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The Randomized Linxian Dysplasia Nutrition Intervention Trial After 26 Years of Follow-up: No Effect of Multivitamin Supplementation on Mortality

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

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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 6 years.[3] Results after the 6-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.

This report updates the results of the Linxian Dysplasia NIT after 26 years of follow-up to provide informative data on the effect of multivitamin supplementation on mortality in an undernourished 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 through 1991 in northern China in an undernourished population of 3318 persons aged 40 to 69 years who had received a previous cytologic diagnosis of esophageal squamous dysplasia. Participants were followed up for 20 additional years after cessation of supplementation. The methods[3] and results[4] for the intervention phase of this trial were previously published and are further detailed in eAppendix, eFigure 1, and eTable 1 in the Supplement.

Results | Baseline characteristics are summarized in eTable 2 in the Supplement. 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% from other causes. Cumulative mortality for all causes, cancer, heart disease, and cerebrovascular disease for all participants is shown in eFigure 2 in the Supplement. 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 sex and age (Table), heart disease deaths were reduced in supplemented men (hazard ratio [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 = .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).

Discussion | In the Linxian Dysplasia NIT, after 6 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 sex and age.

Most prior micronutrient intervention trials tested only 1 or 2 supplements. Among those that tested 3 or more vitamins and minerals, supplements reduced total mortality in 2 trials.[5,6] However, only 1 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 (Pfizer Inc) (31 vitamins and minerals), whereas the Linxian Dysplasia NIT supplemented with 2 Centrum tablets (26 vitamins and minerals). Poorly nourished populations should benefit most from multivitamin supplementation, making the present 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, the PHS II indicated no effect.[2] The different cardiovascular dis-

Table. Death by Cause Stratified by Sex and Age in the Linxian Dysplasia Nutrition Intervention Trial

Cause of Death (1985-2010)	All		Men		Women		Age <55 y		Age ≥55 y	
	No.	HR (95% CI)[a]	No.	HR (95% CI)[b]	No.	HR (95% CI)[b]	No.	HR (95% CI)[a]	No.	HR (95% CI)[a]
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 or 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)[c]	203	1.42 (1.07-1.88)[c]	362	0.96 (0.78-1.18)
Heart	463	0.90 (0.75-1.08)	212	0.73 (0.56-0.96)[c]	251	1.08 (0.85-1.39)	125	1.28 (0.90-1.82)	338	0.79 (0.64-0.98)[c]
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)

Abbreviation: HR, hazard ratio.

[a] Adjusted for age, sex, and commune (administrative unit).

[b] Adjusted for age and commune.

[c] Statistically significant ($P < .05$).

ease results observed in the Linxian Dysplasia NIT compared with other multivitamin trials may be due to differences in nutritional status, trial design, or chance.

In conclusion, during 6 years of multivitamin supplementation and 20 years of postintervention 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.

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The Ongoing Importance of Smoking as a Powerful Risk Factor for ST-Segment Elevation Myocardial Infarction in Young Patients

There has been a recent decline in the incidence of patients presenting with ST-segment elevation myocardial infarction (STEMI).[1] Whereas smoking is historically one of the strongest risk factors associated with STEMI, there has also been a decline in the proportion of current smokers in the United States from 1998 to 2010.[2,3] The overall reduction in both the incidence of STEMI and active smoking makes it unclear what role smoking continues to play as a risk factor for STEMI. Accordingly, we used data from the 44 hospitals participating in the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2) to evaluate the ongoing importance of smoking as a risk factor for STEMI.

Methods | The details of BMC2, a registry that enrolls all patients undergoing percutaneous coronary intervention (PCI) at nonfederal hospitals in Michigan, have been previously described.[4] Our population included all patients who underwent primary PCI for new-onset STEMI between January 2010 and March 2012. Patients with a history of myocardial infarction or revascularization were excluded. Age-specific smoking rates for the general population were estimated using smoking prevalence data from the 2010 National Health Interview survey sample adult data set.[5] Smoking status was defined per patient report, with active smokers including those who had smoked any time within the past 1 year prior to presentation or before answering the survey. Population estimates by age for the state of Michigan were obtained from the 2010 US census and used to estimate primary PCI incidence by age group.[5] Odds ratios (ORs) comparing smoking prevalence among patients with STEMI with the prevalence in the general population were estimated directly. Estimated ORs and PCI prevalence values were used to estimate the number of current smokers needed to quit in order to prevent 1 STEMI, as well as the number and proportion of STEMIs expected to be prevented annually in Michigan at various assumed annual quit rates.

Results | During the study period, 6892 patients underwent primary PCI for STEMI. In these patients, the overall mean (SD) smoking rate was 46.43% (0.60%), compared with 20.53% (0.25%) in the general population (**Table**). Smoking rates among patients with STEMI were highest for those aged 18 to 34 years, at 78.02% (4.34%), compared with a smoking rate of 23.72% (0.48%) in that age stratum of the general population, with smoking rates notably decreasing with increasing age in the STEMI population. The overall OR for smoking in the STEMI population compared with the general population was 3.4 (95% CI, 3.3-3.4), with the highest OR seen in patients aged 18 to 34 years (OR, 11.4 [95% CI, 10.0-12.8]).

We estimated that if 10% of Michigan smokers were to quit, 109 STEMIs would be prevented annually, a reduction of 3.95% in the total number of PCI procedures performed for patients with STEMI. These estimates increased to 544 (19.73%) and 815 (29.63%) STEMIs prevented annually with 50% and 75% quit rates, respectively.

Discussion | The key finding of our study is that smoking is a major risk factor for patients undergoing primary PCI for STEMI in the state of Michigan. We not only demonstrated the ongoing contribution of smoking as a risk factor for STEMI but also estimated the primary preventive benefit of smoking cessation with respect to STEMI. Although smoking is an important risk factor for STEMI at all ages, it is especially relevant in younger age groups.

Cigarettes are the only legal consumer product that cause half their long-term users to die prematurely.[6] Notably, our study estimates that a reduction in the smoking rate down to

Table. Smoking Rate in Patients With STEMI and the General Population and Number Needed to Quit to Prevent 1 STEMI Annually, Stratified by Age

Age, y	Mean (SD), %		STEMI Cases, No.	Odds Ratio (95% CI)	No. Needed to Quit
	Smoking Rate in Patients With STEMI	Estimated Smoking Rate in the General Population			
18-34	78.02 (4.34)	23.72 (0.48)	91	11.4 (10.0-12.8)	17 817
35-39	71.68 (3.43)	22.23 (0.84)	173	8.9 (7.7-10.0)	2694
40-44	69.19 (2.32)	21.43 (0.84)	396	8.2 (7.3-9.2)	1306
45-49	66.53 (1.74)	23.98 (0.86)	735	6.3 (5.6-7.0)	945
50-54	64.75 (1.50)	26.67 (0.90)	1010	5.1 (4.5-5.6)	870
55-59	53.91 (1.49)	22.80 (0.90)	1124	4.0 (3.5-4.4)	794
60-64	43.97 (1.56)	19.62 (0.87)	1012	3.2 (2.8-3.6)	882
≥65	22.85 (0.87)	10.02 (0.41)	2351	2.7 (2.4-3.0)	930
Overall	46.43 (0.60)	20.53 (0.25)	6892	3.4 (3.3-3.4)	1452

Abbreviation: STEMI, ST-segment elevation myocardial infarction.