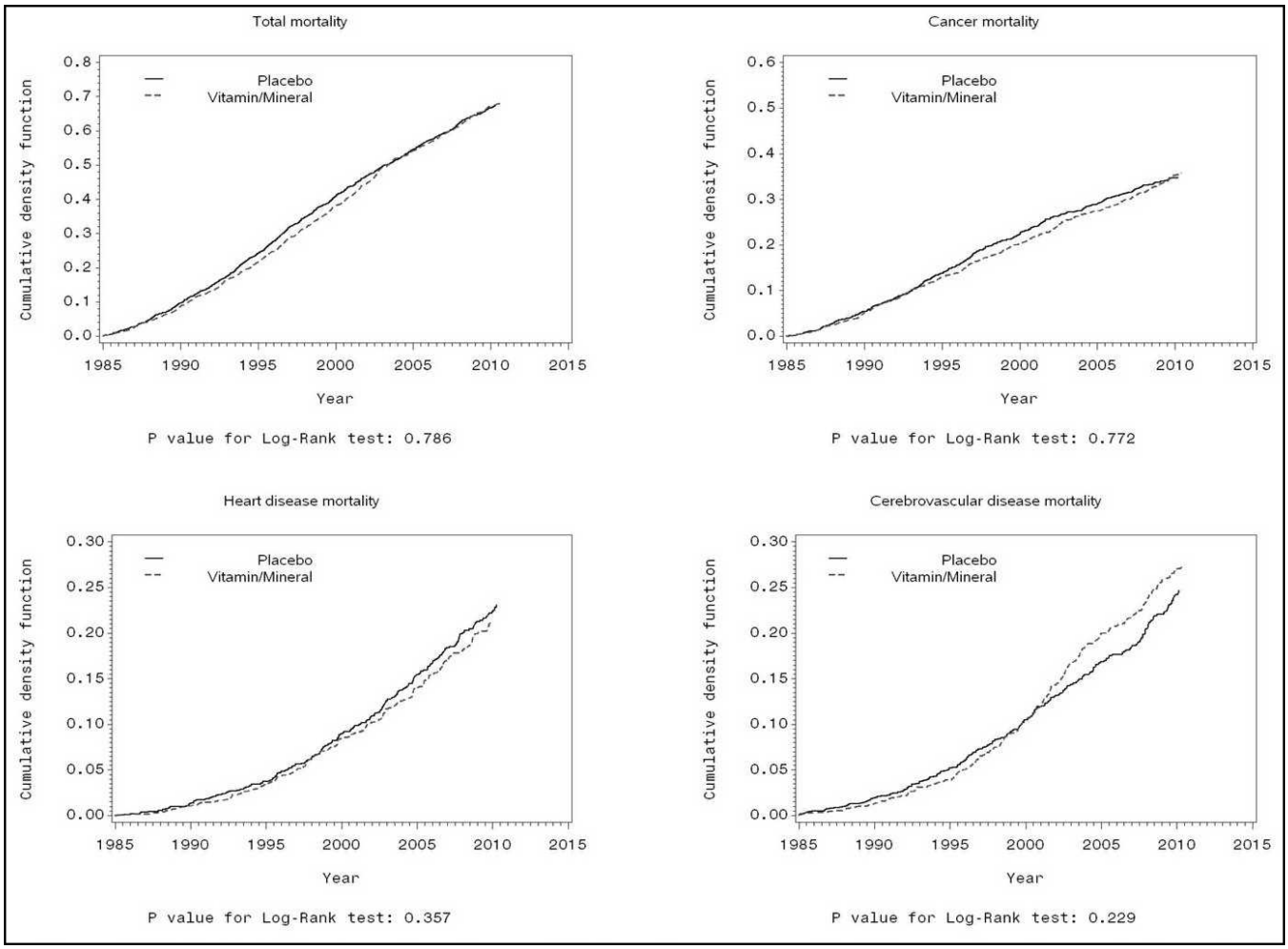


efigure 1.
CONSORT flow diagram of the Linxian Dysplasia Nutrition Intervention Trial



efigure 2.

Effects of multivitamin supplements on mortality from all causes, cancer, heart disease, and cerebrovascular disease for all participants, as shown by cumulative mortality in Kaplan-Meier plots

Table

Hazard ratios and 95% confidence intervals for death by cause stratified by genders and age in the Linxian Dysplasia Nutrition Intervention Trial

Cause of death (1985-2010)	All		Men		Women		Age<55 years		Age≥55 years	
	N	HR (95% CI)[a]	n	HR (95% CI)[b]	n	HR (95% CI)[b]	n	HR (95% CI)[c]	n	HR (95% CI)[c]
Total deaths	2239	0.98 (0.90-1.06)	1090	0.90 (0.80-1.01)	1149	1.06 (0.95-1.19)	885	1.04 (0.91-1.19)	1354	0.94 (0.84-1.04)
Cancer	935	0.97 (0.85-1.10)	489	0.92 (0.77-1.09)	446	1.03 (0.86-1.24)	446	0.90 (0.75-1.09)	489	1.03 (0.86-1.23)
Esophageal	491	0.98 (0.82-1.16)	241	0.87 (0.68-1.12)	250	1.09 (0.85-1.40)	247	0.93 (0.73-1.20)	244	1.01 (0.79-1.30)
Gastric	327	0.91 (0.73-1.13)	188	0.88 (0.66-1.17)	139	0.96 (0.69-1.33)	141	0.76 (0.55-1.06)	186	1.05 (0.79-1.40)
Cardia	265	0.91 (0.72-1.16)	157	0.86 (0.63-1.18)	108	1.00 (0.68-1.45)	113	0.77 (0.53-1.11)	152	1.04 (0.75-1.43)
Noncardia	62	0.91 (0.55-1.49)	31	0.98 (0.49-1.99)	31	0.82 (0.41-1.67)	28	0.74 (0.35-1.56)	34	1.10 (0.56-2.16)
Esophageal/cardia	756	0.95 (0.83-1.10)	398	0.87 (0.71-1.05)	358	1.06 (0.87-1.31)	360	0.88 (0.71-1.08)	396	1.02 (0.84-1.24)
Other cancer	117	1.13 (0.79-1.63)	60	1.29 (0.77-2.15)	57	0.97 (0.58-1.63)	58	1.20 (0.72-2.02)	59	1.06 (0.63-1.76)
Cerebrovascular	565	1.10 (0.93-1.30)	247	0.92 (0.72-1.18)	318	**1.25 (1.00-1.56)** [d]	203	**1.42 (1.07-1.88)** [d]	362	0.96 (0.78-1.18)
Heart	463	0.90 (0.75-1.08)	212	**0.73 (0.56-0.96)** [d]	251	1.08 (0.85-1.39)	125	1.28 (0.90-1.82)	338	**0.79 (0.64-0.98)** [d]
Other	276	0.90 (0.71-1.14)	142	1.04 (0.75-1.45)	134	0.78 (0.55-1.10)	111	0.83 (0.57-1.21)	165	0.95 (0.70-1.29)

HR=hazard ratio; 95% CI=95% confidence intervals.

[a] Adjusted for age, sex and commune.

[b] Adjusted for age and commune.

[c] Adjusted for age, sex and commune.

[d] Statistical significance ($P < 0.05$).

eTable 1

Daily dose and types of nutrients in supplements in the Linxian Dysplasia Nutrition Intervention Trial

Vitamin/mineral	As	Dose
Beta carotene		15 mg
Vitamin A	Acetate	10000 IU
Vitamin E	*dl*-alpha-Tocopheryl 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	15mg
Potassium	Potassium chloride	15.4 mg
Chloride	Potassium chloride	14 mg
Chromium	Chromium chloride	30 μg
Molybdenum	Sodium molybdate	30 μg
Selenium	Sodium selenate	50 μg
Zinc	Zinc sulfate	45 mg

eTable 2

Baseline demographic characteristics and risk factors in the Linxian Dysplasia Nutrition Intervention Trial

	All participants	Placebo	Active
No. of participants (N, %)	3314 (100.0)	1658 (50.0)	1656 (50.0)
Age group (N, %)			
<50	1081 (32.6)	536 (32.3)	545 (32.9)
≥50 to <60	1458 (44.0)	742 (44.8)	716 (43.2)
≥ 60	775 (23.4)	380 (22.9)	395 (23.9)
Sex (N, %)			
Female	1854 (56.0)	927 (55.9)	927 (56.0)
Male	1460 (44.0)	731 (44.1)	729 (44.0)
Smoking [a] (N, %)			
Non-smoker	2344 (71.1)	1173 (71.1)	1171 (71.1)
Smoker	954 (28.9)	477 (28.9)	477 (28.9)
Alcohol drinking [b] (N, %)			
Non-drinker	2683 (81.3)	1356 (82.2)	1327 (80.5)
Drinker	615 (18.7)	294 (17.8)	321 (19.5)
Family history of esophageal or stomach cancer (N, %)			
No	1974 (59.9)	990 (60.0)	984 (59.7)
Yes	1324 (40.1)	660 (40.0)	664 (40.3)
Body Mass Index (Mean, SD)	20.35±2.29	20.36±2.30	20.33±2.28

[a] Ever smoking cigarettes for six or more months.

[b] Ever drinking any alcoholic beverage in the last 12 months.