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Association of a Combined Mineral Intake Score with All-Cause, All-Cancer, and All-Cardiovascular Mortality among Postmenopausal Women

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B.M.
Fudan University
2016

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Abstract

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By Xinying Chen

Introduction: Although various individual minerals have been associated with mortality, there are few such epidemiologic studies, none of which investigated multiple minerals in aggregate.

Methods: We incorporated 11 mineral intakes, including calcium, magnesium, manganese, zinc, selenium, potassium, iodine, iron, copper, phosphorus, and sodium, into a mineral score and investigate its association with all-cause and cause-specific mortality in the Iowa Women's Health Study (1986-2012), a prospective cohort study of 55-69 year-old postmenopausal women. In the analytic cohort (n=35,211), 4,665 cancer-specific deaths, 7,064 cardiovascular-specific deaths, and 18,687 all-cause deaths were documented during follow-up. Participants' mineral intakes were either ranked 1-5 (those hypothesized to decrease risk) or reversely ranked 5-1 (those hypothesized to increase risk). The rankings were summed to create the combined mineral scores for each woman. The mineral-score-mortality associations were analyzed using multivariable Cox proportional hazards regression.

Results: There was borderline decreasing risk for all-cardiovascular, and all-cause mortality with an increasing score (P-trend all-cardiovascular = 0.06; P-trend all-cause = 0.06). The adjusted hazard ratios (HR) and 95% confidence intervals (CI) for all-cardiovascular, and all-cause mortality among participants in the highest relative to the lowest quintile of the combined mineral scores were, respectively, 0.93 (95% CI, 0.85-1.01), 0.96 (95% CI, 0.90-1.01). However, no significant association of combined mineral intakes with all-cancer mortality was observed.

Conclusions: Our findings suggest that high intakes of calcium, magnesium, manganese, zinc, selenium, potassium, and iodine, combined with low intakes of iron, copper, phosphorus, and sodium may be inversely associated with risk of all-cardiovascular and all-cause mortality, however, may have no association with all-cancer mortality.

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ABSTRACT

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Conclusions: Our findings suggest that high intakes of calcium, magnesium, manganese, zinc, selenium, potassium, and iodine, combined with low intakes of iron, copper, phosphorus, and sodium may be inversely associated with risk of all-cardiovascular and all-cause mortality, however, may have no association with all-cancer mortality.

INTRODUCTION

Cancer and cardiovascular diseases (CVDs) are two major public health problems worldwide. In 2012, about 14.1 million new cancer cases and 8.2 million deaths occurred (1, 2). According to WHO statistics, an estimated 17.7 million people died from CVDs in 2015, which represented 31% of all global deaths that year. Findings from previous epidemiologic studies indicated that dietary intakes and mineral supplementation were possibly associated with cancer, cardiovascular and all-cause mortality (3, 4). Considerable biological evidence supports substantial roles for minerals in affecting all-cause and cause-specific mortality (5-9). However, to the best of our knowledge, most studies only addressed a limited numbers of minerals indecisively with inconsistent conclusions (10-14).

Several possible reasons may explain the inconsistencies in the associations of individual mineral intakes with mortality, including that the contributions of individual minerals to mortality may be small and difficult to detect and there may be substantial interactions among minerals. Examples of interactions include those of calcium with magnesium (15), iron and zinc with copper (16) and potassium with sodium (17). Dietary scores are increasingly being used to account for possible combined, even correlated or interactive dietary intakes (18, 19).

We previously reported an association of combined mineral intakes with colorectal cancer incidence among postmenopausal women in the prospective Iowa Women's Health Study (IWHS) (20). There are few data on associations of combined mineral intakes with all-cancer, all-cardiovascular and all-cause mortality, most of which considered only one or two minerals. Accordingly, we investigated associations of combined mineral intakes (including calcium, magnesium, manganese, zinc, selenium, potassium, iodine, iron, copper, phosphorus and sodium) with all-cancer, all-cardiovascular and all-cause mortality among postmenopausal women in a prospective cohort study. We hypothesized that the combined mineral intakes score would be inversely associated with all-cancer, all-cardiovascular, and all-cause mortality.

METHODS

Study design and study population

The Iowa Women's Health Study (IWHS) is a prospective cohort study of post-menopausal Iowa women, started in 1986. Detailed information concerning the study design was described previously (21). Briefly, based on the 1985 current drivers' list from the Iowa Department of Transportation, 195,294 women aged 55-69 years were eligible for the study, from whom a 50% random sample was selected (n=99,929). Excluding those with a mailing address outside of Iowa, those who were deceased, not age-eligible, or were male (n=1,900), among the eligible women, 41,836 (42.7%) returned the questionnaire. Compared to the non-respondents, the respondents were older, had lower body mass index (BMI), and a higher proportion lived in rural regions. All-site cancer incidence and all-cause mortality were statistically significantly higher among respondents than among non-respondents (21). Vital status and residence address were determined via mailed follow-up surveys in 1987, 1989, 1992, 1997 and 2004, as well as through linkage to Iowa Death Certificate records (22).

Data collection

Self-reported demographics, dietary, lifestyle, family history, medical and reproductive history, and body size characteristics were collected at baseline via questionnaire. Detailed written instructions and tape measures were provided so that participants could measure their waist and hip circumferences. BMI was calculated based on self-reported weight (kg) divided by the square of self-reported height (m). A Willett 127-item food frequency questionnaire (FFQ) (23) was used to collect the dietary intake information. Participants were asked to recall their food consumption for the past year, referencing a commonly used serving size, ranging from 0 or less than 1 serving/month up to more than 6 servings/day. Participants were also asked about their intakes of multivitamin/mineral and specific vitamin and mineral supplements. Total energy and nutrient intakes were calculated by summing up energy and nutrients from all food resources using the dietary database developed by Willett et al(24). After baseline (1986), dietary information was comprehensively reassessed only in 1992, at which time only 68% of the participants were still alive.

Exposure assessment

The FFQ and the supplement data were used to calculate mineral scores for all participants. The biological rationales for the 11 included minerals are summarized in **Table 1**. The mineral intakes were calculated by summing the values from foods and supplements. Nutrient densities were calculated as the intake of a mineral per 1,000 kcal of total energy intake per day, and then the nutrient density intake of each mineral was categorized into quintiles according to the distribution of the analytic cohort. Within the analytic cohort, for minerals that were hypothesized to reduce the chronic diseases mortality risk (including calcium, magnesium, manganese, zinc, selenium, potassium, and iodine), participants were assigned a value equal to their quintile rank (e.g. 1-5, with a higher score indicating a higher mineral intake). For minerals that were hypothesized to increase risk for chronic diseases mortality (including iron, copper, phosphorus and sodium), participants were assigned a value equal to the reverse of their quintile rank (e.g. 5-1, with a higher score indicating a lower mineral intake). Finally, the 11 mineral intake values for the score were summed for each participant, yielding a possible range of 11-55.

Outcome assessment

Deaths were identified via linkage with the State Health Registry of Iowa, as well as the National Death Index. Cause of death was ascertained from death certificates. Follow-up time was defined as the time between the completion of the baseline questionnaire and the time of death, date of loss to follow-up, or Dec.31, 2012, whichever came first.

Analytic cohort and all-cancer death, all-cardiovascular death, all-cause death

Prior to analysis, women who reported a history of cancer except for non-melanoma skin cancer (n=3,830) were excluded. Women who left ≥30 FFQ items blank (n=2,499), or reported implausible total daily energy intakes (<600 or >5,000 kcal/day) (n=286) were also excluded, leaving an analytic cohort of 35,221 participants.

Statistical analysis

All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC). All p-values were two-sided and p-values < 0.05 or 95% confidence intervals (95% CI) that excluded 1.0 were considered statistically significant. The participants' characteristics at baseline were summarized and compared across quintiles of the mineral score. The association of the combined mineral score as a continuous variable and as a categorical variable (quintile) with all-cancer, all cardiovascular and all-cause mortality was analyzed using multivariable Cox proportional hazards regression to calculate hazards ratio (HR) and their 95% CIs. Covariates were chosen based on plausibility and previous published literature, and included age, education, family history of cancer, marital status, baseline chronic diseases, hormone replacement therapy (HRT), height, BMI category, waist-hip ratio, physical activity, smoking status, alcohol intake, multivitamin intake, calcium supplemental intake, total vitamin E intake, total energy intake, total fat intake, dietary fiber intake, total fruits and vegetables intake, total red and processed meats intake. Tests for trend were calculated by using the median of each mineral score quintile as a continuous variable in the model. The above model was also used in the stratified analyses, which were used to examine differences in associations of the mineral score with all-cancer, all cardiovascular and all-cause mortality between categories of selected covariates. For continuous variables, including age, height, waist-hip ratio, calcium supplemental intake, total vitamin E, energy, total fat, dietary fiber, total fruits and vegetables, and total red and processed meats intakes, two stratification categories were compared based on the median of the distribution in the analytic cohort. For selected categorical variables, the strata were: education - college and lower, college graduate or higher; family history of cancer - yes, no; currently married - yes, no; Chronic diseases at baseline (participants had at least one of the following chronic diseases at baseline: diabetes, heart diseases and liver diseases.) - yes, no; HRT - never, former, current; BMI - <25 kg/m^2, 25 – 30 kg/m^2, ≥ 30 kg/m^2; physical activity - low, medium, high; smoking status - never, former, current; alcohol intake - none, >0 - <7 g/day, ≥7 g/day; and multivitamin intake - yes, no. Effect measure modification was assessed by comparing the strata-specific hazard ratios.

We also conducted several sensitivity analyses. First, to assess joint/combined associations, we created supplemental-only and diet-only mineral scores, categorized each of the two scores into 4 categories based on their distributions, and assessed their joint/combined association with all-cause and cause-specific mortality. In the analysis, the reference group was participants who had no supplemental mineral intake and low dietary mineral intake. We also created two mineral scores, one of which included only the components that are hypothesized to reduce risk of mortality, while the other included only the components that are hypothesized to increase risk of mortality, we then categorized each of the two scores into 3 categories based on their distributions and assessed their joint/combined association with all-cause and cause-specific mortality. In this analysis, the reference group was people with high intake of minerals that possibly increase the risk of mortality and low intake of minerals that possibly decrease the risk of mortality. Second, because hypotheses related to mineral intakes and colon cancer may be stronger than those for other cancers, we also analyzed and compared the associations of combined mineral intakes with colon cancer-specific mortality and with all-other cancer mortality. Third, we took individual mineral components in and out of the mineral score one at a time and assessed the associations of a) the remaining 10-component mineral scores, and b) each mineral score component individually with all-cause and cause-specific mortality, adjusted for its respective remaining 10-component mineral score. Forth, we excluded the participants who died within the first two years of follow-up.

RESULTS

Selected baseline characteristics of the participants by quintiles of the combined mineral score are summarized in **Table 2**. Study participants were, on average, 61 years of age, and 99% were white. Those in the highest relative to the lowest mineral score quintile tended to be more educated and more likely to be a current or former HRT user, have a BMI less than 30 kg/m^2, be a former smoker, be a moderate to high alcohol user, take multivitamin, and have a higher physical activity level. On average, participants in the highest relative to the lowest quintile had higher supplemental calcium and total vitamin E intakes, and lower total energy, total fat, total red and processed meats intakes.

The associations of the mineral scores with total and cause-specific mortality estimated using Cox proportional hazards regression models are summarized in **Table 3**. In general, multivariable-adjusted analyses attenuated the estimated associations. In the multivariable-adjusted analyses, when the mineral score was treated as a categorical variable (quintiles), there was a statistically significant trend for decreasing all-cause and cause-specific mortality with an increasing score. Those in the upper relative to the lowest quintile were at an approximately 7% lower risk for all-cardiovascular mortality and 4% lower risk for all-cause mortality; the associations were borderline significant. The mineral score with all-cancer mortality association was null. When the mineral score was treated as a continuous variable, each 1-point increase in the mineral score was associated with statistically significant 1% lower risk for all-cardiovascular diseases mortality, but the continuous mineral score was not associated with all-cancer and all-cause mortality.

In the stratified analyses (**Appendix 1-3**), there were no substantial or consistent differences in associations according to levels of selected participants' characteristics. However, there were some suggestions that participants with a BMI of 25-30 kg/m^2 and those with moderate daily alcohol intakes (0-7g/day) may have been at lower risk of all-cause and cause-specific mortality with a higher mineral score. Also, among participants with lower total energy intakes showed to be at lower risk for all-cancer and all-cause mortality, and those with lower dietary fiber intakes showed to be at lower risk for all-cardiovascular and all-cause mortality with higher mineral intake scores.

The joint/combined analysis, the multivariable-adjusted joint/combined associations of the diet-only and supplemental-only mineral score with all-cardiovascular diseases mortality are summarized in **Appendix 4**. In the joint/combined analysis of the diet-only and supplemental-only mineral score, there was decreasing risk for all-cardiovascular mortality with an increasing diet-only mineral score among those who did not take any supplemental minerals, culminating in an HR of 0.91 (95% CI: 0.83-1.01). However, within the lowest diet-only score quintile, there was no evidence for a trend for decreasing all-cardiovascular mortality with an increasing of supplemental-only score. Relative to those in the joint lowest score category, participants in the joint highest score category were at statistically significant 14% lower risk for all-cardiovascular mortality (95% CI: 0.75-0.99). In the joint/combined analysis of the diet-only and supplemental-only mineral scores with all-cause mortality **(Appendix 5)**, there was a trend for decreasing all-cause mortality risk with an increasing diet-only mineral score among those who did not take any supplemental minerals, culminating in an HR of 0.90 (95% CI: 0.85-0.96). However, within the lowest diet-only score quintile, there was no evidence for a trend for decreasing all-cause mortality with an increasing of supplemental-only score. Relative to those in the joint lowest score category, participants in the joint highest score category were at an estimated 5% lower risk (HR: 0.95, 95% CI: 0.87-1.03) for all-cause mortality. In the joint/combined analysis of the diet-only and supplemental-only mineral scores with all-cancer mortality **(Appendix 6)**, there was no evidence for a trend for decreasing all-cancer mortality risk with an increasing diet-only mineral score among those who did not take any supplemental minerals. And within the lowest diet-only score quintile, there was no evidence for a trend for decreasing all-cancer mortality with an increasing of supplemental-only score. Relative to those in the joint lowest score category, participants in the joint highest score category were at a similar risk (HR: 1.00, 95% CI: 0.84-1.18) for all-cancer mortality.

The multivariable-adjusted joint/combined associations of the putative pro- and anti-high risk components of the mineral scores with all-cardiovascular mortality are summarized in **Appendix 7**. In the joint/combined analysis of the putative pro- and anti-high risk components of the mineral score, there was decreasing risk for all-cardiovascular diseases mortality with an increasing anti-high risk mineral score among participants in the lowest quintile of the pro-high risk mineral score, culminating in an HR of 0.97 (95% CI: 0.86-1.09). Within the lowest anti-high risk score quintile, there was no evidence for a trend for decreasing risk of all-cardiovascular mortality with an increasing of pro-high risk score. Relative to those in the joint lowest score category, participants in the joint highest score category were at an estimated 5% lower risk (HR: 0.95, 95% CI: 0.81-1.11) for all-cardiovascular diseases mortality. In the joint/combined analysis of the putative pro- and anti-high risk mineral scores with all-cause mortality **(Appendix 8)**, there was no evidence for a trend for decreasing all-cause mortality risk with an increasing anti-high risk mineral score among people with lowest pro-high risk mineral score. However, within the lowest anti-high risk score quintile, comparing to the lowest quintile of pro-high risk mineral score, there was a trend for decreasing all-cause mortality risk with an increasing pro-high risk mineral score, culminating in an HR of 0.94 (95% CI: 0.88-1.01). Relative to those in the joint lowest score category, participants in the joint highest score category were at an estimated 8% lower risk (HR: 0.92, 95% CI: 0.83-1.01) for all-cause mortality. In the joint/combined analysis of the putative pro- and anti-high risk mineral scores with all-cancer mortality **(Appendix 9)**, there was no evidence for a trend for decreasing all-cancer mortality risk with an increasing anti-high risk mineral score among people with lowest pro-high risk mineral score. However, within the lowest anti-high risk score quintile, comparing to the lowest quintile of pro-high risk mineral score, there was a trend for decreasing all-cancer mortality risk with an increasing pro-high risk mineral score, culminating in an HR of 0.94 (95% CI: 0.81-1.08). Relative to those in the joint lowest score category, participants in the joint highest score category were at an estimated 14% lower risk (HR: 0.86, 95% CI: 0.70-1.04) for all-cancer mortality.

In the multivariable-adjusted analysis of the associations of the total mineral intake score with colon cancer-specific and with all-other cancer mortality **(Appendix 10)**, when the mineral score was treated as a categorical variable (quintiles), there was a statistically significant trend for decreasing colon cancer mortality with an increasing score after only adjusted for age and total energy intake. Those in the upper relative to the lowest quintile were at an approximately 21% lower risk for colon cancer mortality, however the association was not statistically significant (95% CI: 0.56-1.12). The association of the total mineral score with all-other cancer mortality was null.

The risk estimates after removal and replacement of each score component one at a time **(Appendix 11)** differed only minimally from those with the full score. The associations of each individual score mineral—adjusted for its respective remaining 10-component mineral score—with all-cause and cause-specific mortality were almost null **(Appendix 12)**. Finally, the associations of mineral score with all-cause and cause-specific mortality after excluding the participants who died in the first two years of follow-up were not meaningfully different from those reported in Table 2 **(Appendix 13)**.

DISCUSSION

Our findings suggest that higher intakes of calcium, magnesium, manganese, zinc, selenium, potassium, and iodine, combined with lower intakes of iron, copper, phosphorus, and sodium may be modestly inversely associated with all-cardiovascular diseases and all-cause mortality. Although our results suggested that there may not be an association of the mineral score with all-cancer mortality, there was a suggestion that it may be inversely associated with colon cancer-specific mortality. In secondary analyses, our findings also suggested that women with a BMI of 25-30 kg/m^2 or with moderate daily alcohol intakes (0-7g/day) may be at lower risk of all-cause and cause-specific mortality with a higher mineral score than women with other BMI and alcohol intakes.

As discussed below, the combined mineral score had several components that could plausibly reduce risk of all-cardiovascular and all-cause mortality. Higher circulating calcium concentrations could affect vascular tone and blood coagulation, which may influence risk for CVD (25). Low magnesium intake may affect all-cardiovascular and all-cause mortality by generating a pro-inflammatory, pro-thrombotic and pro-atherogenic environment by maintaining genomic stability, regulation of cell differentiation, proliferation and apoptosis, and prevention of angiogenesis (26, 27). Selenium could reduce disease mortality through selenoproteins, which are important enzymes involved in several physical mechanisms (28), including preventing oxidative modification of lipids, inhibiting platelet aggregation, and reducing inflammation in addition to many cardio-metabolic effects that are linked to polymorphisms in GPx1, GPx3, Dio2, and SEPS1 (29-31). Increasing Fe level following the mutation in HEE-gene haemochromatosis was associated with an increased risk of coronary heart diseases, and low Fe level during menstrual period among women may decrease the availability of redox-active Fe, and then lower oxidative or inflammatory damage (32, 33). Low Zinc level could cause apoptosis, oxidative stress and inflammation through metallic enzymes including angiotensin-converting enzyme, Cu/Zn-superoxide dismutase and transcription factors (34). For the rest of minerals, the positive and negative effect of them was still under debate or only with little reference.

Epidemiological evidence supports the biological plausibility of the individual minerals being associated with all-cardiovascular diseases and all-cause mortality that mentioned above. In one multi-area prospective cohort study among men and women older than 65 years-old in France (n_{death} = 14,311), the adjusted RR for associations of Ca intake with CVD mortality was 0.90 (95% CI: 0.84-0.96) (35). Another 14-year prospective cohort study among women older than 65 year-old found a borderline association of calcium with all-cause mortality: HR 0.89 (95% CI: 0.78-1.01). In several long-term cohort studies with large sample sizes, statistically significant associations of serum selenium levels with all-cause mortality were observed (36, 37). In a 12-year cohort study, the multivariable-adjusted HR comparing the highest (≥ 130.39 ng/mL) to the lowest (< 117.31 ng/mL) serum selenium level tertile was 0.83 (95% CI: 0.72-0.96) for all-cause mortality (38). An 8-year prospective cohort study among female in urban China observed that when comparing the highest vs. lowest quintile of selenium intake, the adjusted HR for all-cardiovascular mortality was 0.89 (95% CI: 0.82-0.96), and the adjusted HR for all-cause mortality was 0.80 (95% CI: 0.66-0.98) (39). A statistically significant inverse association of phosphorus intakes with all-cause mortality was observed in one long-term prospective cohort study in Britain among women aged 65 years or older (HR: 0.82, 95% CI: 0.72-0.95) (40). A 15-year cohort study of Singapore Chinese men and women aged 45-74 years found an inverse association of potassium intake with CAD mortality (highest vs. lowest quintile: HR: 0.82, 95% CI: 0.69-0.97) (41). In a national nutrition cohort study of people aged 65 years or older in Britain, zinc intake was inversely associated with all-cause mortality with HR of 0.89 (95% CI: 0.82-0.96), and copper intake was borderline inversely associated with all-cause mortality, with an HR of 0.91 (95% CI: 0.84-1.00) (42).

To the best of our knowledge, few studies investigated associations of limited combinations of certain minerals with all-cause and cause-specific mortality. For some previous studies, when investigated the combination of some of the minerals we are interested with the all-cardiovascular and all-cause mortality, they also got similar null results. In a prospective cohort study of 3,081 women diagnosed with early stage breast cancer in the United States, no statistically significant associations of individual mineral intakes (including calcium, copper, iron, magnesium, phosphorus, selenium, and zinc) with all-cause mortality were observed (Ca: HR: 0.90, 95% CI: 0.74-1.12; Cu: HR: 1.06, 95% CI: 0.86-1.30; Fe: HR: 1.60, 95% CI: 0.91-2.90; Mg: HR: 1.02, 95% CI: 0.68-1.53; P: HR: 1.04, 95% CI: 0.64-1.67; Se: HR: 1.20, 95% CI: 0.55-2.50; Zn: HR: 1.10, 95% CI: 0.83-1.45) (43). In a recent prospective cohort study among people aged older than 65 years in Iceland, there was no statistically significant association between dietary supplements use (including vitamins and several mineral intakes: vitamins A, Bs, C, D, E and K, thiamine, riboflavin, niacin, biotin, Ca, Zn, Mn, Se, Cr, Mg, Fe, Cu, I, and K) with all-cause (HR: 0.91, 95% CI: 0.77-1.08) and all-cardiovascular mortality (HR: 0.91, 95% CI: 0.70-1.10) either (44). A study based on the National Diet and Nutrition Survey in Britain also found no statistically significant associations of individual dietary mineral intakes (per SD) of food energy (including zinc, copper and iron) with all-cardiovascular diseases (Zn: HR: 0.84, 95% CI: 0.71-0.99; Cu: HR: 0.92, 95% CI: 0.78-1.10; Non-haem Fe: HR: 1.06, 95% CI: 0.94-1.20) and all-cancer mortality (Zn: HR: 0.86, 95% CI: 0.71-1.04; Cu: HR: 0.87, 95% CI: 0.71-1.04; Non-haem Fe: HR: 1.05, 95% CI: 0.93-1.18) (42).

In our study, in our analyses of associations of the total mineral intake score with colon cancer-specific and with all-other cancer mortality, we found that when the mineral score was treated as a categorical variable (quintiles), there was a trend for decreasing colon cancer-specific mortality with an increasing score. Some previous epidemiologic studies found similar results; however, most of them investigated associations of only one or two minerals with colon cancer mortality, and only one study focused on the combined intakes of multiple minerals, and that was in relation to colorectal cancer incidence. A case-control study in Taiwan found that a high calcium concentration in drinking water was statistically significantly associated with lower risk of colon cancer-specific mortality (OR: 0.58, 95% CI: 0.47-0.73), but that a higher magnesium level in drinking water was not (OR: 1.06, 95% CI: 0.85-1.32) (45). Another case-control study in Taiwan from 1998-2007 found that lower magnesium levels in drinking water were associated with higher odds of colon cancer-specific mortality (OR: 1.31, 95% CI: 1.06-1.62) (46).

A study based on NHANES I data (n = 14,407) indicated that risk of colon cancer increased with increasing iron intakes among females aged from 25-74 (RR: 1.51, 95% CI: 1.41-1.60) (47). A prospective cohort study of men and women in Japan (n = 6,830) found that a higher sodium intake was associated with higher colon cancer-specific mortality (HR: 2.21, 95% CI: 0.63-7.78); however, the association was not statistically significant (48). In a previous study based on Iowa Women Health Study data, combined mineral intakes were statistically significantly inversely associated with incident colorectal cancer (HR 0.75; 95% CI: 0.71-0.95) (20).

Our study had several strengths. First was the large sample size, second was the prospective design, which reduces reporting biases. Third, was our mineral intake score to investigate the associations of combined mineral intakes with mortalities. Fourth, we had complete, comprehensive data on potentially confounding variables and no loss of mortality follow-up. Fifth, was our multiple sensitivity analyses supporting the robustness of our findings.

Our study also had several limitations. Frist is the known limitations of FFQs (e.g., self-report, recall error, limited food item). Second, our study population was limited to white women, which may limit generalizability of our findings. Third, we measured the mineral intakes only at baseline. So, participants who may have been substantially changed their diets during follow-up may have been somewhat misclassified hereby attenuating results. Fourth, we consider the mineral intakes from diet and supplements, but not from water.

In conclusion, our findings, taken in context with those from previous studies, suggest that higher calcium, magnesium, manganese, zinc, selenium, potassium, and iodine intakes, combined with lower iron, copper, phosphorus, and sodium intakes may be associated with lower all-cardiovascular diseases, colon cancer-specific and all-cause mortality.

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TABLES

Table 1. Mineral score components, rationale for their inclusion, and common dietary sources

Components	Rationale for inclusion		
	All-cancer mortality	All-cardiovascular mortality	All-cause mortality
Possibly predominately anti-chronic disease risk			
Calcium	Bind bile acids and fatty acids, and consequently prohibit the proliferation and differentiation of epithelial cell (49, 50).	Reduce calcitriol, and increase serum levels of fibroblast growth factor 23 leading to increased risk of cardiovascular events (51).	Effect many physiologic pathways, including muscle contraction, blood coagulation, nerve transmission, energy and fat metabolism (25).
Magnesium	Essential for maintenance of genomic stability and DNA repair by modulating cell proliferation, cell cycle progression, and cell proliferation (27). Low level may associated with increased oxidative stress and systematic inflammation (52, 53).	Enhance ANG II levels then stimulate cardiac fibroblast activity (54). Improve endothelial function, induce direct and indirect vasodilation, beneficial effects on arrhythmias, inflammatory reactions, and platelet aggregation (55).	Increase vasodilation, anti-inflammatory responses, reduce blood pressure, and directly cause tissue insulin resistance (56, 57). Affect airway smooth muscle relaxation, stabilization of mast cells, and various immune responses (58).
Manganese	Inhibit detoxification of reactive oxygen species, and slow down or deactivate metastasis (59).	Act as a calcium channel blocker and uncouple excitation and contraction in the myocardium, then decrease cardiac contractility (60, 61).	Block excitation–contraction coupling in vascular smooth muscle leading to hypotension (60).
Zinc	Stabilize cell division, and effects on immune function, rumor surveillance and apoptosis via changes in the expression of zinc transporters in cancer cell (62).	Occupy sites and the synergize with lipid and water-soluble antioxidants to prevent lipid oxidation (63). Preventing derangements of the vascular endothelium through its antioxidant and membrane-stabilizing properties (64).	Play a significant role in normal cell structure, catalytic function, cell growth, cell division and repair, energy producing (65, 66).
Selenium	Inhibit reactive oxygen species generation by being main element in glutathione peroxidase (67). Effect GPx-1, and reduce DNA damage (68).	Prevent atherosclerosis via inhibiting oxidative stress, modulating inflammation, suppressing endothelial dysfunction, and protecting vascular cells against apoptosis and calcification (69).	Prevent oxidative stress, affect thyroid hormone metabolism and maintain antioxidant enzyme, redox position of vitamin C and other antioxidant components (70).

Potassium	Regulate cancer cell proliferation and migration through both canonical ion permeation–dependent and non-canonical ion permeation–independent functions (71).	Increase sodium excretion, modulating baroreceptor sensitivity, reducing sensitivity to catecholamine related vasoconstriction, and decreasing oxidative stress and inflammation (72, 73).	Stimulate Na^+-K^+ ATPase pumps and the opening of potassium channels in vascular smooth muscle cells and adrenergic nerve receptors (74). Induce cell depolarization and result in insulin secretion from pancreatic β-cells (75).
Iodine	Inhibit cell growth into cancer cell (76).	Bind to thyroid hormone nuclear receptor isoforms, alter the vascular system and decrease afterload of the left ventricle trough iodine-containing thyroid hormones (77, 78).	Iodine deficiency has been associated with the development of goiter, hypothyroidism, hyperthyroidism, and thyroid autoimmunity (79, 80).
Possibly predominately pro-chronic disease risk			
Iron	High intakes of iron might increase the risk for colorectal cancer by promoting oxidation (81).	Contribute to both the onset and progression of atherosclerosis by associating with C-reactive protein (82).	Act as a powerful pro-oxidant and catalyst that promote the formation of hydroxyl radicals and increase oxidative stress (83).
Copper	Causing Oxidative stress and associated damage in cells (84).	Oxidize low density lipoprotein cholesterol and increasing its atherogenicity (85). And an overload of serum copper concentrations leads to oxidative cell damage via a Fenton-type redox reaction (86).	Cu is essential to mitochondrial respiration and Fe absorption. Elevated Cu level may increase the production of reactive oxygen species and consequently oxidative stress (87).
Phosphorus	Phosphate supplements may increase the risk of CRC by reducing the bile acids (88).	Inhibit nitric oxide production through increased reactive oxygen species production and endothelial nitric oxide synthase inactivation, resulting in impaired endothelium-dependent vasodilation (89).	High sodium level may impaired physiological mechanisms, including renal function, fluid hormone, salt sensitivity, smooth muscle in peripheral vasculature and sympathetic nervous system (90).
Sodium	Synergy with Helicobacter pylori infection, and some independent effects such as increase cell proliferation and endogenous mutations (91).	Stiff endothelial cells, thicken and narrow resistance arteries, and block nitric oxide synthesis (92).	High dietary phosphorus intake induced phosphate-dependent phagocyte injury and damaged the glomerular barrier, which resulted in the progression of glomerular sclerosis (93).

Table 2. Participant Characteristics at Baseline across Quintiles of the Mineral Score[a] in the Iowa Women's Health Study, 1986-2012

Characteristics	Mineral score quintiles				
	1 (≤ 26, N = 8,348)	2 (26 - 28, N = 6,500)	3 (28 - 30, N = 6,621)	4 (30 - 33, N = 7,660)	5 (> 33, N = 6,092)
Age, years [b]	61.5 ± 4.2	61.4 ± 4.2	61.5 ± 4.2	61.5 ± 4.2	61.6 ± 4.2
Education, less than college graduate, %	91.1	88.3	87.0	84.7	82.4
Family cancer history, %	38.1	37.8	38.6	37.3	37.6
Married, %	77.2	77.9	77.3	77.2	74.9
Morbidity at baseline, %					
Hypertension	37.0	36.8	36.6	36.5	35.9
Chronic diseases[c]	15.0	13.8	14.7	14.1	14.6
Hormone replacement therapy, %					
Never	65.6	63.1	61.5	58.6	54.9
Current	9.0	10.2	10.6	13.2	14.6
Height (cm) [b]	160.3 ± 6.4	160.2 ± 6.3	160.2 ± 6.1	160.4 ± 6.1	160.4 ± 6.3
Body mass index category, %					
< 25 kg/m^2	36.1	38.7	40.9	42.8	46.6
25 — 30 kg/m^2	36.5	36.9	36.5	36.9	36.0
≥ 30 kg/m^2	27.5	24.5	22.6	20.2	17.4
Waist-hip ratio [b]	0.9 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1
Physical activity, %					
Low	55.7	50.4	46.4	41.6	37.5
High	17.4	21.6	24.6	28.8	32.6
Smoking status, %					
Never	66.2	66.5	65.1	64.1	61.6
Current	16.4	15.2	14.3	13.8	13.5
Alcohol intake, %					
None	59.1	55.4	54.8	52.7	51.4
> 0 — < 7 g/day	35.5	37.4	39.1	40.1	41.5
≥ 7 g/day	5.4	7.2	6.1	7.2	7.1
Multivitamin intake	20.6	23.0	27.5	36.6	61.9
Supplemental calcium intake (mg/day) [b]	110.7 ± 246.6	182.9 ± 314.0	260.0 ± 375.6	380.7 ± 430.8	577.7 ± 478.1
Total Vitamin E intake (mg/day) [b]	37.2 ± 104.7	44.3 ± 116.0	55.1 ± 131.9	77.2 ± 162.0	130.7 ± 205.3
Total energy intake (kcal/day) [b]	1961 ± 659	1911 ± 633	1812 ± 590	1706 ± 546	1559 ± 487
Total fat intake (% kcal/day) [b]	78.3 ± 29.9	74.6 ± 29.3	68.9 ± 26.7	62.6 ± 23.6	55.2 ± 20.5
Dietary fiber intake (g/1,000 kcal/day) [b]	19.0 ± 7.4	19.6 ± 7.9	20.1 ± 8.2	20.4 ± 8.4	19.7 ± 8.1
Total fruits & vegetables intake (servings/wk.) [b]	39.5 ± 18.5	42.9 ± 21.2	45.2 ± 22.3	47.1 ± 23.1	46.9 ± 22.9
Total red & processed meats intake (servings/wk.) [b]	15.5 ± 8.0	14.7 ± 7.4	13.6 ± 6.5	12.5 ± 5.8	11.2 ± 5.3

[a] Mineral score calculated from food and supplemental intakes of calcium, magnesium, manganese, zinc, selenium, potassium, iodine, iron, copper, phosphorus and sodium as described in the text. A higher score indicates a predominance of putative predominately anti- relative to pro-carcinogenetic minerals.

[b] All variables measured at baseline (1986) are presented as mean ± sd, except for where otherwise indicated

[c] Chronic Disease indicates that participants had at least one of the following chronic diseases: Diabetes, Heart diseases and Liver diseases.

Table 3. Associations[a] of the Mineral Score[b] with Risk for All-Cancer, All-Cardiovascular Disease, and All-Cause Mortality in the Iowa Women's Study, 1986-2012.

	All-cancer mortality					All-cardiovascular mortality					All-cause mortality				
	# Cases	Minimally-adjusted[c] associations		Fully-adjusted[d] associations		# Cases	Minimally-adjusted[c] associations		Fully-adjusted[d] associations		# Cases	Minimally-adjusted[c] associations		Fully-adjusted[d] associations	
		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI
Mineral score, continuous	4,665	0.99	(0.98, 1.00)	1.00	(0.99, 1.01)	7,063	0.98	(0.97, 0.99)	0.99	(0.98, 1.00)	18,685	0.99	(0.98, 0.99)	1.00	0.99, 1.00)
Mineral Score, quintiles															
1	1,152	1.00	ref	1.00	ref	1,822	1.00	ref	1.00	ref	4,698	1.00	ref	1.00	ref
2	863	0.93	(0.86, 1.02)	0.98	(0.90, 1.08)	1,278	0.88	(0.82, 0.94)	0.95	(0.88, 1.02)	3,433	0.91	(0.87, 0.95)	0.97	(0.93, 1.02)
3	871	0.91	(0.84, 1.00)	0.99	(0.90, 1.08)	1,322	0.87	(0.81, 0.93)	0.96	(0.89, 1.03)	3,491	0.89	(0.85, 0.93)	0.97	(0.92, 1.01)
4	997	0.89	(0.82, 0.97)	1.00	(0.91, 1.10)	1,473	0.82	(0.76, 0.88)	0.93	(0.86, 1.00)	3,919	0.85	(0.81, 0.88)	0.95	(0.90, 0.99)
5	782	0.88	(0.80, 0.96)	1.01	(0.90, 1.12)	1,168	0.80	(0.74, 0.86)	0.93	(0.85, 1.01)	3,144	0.85	(0.81, 0.89)	0.96	(0.90, 1.01)
P-trend		0.003		0.86			<0.0001		0.06			<0.0001		0.06	

Abbreviations: CI, confidence interval; HR, hazards ratio; ref, referent.
[a] From Cox proportional hazards regression.
[b] Mineral score calculated from food and supplemental intakes of calcium, magnesium, manganese, zinc, selenium, potassium, iodine, iron, copper, phosphorus and sodium as described in the text. A higher score indicates a predominance of putative predominately anti- relative to pro-carcinogenetic minerals.
[c] Model covariates: age, total energy intake.
[d] Model covariates: age, education, family history of cancer, marital status, baseline chronic diseases, hormone replacement therapy, height, BMI category, waist-hip ratio, physical activity, smoking status, alcohol intake, multivitamin intake, calcium supplemental intake, total vitamin E intake, total energy intake, total fat intake, dietary fiber intake, total fruits & vegetables intake, total red & processed meats intake.

APPENDICES

Appendix 1. Multivariable-Adjusted Associations[a] of the Mineral Score[b] with All-cancer Mortality, According to Levels of Selected Other Risk Factors in Iowa Women's Health Study, 1986-2012

Characteristics	Strata	# of cases /Total	Mineral Score Quintiles 1	2		3		4		5	
			HR	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Age (Years)	< 61	2,247/18,245	1.00	0.96	(0.84, 1.10)	1.01	(0.88, 1.15)	1.03	(0.90, 1.18)	1.09	(0.93, 1.27)
	≥ 61	2,418/16,974	1.00	1.00	(0.88, 1.14)	0.96	(0.85, 1.10)	0.97	(0.85, 1.10)	0.92	(0.79, 1.07)
Education	College and lower	4,109/30,612	1.00	0.97	(0.88, 1.07)	1.00	(0.91, 1.10)	1.03	(0.93, 1.13)	1.01	(0.90, 1.14)
	College graduate or higher	543/4,539	1.00	1.16	(0.86, 1.57)	0.94	(0.69, 1.28)	0.85	(0.63, 1.16)	0.94	(0.68, 1.30)
Family history of cancer	No	2,836/21,792	1.00	0.95	(0.84, 1.06)	0.94	(0.83, 1.06)	0.97	(0.86, 1.10)	1.03	(0.89, 1.18)
	Yes	1,817/13,334	1.00	1.04	(0.90, 1.20)	1.06	(0.92, 1.23)	1.05	(0.90, 1.22)	0.96	(0.80, 1.15)
Currently married	No	1,161/7,918	1.00	0.96	(0.79, 1.15)	1.03	(0.85, 1.23)	0.88	(0.72, 1.06)	0.94	(0.76, 1.16)
	Yes	3,471/27,096	1.00	0.99	(0.89, 1.11)	0.98	(0.88, 1.09)	1.05	(0.94, 1.17)	1.04	(0.91, 1.18)
Morbidity at baseline	No	3,951/29,697	1.00	1.00	(0.90, 1.10)	0.97	(0.88, 1.07)	0.99	(0.89, 1.10)	1.04	(0.92, 1.17)
	Yes	656/5,097	1.00	0.89	(0.69, 1.14)	1.14	(0.90, 1.45)	1.10	(0.86, 1.41)	0.83	(0.62, 1.13)
Hormone replacement therapy	Never	2,848/21,481	1.00	0.94	(0.84, 1.05)	0.98	(0.88, 1.11)	0.97	(0.86, 1.09)	0.99	(0.86, 1.15)
	Current	527/4,023	1.00	1.28	(0.96, 1.71)	0.81	(0.59, 1.12)	0.96	(0.72, 1.30)	0.97	(0.69, 1.35)
	Former	1,275/9,586	1.00	0.98	(0.82, 1.18)	1.05	(0.88, 1.27)	1.09	(0.91, 1.31)	1.04	(0.84, 1.29)
Height (cm)	< 160	2,592/20,424	1.00	1.01	(0.90, 1.15)	0.98	(0.86, 1.11)	0.99	(0.87, 1.13)	0.96	(0.83, 1.11)
	≥ 160	2,073/14,795	1.00	0.94	(0.82, 1.08)	1.00	(0.87, 1.15)	1.01	(0.88, 1.17)	1.06	(0.90, 1.25)
Body mass index	$< 25\ kg/m^2$	1,903/14,352	1.00	0.96	(0.83, 1.12)	0.96	(0.83, 1.12)	0.98	(0.84, 1.13)	1.05	(0.89, 1.24)
	$25 - 30\ kg/m^2$	1,636/12,880	1.00	0.97	(0.83, 1.13)	0.92	(0.79, 1.08)	1.00	(0.85, 1.17)	0.92	(0.76, 1.11)
	$\geq 30\ kg/m^2$	1,126/7,987	1.00	1.01	(0.85, 1.21)	1.12	(0.93, 1.34)	1.03	(0.85, 1.25)	1.04	(0.82, 1.31)
Waist-hip ratio	< 0.83	2,331/18,609	1.00	1.01	(0.88, 1.16)	1.01	(0.88, 1.16)	1.06	(0.92, 1.21)	1.13	(0.97, 1.32)
	≥ 0.83	2,320/16,488	1.00	0.96	(0.85, 1.09)	0.98	(0.86, 1.11)	0.96	(0.84, 1.09)	0.88	(0.75, 1.03)
Physical activity	Low	2,294/16,465	1.00	1.00	(0.88, 1.13)	1.04	(0.92, 1.19)	1.05	(0.92, 1.20)	1.02	(0.87, 1.20)
	Medium	1,223/9,551	1.00	0.97	(0.81, 1.17)	0.91	(0.76, 1.09)	0.89	(0.74, 1.08)	1.02	(0.82, 1.25)
	High	1,080/8,673	1.00	0.93	(0.75, 1.15)	0.93	(0.76, 1.15)	0.99	(0.81, 1.22)	0.92	(0.73, 1.16)
Smoking status	Current	1,129/5,182	1.00	1.08	(0.90, 1.30)	1.09	(0.91, 1.32)	1.11	(0.92, 1.34)	1.06	(0.85, 1.32)
	Former	899/6,748	1.00	0.94	(0.76, 1.18)	0.95	(0.76, 1.18)	0.93	(0.74, 1.16)	1.02	(0.80, 1.30)
	Never	2,568/22,817	1.00	0.94	(0.83, 1.06)	0.94	(0.83, 1.06)	0.97	(0.85, 1.10)	0.96	(0.82, 1.11)
Alcohol intake	None	2,467/19,327	1.00	0.94	(0.83, 1.06)	1.03	(0.91, 1.17)	0.95	(0.83, 1.08)	1.00	(0.86, 1.17)
	$> 0 - < 7\ g/day$	1,372/10,578	1.00	1.02	(0.86, 1.21)	0.89	(0.74, 1.06)	1.05	(0.88, 1.25)	0.93	(0.76, 1.14)
	$\geq 7\ g/day$	826/5,314	1.00	1.03	(0.82, 1.29)	1.02	(0.81, 1.29)	1.07	(0.85, 1.34)	1.16	(0.89, 1.51)
Multivitamin intake	No	3,114/23,135	1.00	0.97	(0.87, 1.07)	1.00	(0.90, 1.11)	1.02	(0.91, 1.14)	1.05	(0.90, 1.22)
	Yes	1,499/11,611	1.00	1.03	(0.85, 1.26)	0.95	(0.78, 1.15)	0.95	(0.80, 1.14)	0.95	(0.79, 1.14)
Calcium supplemental intake (mg/day)	< 291.59	3,147/22,785	1.00	0.97	(0.88, 1.07)	1.00	(0.90, 1.11)	1.02	(0.91, 1.14)	1.00	(0.87, 1.16)
	≥ 291.59	1,518/12,434	1.00	1.05	(0.84, 1.32)	0.98	(0.79, 1.22)	1.02	(0.83, 1.25)	1.06	(0.85, 1.31)
Total vitamin E intake (mg/day)	< 9.70	4,036/30,255	1.00	0.97	(0.89, 1.07)	0.98	(0.89, 1.08)	1.01	(0.91, 1.12)	1.00	(0.89, 1.13)
	≥ 9.70	629/4,964	1.00	1.10	(0.79, 1.53)	1.06	(0.77, 1.45)	0.99	(0.73, 1.33)	1.03	(0.76, 1.40)
Total energy intake (kcal/day)	< 1717.40	2,595/19,645	1.00	0.94	(0.82, 1.07)	0.99	(0.87, 1.13)	0.94	(0.83, 1.07)	0.94	(0.81, 1.08)
	≥ 1717.40	2,070/15,574	1.00	1.02	(0.90, 1.16)	0.97	(0.85, 1.11)	1.08	(0.94, 1.24)	1.10	(0.91, 1.32)
Total fat intake (% kcal/day)	< 64.20	2,622/19,941	1.00	0.92	(0.80, 1.06)	1.00	(0.87, 1.14)	0.97	(0.85, 1.11)	0.98	(0.85, 1.12)
	≥ 64.20	2,043/15,278	1.00	1.03	(0.91, 1.17)	0.96	(0.84, 1.10)	1.04	(0.90, 1.20)	1.05	(0.86, 1.27)
Dietary fiber intake (g/1000 kcal/day)	< 18.60	2,766/19,821	1.00	0.94	(0.83, 1.06)	0.97	(0.86, 1.09)	1.02	(0.90, 1.15)	0.99	(0.86, 1.13)
	≥ 18.60	1,899/15,398	1.00	1.06	(0.92, 1.23)	1.03	(0.88, 1.19)	1.00	(0.85, 1.16)	1.06	(0.88, 1.27)
Total fruits & vegetables intake (servings/wk.)	< 40.50	2,827/20,481	1.00	0.89	(0.79, 1.00)	0.93	(0.83, 1.05)	0.98	(0.87, 1.11)	0.97	(0.84, 1.11)
	≥ 40.50	1,838/14,738	1.00	1.19	(1.02, 1.39)	1.13	(0.96, 1.32)	1.09	(0.93, 1.28)	1.13	(0.94, 1.36)
Total red & processed meats intake (servings/wk.)	< 12.50	2,728/20,524	1.00	0.96	(0.84, 1.09)	1.01	(0.89, 1.14)	1.00	(0.88, 1.13)	0.94	(0.81, 1.08)
	≥ 12.50	1,937/14,695	1.00	1.00	(0.88, 1.14)	0.95	(0.83, 1.10)	0.99	(0.86, 1.15)	1.16	(0.96, 1.40)

Abbreviations: CI, confidence interval; HR, hazards ratio.

[a] From Cox proportional hazards regression: adjusted for all the potential confounders (age, education, family history of cancer, marital status, baseline chronic diseases, hormone replacement therapy, height, BMI category, waist-hip ratio, physical activity, smoking status, alcohol intake, multivitamin intake, calcium supplemental intake, total vitamin E intake, total energy intake, total fat intake, dietary fiber intake, total fruits & vegetables intake, total red & processed meats intake).

[b] Mineral score calculated from food and supplemental intakes of calcium, magnesium, manganese, zinc, selenium, potassium, iodine, iron, copper, phosphorus and sodium as described in the text. A higher score indicates a predominance of putative predominately anti- relative to pro-carcinogenetic minerals.

Appendix 2. Multivariable-Adjusted Associations[a] of the Mineral Score[b] with All-Cardiovascular Mortality, According to Levels of Selected Other Risk Factors in Iowa Women's Health Study, 1986-2012

Characteristics	Strata	# of cases /Total	Mineral Score Quintiles								
			1	2		3		4		5	
			HR	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Age (Years)	< 61	2,314/18,245	1.00	0.97	(0.85, 1.10)	0.97	(0.85, 1.11)	0.78	(0.68, 0.90)	0.83	(0.70, 0.97)
	≥ 61	4,749/16,974	1.00	0.93	(0.84, 1.02)	0.94	(0.85, 1.03)	0.97	(0.89, 1.07)	0.95	(0.85, 1.06)
Education	College and lower	6,260/30,612	1.00	0.97	(0.89, 1.04)	0.94	(0.87, 1.02)	0.92	(0.85, 1.00)	0.94	(0.85, 1.03)
	College graduate or higher	785/4,539	1.00	0.81	(0.63, 1.05)	1.05	(0.83, 1.33)	0.93	(0.74, 1.18)	0.81	(0.62, 1.05)
Family history of cancer	No	4,409/21,792	1.00	0.91	(0.83, 1.01)	0.95	(0.87, 1.05)	0.89	(0.80, 0.98)	0.93	(0.83, 1.04)
	Yes	2,633/13,334	1.00	1.01	(0.90, 1.15)	0.96	(0.85, 1.09)	0.99	(0.88, 1.13)	0.91	(0.79, 1.06)
Currently married	No	1,930/7,918	1.00	1.04	(0.90, 1.21)	0.99	(0.85, 1.14)	0.94	(0.81, 1.09)	0.92	(0.78, 1.09)
	Yes	5,078/27,096	1.00	0.92	(0.84, 1.00)	0.95	(0.87, 1.04)	0.92	(0.84, 1.01)	0.93	(0.84, 1.04)
Morbidity at baseline	No	5,229/29,697	1.00	0.96	(0.88, 1.04)	0.96	(0.88, 1.04)	0.90	(0.82, 0.98)	0.92	(0.83, 1.02)
	Yes	1,729/5,097	1.00	0.94	(0.80, 1.09)	0.97	(0.83, 1.12)	1.00	(0.86, 1.17)	0.98	(0.82, 1.17)
Hormone replacement therapy	Never	4,407/21,481	1.00	0.99	(0.90, 1.08)	1.00	(0.91, 1.10)	0.91	(0.83, 1.01)	0.92	(0.82, 1.04)
	Current	621/4,023	1.00	0.84	(0.63, 1.12)	0.93	(0.70, 1.23)	0.95	(0.72, 1.25)	0.90	(0.66, 1.22)
	Former	1,999/9,586	1.00	0.91	(0.79, 1.05)	0.88	(0.76, 1.02)	0.94	(0.81, 1.09)	0.94	(0.80, 1.11)
Height (cm)	< 160	4,328/20,424	1.00	0.95	(0.86, 1.04)	0.96	(0.88, 1.06)	0.96	(0.87, 1.06)	0.98	(0.87, 1.10)
	≥ 160	2,735/14,795	1.00	0.96	(0.85, 1.09)	0.95	(0.84, 1.08)	0.87	(0.77, 0.99)	0.85	(0.73, 0.98)
Body mass index	$< 25\ kg/m^2$	2,510/14,352	1.00	0.97	(0.85, 1.10)	0.95	(0.83, 1.08)	0.92	(0.81, 1.05)	0.89	(0.76, 1.03)
	$25 - 30\ kg/m^2$	2,534/12,880	1.00	0.94	(0.83, 1.07)	0.92	(0.81, 1.05)	0.89	(0.78, 1.01)	0.90	(0.78, 1.05)
	$\geq 30\ kg/m^2$	2,019/7,987	1.00	0.93	(0.82, 1.07)	1.01	(0.88, 1.16)	0.96	(0.83, 1.11)	1.01	(0.85, 1.20)
Waist-hip ratio	< 0.83	3,045/18,609	1.00	0.91	(0.81, 1.03)	0.90	(0.80, 1.01)	0.88	(0.78, 0.99)	0.86	(0.75, 0.99)
	≥ 0.83	3,986/16,488	1.00	0.97	(0.88, 1.07)	1.00	(0.90, 1.10)	0.95	(0.86, 1.05)	0.97	(0.86, 1.10)
Physical activity	Low	3,433/16,465	1.00	0.95	(0.86, 1.05)	0.94	(0.84, 1.04)	0.95	(0.86, 1.06)	0.97	(0.85, 1.11)
	Medium	1,889/9,551	1.00	1.04	(0.89, 1.20)	1.01	(0.87, 1.17)	0.97	(0.83, 1.12)	0.94	(0.79, 1.11)
	High	1,631/8,673	1.00	0.85	(0.71, 1.00)	0.93	(0.79, 1.09)	0.83	(0.71, 0.98)	0.83	(0.69, 1.00)
Smoking status	Current	1,215/5,182	1.00	0.97	(0.81, 1.16)	0.90	(0.75, 1.08)	0.87	(0.72, 1.04)	0.89	(0.72, 1.09)
	Former	1,364/6,748	1.00	0.89	(0.74, 1.07)	0.99	(0.83, 1.17)	0.98	(0.82, 1.17)	0.91	(0.75, 1.12)
	Never	4,378/22,817	1.00	0.97	(0.88, 1.06)	0.97	(0.88, 1.07)	0.92	(0.84, 1.02)	0.95	(0.85, 1.07)
Alcohol intake	None	4,265/19,327	1.00	1.00	(0.91, 1.10)	0.98	(0.89, 1.09)	1.00	(0.90, 1.10)	1.00	(0.89, 1.13)
	$> 0 - < 7\ g/day$	1,884/10,578	1.00	0.83	(0.71, 0.96)	0.91	(0.79, 1.05)	0.85	(0.73, 0.99)	0.79	(0.67, 0.94)
	$\geq 7\ g/day$	914/5,314	1.00	0.98	(0.80, 1.21)	0.92	(0.74, 1.15)	0.78	(0.62, 0.97)	0.88	(0.69, 1.14)
Multivitamin intake	No	4,662/23,135	1.00	0.96	(0.88, 1.05)	0.95	(0.87, 1.03)	0.94	(0.86, 1.03)	0.96	(0.85, 1.09)
	Yes	2,301/11,611	1.00	0.93	(0.79, 1.09)	0.99	(0.85, 1.16)	0.90	(0.78, 1.04)	0.89	(0.77, 1.03)
Calcium supplemental intake (mg/day)	< 291.59	4,882/22,785	1.00	0.98	(0.91, 1.07)	0.97	(0.89, 1.06)	0.95	(0.87, 1.05)	0.95	(0.84, 1.06)
	≥ 291.59	2,181/12,434	1.00	0.81	(0.67, 0.97)	0.89	(0.75, 1.05)	0.84	(0.71, 0.99)	0.86	(0.73, 1.02)
Total Vitamin E intake (mg/day)	< 9.70	6,068/30,255	1.00	0.95	(0.88, 1.02)	0.94	(0.87, 1.02)	0.93	(0.85, 1.01)	0.93	(0.84, 1.03)
	≥ 9.70	995/4,964	1.00	0.98	(0.75, 1.29)	1.09	(0.85, 1.41)	0.97	(0.76, 1.23)	0.95	(0.74, 1.21)
Total energy intake (kcal/day)	< 1717.40	3,966/19,645	1.00	0.98	(0.88, 1.09)	0.92	(0.83, 1.03)	0.92	(0.83, 1.02)	0.91	(0.81, 1.02)
	≥ 1717.40	3,097/15,574	1.00	0.92	(0.83, 1.02)	1.01	(0.90, 1.12)	0.93	(0.83, 1.05)	0.96	(0.82, 1.11)
Total fat intake (% kcal/day)	< 64.20	4,072/19,941	1.00	1.01	(0.91, 1.13)	0.95	(0.85, 1.06)	0.96	(0.87, 1.06)	0.94	(0.83, 1.05)
	≥ 64.20	2,991/15,278	1.00	0.90	(0.81, 1.00)	0.99	(0.88, 1.10)	0.89	(0.78, 1.00)	0.94	(0.80, 1.11)
Dietary fiber intake (g/1000 kcal/day)	< 18.60	3,946/19,821	1.00	0.93	(0.85, 1.03)	0.92	(0.83, 1.02)	0.85	(0.77, 0.95)	0.88	(0.79, 0.99)
	≥ 18.60	3,117/15,398	1.00	0.99	(0.88, 1.11)	1.02	(0.91, 1.15)	1.02	(0.91, 1.15)	1.00	(0.87, 1.15)
Total fruits & vegetables intake (servings/wk.)	< 40.50	4,024/20,481	1.00	0.98	(0.89, 1.07)	0.94	(0.85, 1.04)	0.88	(0.79, 0.97)	0.94	(0.83, 1.05)
	≥ 40.50	3,039/14,738	1.00	0.91	(0.81, 1.03)	0.99	(0.88, 1.11)	1.00	(0.88, 1.12)	0.94	(0.82, 1.09)
Total red & processed meats intake (servings/wk.)	< 12.50	4,105/20,524	1.00	0.98	(0.88, 1.09)	0.94	(0.85, 1.05)	0.94	(0.85, 1.04)	0.92	(0.82, 1.03)
	≥ 12.50	2,958/14,695	1.00	0.92	(0.83, 1.02)	0.98	(0.88, 1.10)	0.91	(0.80, 1.02)	0.95	(0.81, 1.11)

Abbreviations: CI, confidence interval; HR, hazards ratio.

[a] From Cox proportional hazards regression: adjusted for all the potential confounders (age, education, family history of cancer, marital status, baseline chronic diseases, hormone replacement therapy, height, BMI category, waist-hip ratio, physical activity, smoking status, alcohol intake, multivitamin intake, calcium supplemental intake, total vitamin E intake, total energy intake, total fat intake, dietary fiber intake, total fruits & vegetables intake, total red & processed meats intake).

[b] Mineral score calculated from food and supplemental intakes of calcium, magnesium, manganese, zinc, selenium, potassium, iodine, iron, copper, phosphorus and sodium as described in the text. A higher score indicates a predominance of putative predominately anti- relative to pro-carcinogenetic minerals.

Appendix 3. Multivariable-Adjusted Associations[a] of the Mineral Score[b] with All-Cause Mortality, According to Levels of Selected Other Risk Factors in Iowa Women's Health Study, 1986-2012

Characteristics	Strata	# of cases /Total	Mineral Score Quintiles								
			1	2		3		4		5	
			HR	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Age (Years)	< 61	7,199/18,245	1.00	0.96	(0.89, 1.03)	0.97	(0.90, 1.05)	0.89	(0.82, 0.96)	0.95	(0.87, 1.04)
	≥ 61	11,486/16,974	1.00	0.97	(0.92, 1.03)	0.96	(0.90, 1.02)	0.96	(0.91, 1.02)	0.93	(0.87, 1.00)
Education	College and lower	16,516/30,612	1.00	0.98	(0.93, 1.02)	0.96	(0.92, 1.01)	0.95	(0.90, 1.00)	0.96	(0.90, 1.02)
	College graduate or higher	2,124/4,539	1.00	0.95	(0.81, 1.11)	0.98	(0.84, 1.15)	0.91	(0.79, 1.06)	0.86	(0.73, 1.02)
Family history of cancer	No	11,489/21,792	1.00	0.92	(0.86, 0.97)	0.93	(0.87, 0.98)	0.90	(0.84, 0.95)	0.95	(0.88, 1.02)
	Yes	7,138/13,334	1.00	1.06	(0.98, 1.14)	1.02	(0.94, 1.10)	1.02	(0.94, 1.10)	0.95	(0.87, 1.04)
Currently married	No	4,990/7,918	1.00	0.98	(0.89, 1.07)	1.00	(0.91, 1.09)	0.92	(0.84, 1.01)	0.96	(0.87, 1.07)
	Yes	13,564/27,096	1.00	0.97	(0.92, 1.03)	0.96	(0.91, 1.01)	0.96	(0.91, 1.02)	0.96	(0.90, 1.02)
Morbidity at baseline	No	14,667/29,697	1.00	0.97	(0.92, 1.02)	0.95	(0.90, 1.00)	0.93	(0.88, 0.98)	0.95	(0.90, 1.01)
	Yes	3,767/5,097	1.00	0.98	(0.88, 1.09)	1.04	(0.93, 1.15)	1.03	(0.92, 1.14)	0.98	(0.87, 1.11)
Hormone replacement therapy	Never	11,490/21,481	1.00	0.98	(0.92, 1.03)	0.99	(0.93, 1.05)	0.93	(0.88, 0.99)	0.96	(0.89, 1.03)
	Current	1,829/4,023	1.00	0.91	(0.77, 1.07)	0.85	(0.72, 1.00)	0.87	(0.74, 1.02)	0.86	(0.72, 1.02)
	Former	5,287/9,586	1.00	0.99	(0.91, 1.08)	0.96	(0.88, 1.05)	1.00	(0.91, 1.09)	0.99	(0.89, 1.09)
Height (cm)	< 160	10,941/20,424	1.00	0.97	(0.91, 1.03)	0.98	(0.93, 1.05)	0.98	(0.92, 1.05)	0.99	(0.92, 1.06)
	≥ 160	7,744/14,795	1.00	0.98	(0.91, 1.05)	0.93	(0.87, 1.01)	0.89	(0.82, 0.96)	0.90	(0.82, 0.98)
Body mass index	$< 25\ kg/m^2$	7,297/14,352	1.00	0.96	(0.89, 1.04)	0.93	(0.86, 1.01)	0.90	(0.83, 0.97)	0.93	(0.85, 1.02)
	$25 - 30\ kg/m^2$	6,551/12,880	1.00	0.98	(0.91, 1.06)	0.95	(0.88, 1.03)	0.95	(0.87, 1.03)	0.91	(0.83, 1.00)
	$\geq 30\ kg/m^2$	4,837/7,987	1.00	0.96	(0.88, 1.05)	1.03	(0.94, 1.13)	1.01	(0.92, 1.11)	1.06	(0.95, 1.18)
Waist-hip ratio	< 0.83	8,691/18,609	1.00	0.95	(0.89, 1.02)	0.93	(0.86, 1.00)	0.91	(0.85, 0.98)	0.92	(0.85, 1.00)
	≥ 0.83	9,920/16,488	1.00	0.99	(0.93, 1.05)	1.00	(0.93, 1.06)	0.97	(0.91, 1.04)	0.98	(0.90, 1.06)
Physical activity	Low	9,245/16,465	1.00	0.97	(0.91, 1.03)	0.95	(0.89, 1.01)	0.95	(0.89, 1.01)	0.95	(0.88, 1.03)
	Medium	4,894/9,551	1.00	1.01	(0.92, 1.11)	0.97	(0.89, 1.07)	0.95	(0.86, 1.04)	0.98	(0.88, 1.09)
	High	4,242/8,673	1.00	0.94	(0.84, 1.05)	1.01	(0.91, 1.12)	0.96	(0.86, 1.06)	0.94	(0.84, 1.05)
Smoking status	Current	3,731/5,182	1.00	1.04	(0.94, 1.15)	1.00	(0.90, 1.11)	0.93	(0.83, 1.03)	0.92	(0.82, 1.04)
	Former	3,694/6,748	1.00	0.93	(0.84, 1.04)	0.93	(0.83, 1.04)	0.96	(0.86, 1.07)	0.92	(0.81, 1.04)
	Never	10,986/22,817	1.00	0.96	(0.90, 1.02)	0.96	(0.90, 1.02)	0.94	(0.88, 1.00)	0.98	(0.91, 1.05)
Alcohol intake	None	10,732/19,327	1.00	0.97	(0.91, 1.03)	0.98	(0.92, 1.04)	0.97	(0.91, 1.03)	1.01	(0.94, 1.08)
	$> 0 - < 7\ g/day$	5,184/10,578	1.00	0.94	(0.86, 1.03)	0.91	(0.83, 0.99)	0.95	(0.87, 1.04)	0.87	(0.78, 0.97)
	$\geq 7\ g/day$	2,769/5,314	1.00	1.03	(0.91, 1.16)	1.01	(0.89, 1.15)	0.90	(0.79, 1.03)	0.97	(0.84, 1.13)
Multivitamin intake	No	12,198/23,135	1.00	0.97	(0.92, 1.03)	0.97	(0.92, 1.03)	0.96	(0.90, 1.01)	1.00	(0.93, 1.08)
	Yes	6,217/11,611	1.00	0.98	(0.89, 1.08)	0.95	(0.87, 1.05)	0.93	(0.85, 1.01)	0.92	(0.84, 1.01)
Calcium supplemental intake (mg/day)	< 291.59	12,547/22,785	1.00	1.00	(0.95, 1.05)	0.97	(0.91, 1.02)	0.95	(0.90, 1.01)	0.97	(0.90, 1.05)
	≥ 291.59	6,138/12,434	1.00	0.88	(0.79, 0.98)	0.95	(0.85, 1.05)	0.92	(0.83, 1.02)	0.92	(0.83, 1.02)
Total Vitamin E intake (mg/day)	< 9.70	16,078/30,255	1.00	0.97	(0.93, 1.02)	0.95	(0.91, 1.00)	0.95	(0.90, 1.00)	0.95	(0.89, 1.01)
	≥ 9.70	2,607/4,964	1.00	1.02	(0.86, 1.21)	1.06	(0.90, 1.24)	0.99	(0.85, 1.15)	1.00	(0.86, 1.17)
Total energy intake (kcal/day)	< 1717.40	10,480/19,645	1.00	0.98	(0.92, 1.05)	0.96	(0.89, 1.02)	0.92	(0.87, 0.98)	0.93	(0.86, 1.00)
	≥ 1717.40	8,205/15,574	1.00	0.96	(0.90, 1.03)	0.97	(0.91, 1.04)	0.96	(0.89, 1.03)	0.96	(0.88, 1.06)
Total fat intake (% kcal/day)	< 64.20	10,654/19,941	1.00	0.97	(0.90, 1.04)	0.95	(0.89, 1.02)	0.94	(0.88, 1.00)	0.94	(0.87, 1.01)
	≥ 64.20	8,031/15,278	1.00	0.97	(0.91, 1.04)	0.97	(0.91, 1.04)	0.96	(0.89, 1.03)	0.97	(0.88, 1.07)
Dietary fiber intake (g/1000 kcal/day)	< 18.60	10,698/19,821	1.00	0.94	(0.89, 1.00)	0.95	(0.89, 1.01)	0.92	(0.86, 0.98)	0.93	(0.86, 1.00)
	≥ 18.60	7,987/15,398	1.00	1.03	(0.95, 1.10)	1.00	(0.93, 1.08)	0.99	(0.92, 1.07)	1.00	(0.92, 1.10)
Total fruits & vegetables intake (servings/wk.)	< 40.50	10,970/20,481	1.00	0.96	(0.90, 1.01)	0.94	(0.88, 0.99)	0.92	(0.86, 0.98)	0.96	(0.89, 1.03)
	≥ 40.50	7,715/14,738	1.00	1.01	(0.94, 1.09)	1.03	(0.95, 1.11)	1.01	(0.93, 1.09)	0.98	(0.89, 1.07)
Total red & processed meats intake (servings/wk.)	< 12.50	10,982/20,524	1.00	0.97	(0.91, 1.04)	0.96	(0.90, 1.03)	0.95	(0.89, 1.01)	0.94	(0.88, 1.01)
	≥ 12.50	7,703/14,695	1.00	0.97	(0.91, 1.04)	0.96	(0.89, 1.03)	0.93	(0.86, 1.00)	0.97	(0.88, 1.06)

Abbreviations: CI, confidence interval; HR, hazards ratio.

[a] From Cox proportional hazards regression: adjusted for all the potential confounders (age, education, family history of cancer, marital status, baseline chronic diseases, hormone replacement therapy, height, BMI category, waist-hip ratio, physical activity, smoking status, alcohol intake, multivitamin intake, calcium supplemental intake, total vitamin E intake, total energy intake, total fat intake, dietary fiber intake, total fruits & vegetables intake, total red & processed meats intake).

[b] Mineral score calculated from food and supplemental intakes of calcium, magnesium, manganese, zinc, selenium, potassium, iodine, iron, copper, phosphorus and sodium as described in the text. A higher score indicates a predominance of putative predominately anti- relative to pro-carcinogenetic minerals.

Appendix 4. Multivariable-adjusted joint/combined associations[a] of dietary-only[b] and supplemental-only[c] mineral score with all-cardiovascular mortality in the Iowa Women's Health Study, 1986 – 2012

		Diet-only mineral score quartiles			
		1	**2**	**3**	**4**
Supplemental-only mineral score quartiles		HR (95% CI), #Case	HR (95% CI), #Case	HR (95% CI), #Case	HR (95% CI), #Case
	1	1.00 (Ref)[d], 1,084	0.94 (0.85, 1.03), 740	0.92 (0.84, 1.01), 1,062	0.91 (0.83, 1.01), 824
	2	0.91 (0.76, 1.09), 162	0.86 (0.71, 1.05), 134	0.92 (0.78, 1.08), 210	0.75 (0.62, 0.91), 139
	3	0.84 (0.73, 0.98), 269	0.78 (0.66, 0.92), 209	0.85 (0.74, 0.97), 364	0.82 (0.72, 0.94), 411
	4	0.97 (0.80, 1.17), 184	0.80 (0.66, 0.97), 184	0.89 (0.77, 1.04), 379	0.86 (0.75, 0.99), 708

Abbreviations: CI, confidence interval; HR, hazards ratio; Ref, referent.

[a] From Cox proportional hazards regression: adjusted for age, education, family history of cancer, marital status, baseline chronic diseases, hormone replacement therapy, height, BMI category, waist-hip ratio, physical activity, smoking status, alcohol intake, multivitamin intake, calcium supplemental intake, total vitamin e intake, total energy intake, total fat intake, dietary fiber intake, total fruits & vegetables intake, total red & processed meats intake.

[b] Mineral score calculated from dietary intakes of calcium, magnesium, manganese, zinc, selenium, potassium, iodine, iron, copper, phosphorus and sodium as described in the text.

[c] Mineral score calculated from supplemental intakes of calcium, magnesium, manganese, zinc, selenium, potassium, iodine, iron, copper, phosphorus and sodium as described in the text.

[d] Participants with lowest diet-only mineral intake and no supplemental mineral intake.

Appendix 5. Multivariable-adjusted joint/combined associations[a] of dietary-only[b] and supplemental-only[c] mineral score with all-cause mortality in the Iowa Women's Health Study, 1986 – 2012

		Diet-only mineral score quartiles			
		1	**2**	**3**	**4**
Supplemental-only mineral score quartiles		HR (95% CI), #Case	HR (95% CI), #Case	HR (95% CI), #Case	HR (95% CI), #Case
	1	1.00 (Ref)[d], 2,744	0.94 (0.88, 1.00), 1,901	0.95 (0.90, 1.01), 2,779	0.90 (0.85, 0.96), 2,055
	2	0.94 (0.85, 1.05), 414	0.92 (0.82, 1.04), 363	0.91 (0.82, 1.01), 526	0.87 (0.78, 0.98), 380
	3	0.86 (0.79, 0.95), 709	0.92 (0.84, 1.02), 632	0.93 (0.85, 1.01), 1,016	0.90 (0.83, 0.97), 1,136
	4	0.97 (0.87, 1.09), 494	0.96 (0.86, 1.07), 543	0.96 (0.88, 1.06), 1,033	0.95 (0.87, 1.03), 1,960

Abbreviations: CI, confidence interval; HR, hazards ratio; Ref, referent.
[a] From Cox proportional hazards regression: adjusted for age, education, family history of cancer, marital status, baseline chronic diseases, hormone replacement therapy, height, BMI category, waist-hip ratio, physical activity, smoking status, alcohol intake, multivitamin intake, calcium supplemental intake, total vitamin e intake, total energy intake, total fat intake, dietary fiber intake, total fruits & vegetables intake, total red & processed meats intake.
[b] Mineral score calculated from dietary intakes of calcium, magnesium, manganese, zinc, selenium, potassium, iodine, iron, copper, phosphorus and sodium as described in the text.
[c] Mineral score calculated from supplemental intakes of calcium, magnesium, manganese, zinc, selenium, potassium, iodine, iron, copper, phosphorus and sodium as described in the text.
[d] Participants with lowest diet-only mineral intake and no supplemental mineral intake.

Appendix 6. Multivariable-adjusted joint/combined associations[a] of dietary-only[b] and supplemental-only[c] mineral score with all-cancer mortality in the Iowa Women's Health Study, 1986 – 2012

		Diet-only mineral score quartiles			
		1	**2**	**3**	**4**
Supplemental-only mineral score quartiles		HR (95% CI), #Case	HR (95% CI), #Case	HR (95% CI), #Case	HR (95% CI), #Case
	1	1.00 (Ref)[d], 704	0.86 (0.76, 0.97), 456	0.94 (0.84, 1.04), 710	0.92 (0.82, 1.04), 525
	2	0.85 (0.68, 1.07), 92	0.84 (0.66, 1.06), 83	0.90 (0.74, 1.09), 126	0.92 (0.74, 1.16), 97
	3	0.81 (0.67, 0.98), 165	0.96 (0.80, 1.16), 166	0.95 (0.81, 1.12), 264	0.92 (0.78, 1.07), 294
	4	0.82 (0.65, 1.05), 104	0.94 (0.75, 1.17), 130	0.90 (0.74, 1.09), 240	1.00 (0.84, 1.18), 509

Abbreviations: CI, confidence interval; HR, hazards ratio; Ref, referent.

[a] From Cox proportional hazards regression: adjusted for age, education, family history of cancer, marital status, baseline chronic diseases, hormone replacement therapy, height, BMI category, waist-hip ratio, physical activity, smoking status, alcohol intake, multivitamin intake, calcium supplemental intake, total vitamin e intake, total energy intake, total fat intake, dietary fiber intake, total fruits & vegetables intake, total red & processed meats intake.

[b] Mineral score calculated from dietary intakes of calcium, magnesium, manganese, zinc, selenium, potassium, iodine, iron, copper, phosphorus and sodium as described in the text.

[c] Mineral score calculated from supplemental intakes of calcium, magnesium, manganese, zinc, selenium, potassium, iodine, iron, copper, phosphorus and sodium as described in the text.

[d] Participants with lowest diet-only mineral intake and no supplemental mineral intake.

Appendix 7. Multivariable-adjusted joint/combined associations[a] of pro-chronic-diseases-risk[b] and anti-chronic-diseases-riak[c] mineral scores with all-cardiovascular mortality in the Iowa Women's Health Study, 1986 – 2012

		Anti-chronic-diseases-risk mineral score categories[d]		
Pro-chronic-diseases-risk mineral score categories[d]		**1** HR (95% CI), #Case	**2** HR (95% CI), #Case	**3** HR (95% CI), #Case
	1	1.00 (Ref)[e], 402	0.98 (0.86, 1.13), 484	0.97 (0.86, 1.09), 1,647
	2	1.01 (0.89, 1.16), 627	0.95 (0.82, 1.11), 354	0.92 (0.80, 1.07), 415
	3	0.99 (0.88, 1.11), 2,292	0.96 (0.84, 1.11), 516	0.95 (0.81, 1.11), 326

Abbreviations: CI, confidence interval; HR, hazards ratio; Ref, referent.

[a] From Cox proportional hazards regression: adjusted for age, education, family history of cancer, marital status, baseline chronic diseases, hormone replacement therapy, height, BMI category, waist-hip ratio, physical activity, smoking status, alcohol intake, multivitamin intake, calcium supplemental intake, total vitamin e intake, total energy intake, total fat intake, dietary fiber intake, total fruits & vegetables intake, total red & processed meats intake.

[b] Mineral score calculated from total intakes of calcium, magnesium, manganese, zinc, selenium, potassium, and iodine as described in the text.

[c] Mineral score calculated from total intakes of iron, copper, phosphorus and sodium as described in the text.

[d] Category 1 = quintiles 1 + 2; Category2 = quintile 3; Category 3 = quintile 4 + 5.

[e] Participants with the lowest anti-chronic-diseases-risk mineral score and the highest pro-chronic-diseases-risk mineral score.

Appendix 8. Multivariable-adjusted joint/combined associations[a] of pro-chronic-diseases-risk[b] and anti-chronic-diseases-riak[c] mineral scores with all-cause mortality in the Iowa Women's Health Study, 1986 – 2012

Pro-chronic-diseases-risk mineral score categories[d]		Anti-chronic-diseases-risk mineral score categories[d]		
		1 HR (95% CI), #Case	2 HR (95% CI), #Case	3 HR (95% CI), #Case
	1	1.00 (Ref)[e], 1,046	1.00 (0.92, 1.09), 1,286	0.96 (0.89, 1.03), 4,359
	2	0.93 (0.86, 1.01), 1,545	0.94 (0.85, 1.03), 946	0.92 (0.84, 1.01), 1,106
	3	0.94 (0.88, 1.01), 6,130	0.97 (0.89, 1.06), 1,425	0.92 (0.83, 1.01), 842

Abbreviations: CI, confidence interval; HR, hazards ratio; Ref, referent.

[a] From Cox proportional hazards regression: adjusted for age, education, family history of cancer, marital status, baseline chronic diseases, hormone replacement therapy, height, BMI category, waist-hip ratio, physical activity, smoking status, alcohol intake, multivitamin intake, calcium supplemental intake, total vitamin e intake, total energy intake, total fat intake, dietary fiber intake, total fruits & vegetables intake, total red & processed meats intake.

[b] Mineral score calculated from total intakes of calcium, magnesium, manganese, zinc, selenium, potassium, and iodine as described in the text.

[c] Mineral score calculated from total intakes of iron, copper, phosphorus and sodium as described in the text.

[d] Category 1 = quintiles 1 + 2; Category2 = quintile 3; Category 3 = quintile 4 + 5.

[e] Participants with the lowest anti-chronic-diseases-risk mineral score and the highest pro-chronic-diseases-risk mineral score.

Appendix 9. Multivariable-adjusted joint/combined associations[a] of pro-chronic-diseases-risk[b] and anti-chronic-diseases-riak[c] mineral scores with all-cancer mortality in the Iowa Women's Health Study, 1986 – 2012

Pro-chronic-diseases-risk mineral score categories[d]		**Anti-chronic-diseases-risk mineral score categories**[d]		
		1 HR (95% CI), #Case	**2** HR (95% CI), #Case	**3** HR (95% CI), #Case
	1	1.00 (Ref)[e], 247	0.99 (0.83, 1.18), 310	0.99 (0.85, 1.15), 1,059
	2	0.92 (0.78, 1.08), 376	0.97 (0.80, 1.16), 245	1.07 (0.90, 1.28), 304
	3	0.94 (0.81, 1.08), 1,570	0.99 (0.84, 1.18), 363	0.86 (0.70, 1.04), 191

Abbreviations: CI, confidence interval; HR, hazards ratio; Ref, referent.

[a] From Cox proportional hazards regression: adjusted for age, education, family history of cancer, marital status, baseline chronic diseases, hormone replacement therapy, height, BMI category, waist-hip ratio, physical activity, smoking status, alcohol intake, multivitamin intake, calcium supplemental intake, total vitamin e intake, total energy intake, total fat intake, dietary fiber intake, total fruits & vegetables intake, total red & processed meats intake.

[b] Mineral score calculated from total intakes of calcium, magnesium, manganese, zinc, selenium, potassium, and iodine as described in the text.

[c] Mineral score calculated from total intakes of iron, copper, phosphorus and sodium as described in the text.

[d] Category 1 = quintiles 1 + 2; Category2 = quintile 3; Category 3 = quintile 4 + 5.

[e] Participants with the lowest anti-chronic-diseases-risk mineral score and the highest pro-chronic-diseases-risk mineral score.

Appendix 10. Associations[a] of the Mineral Score[b] with Risk for Colon Cancer-Specific Mortality and All-other Cancer Mortality in the Iowa Women's Study, 1986-2012.

	Colon cancer mortality					All-other cancer mortality				
	cases	Minimally-adjusted[c]		Fully-adjusted[d]		cases	Minimally-adjusted[c]		Fully-adjusted[d]	
		HR	95%CI	HR	95%CI		HR	95%CI	HR	95%CI
Mineral score, continuous	510	0.97	(0.95, 0.99)	0.98	(0.96, 1.01)	4155	0.99	(0.98, 1.00)	1.00	(0.99, 1.01)
Mineral Scores, quintiles										
1	132	1.00	ref	1.00	ref	1020	1.00	ref	1.00	ref
2	98	0.93	(0.71, 1.20)	0.99	(0.76, 1.30)	765	0.94	(0.85, 1.03)	0.98	(0.89, 1.08)
3	100	0.91	(0.70, 1.18)	0.98	(0.74, 1.30)	771	0.92	(0.83, 1.01)	0.99	(0.89, 1.09)
4	111	0.85	(0.66, 1.10)	0.97	(0.73, 1.29)	886	0.90	(0.82, 0.98)	1.00	(0.91, 1.11)
5	69	0.66	(0.49, 0.88)	0.79	(0.56, 1.12)	713	0.91	(0.82, 1.00)	1.03	(0.92, 1.16)
P-trend		0.005		0.25			0.03		0.55	

Abbreviations: CI, confidence interval; HR, hazards ratio; ref, referent.

[a] From Cox Proportional hazards regression.

[b] Mineral score calculated from food and supplemental intakes of calcium, magnesium, manganese, zinc, selenium, potassium, iodine, iron, copper, phosphorus and sodium as described in the text. A higher score indicates a predominance of putative predominately anti- relative to pro-carcinogenetic minerals.

[c] The covariates in this model are: age, total energy intake.

[d] The covariates in this model are: age, education, family history of cancer, marital status, baseline chronic diseases, hormone replacement therapy, height, BMI category, waist-hip ratio, physical activity, smoking status, alcohol intake, multivitamin intake, calcium supplemental intake, total vitamin e intake, total energy intake, total fat intake, dietary fiber intake, total fruits & vegetables intake, total red & processed meats intake.

Appendix 11. Associations[a] of the mineral score[b] with risk for all-cancer mortality, all-cardiovascular mortality and all-cause mortality, with removal/replacement of each score component one at a time.

Mineral removed	All-cancer		All-cardiovascular		All-cause	
	HR	95% CI	HR	95% CI	HR	95% CI
Ca	1.00	(0.89, 1.12)	0.97	(0.88, 1.06)	0.96	(0.91, 1.02)
Mg	0.94	(0.85, 1.05)	0.95	(0.87, 1.03)	0.92	(0.88, 0.97)
Mn	0.97	(0.86, 1.09)	0.95	(0.86, 1.04)	0.93	(0.87, 0.98)
Zn	0.97	(0.86, 1.09)	0.88	(0.80, 0.96)	0.93	(0.88, 0.98)
Se	1.01	(0.90, 1.14)	0.91	(0.83, 1.01)	0.95	(0.90, 1.01)
K	1.02	(0.93, 1.13)	0.92	(0.85, 1.00)	0.97	(0.92, 1.02)
Iodine	1.00	(0.89, 1.13)	0.89	(0.81, 0.98)	0.94	(0.89, 1.00)
Iron	1.00	(0.89, 1.12)	0.88	(0.80, 0.97)	0.92	(0.87, 0.98)
Cu	1.01	(0.90, 1.14)	0.92	(0.83, 1.01)	0.94	(0.89, 1.00)
Ph	1.05	(0.92, 1.20)	0.85	(0.76, 0.95)	0.94	(0.88, 1.00)
Na	1.01	(0.90, 1.14)	0.90	(0.82, 1.00)	0.96	(0.90, 1.02)

Abbreviations: CI, confidence interval; HR, hazards ratio.

[a] From Cox proportional hazards regression model: adjusted for age, education, family history of cancer, marital status, baseline chronic diseases, hormone replacement therapy, height, BMI category, waist-hip ratio, physical activity, smoking status, alcohol intake, multivitamin intake, calcium supplemental intake, total vitamin e intake, total energy intake, total fat intake, dietary fiber intake, total fruits & vegetables intake, total red & processed meats intake.

[b] Mineral score calculated from food and supplemental intakes of calcium, magnesium, manganese, zinc, selenium, potassium, iodine, iron, copper, phosphorus and sodium as described in the text. A higher score indicates a predominance of putative predominately anti- relative to pro-carcinogenetic minerals. Comparing the highest to the lowest quintile.

Appendix 12. Associations[a] of each individual mineral score[b] component with risk for all-cancer mortality, all-cardiovascular mortality and all-cause mortality, adjusted for the remaining 10-component score.

Mineral	All-cancer		All-cardiovascular		All-cause	
	HR	95% CI	HR	95% CI	HR	95% CI
Ca	1.01	(0.88, 1.16)	0.96	(0.86, 1.08)	0.98	(0.91, 1.05)
Mg	1.16	(1.03, 1.30)	0.96	(0.87, 1.06)	1.04	(0.98, 1.11)
Mn	1.03	(0.91, 1.16)	0.89	(0.80, 0.98)	0.98	(0.93, 1.04)
Zn	1.03	(0.93, 1.15)	0.96	(0.88, 1.04)	0.98	(0.93, 1.04)
Se	1.10	(0.91, 1.34)	1.01	(0.86, 1.19)	1.03	(0.93, 1.14)
K	1.03	(0.91, 1.17)	0.98	(0.88, 1.08)	1.00	(0.94, 1.07)
Iodine	1.00	(0.83, 1.20)	1.08	(0.94, 1.25)	1.05	(0.97, 1.15)
Iron	1.07	(0.96, 1.20)	1.10	(1.00, 1.20)	1.06	(1.01, 1.12)
Cu	1.00	(0.90, 1.12)	1.00	(0.91, 1.09)	1.04	(0.99, 1.10)
Ph	0.99	(0.89, 1.11)	1.09	(0.99, 1.19)	1.03	(0.98, 1.09)
Na	1.08	(0.99, 1.19)	0.97	(0.90, 1.05)	1.03	(0.98, 1.08)

Abbreviations: CI, confidence interval; HR, hazards ratio.

[a] From Cox proportional hazards regression model: adjusted for age, education, family history of cancer, marital status, baseline chronic diseases, hormone replacement therapy, height, BMI category, waist-hip ratio, physical activity, smoking status, alcohol intake, multivitamin intake, calcium supplemental intake, total vitamin e intake, total energy intake, total fat intake, dietary fiber intake, total fruits & vegetables intake, total red & processed meats intake.

[b] Mineral score calculated from food and supplemental intakes of calcium, magnesium, manganese, zinc, selenium, potassium, iodine, iron, copper, phosphorus and sodium as described in the text. A higher score indicates a predominance of putative predominately anti- relative to pro-carcinogenetic minerals. Comparing the highest to the lowest quintile.

Appendix 13. Associations[a] of the Mineral Score[b] with Risk for All-Cancer Mortality, All-Cardiovascular Mortality and All-Cause Mortality after exclusion of participants who died within the first two years of follow-up in the Iowa Women's Study, 1986-2012.

	All-cancer mortality					All-cardiovascular mortality					All-cause mortality				
	#Cases	Minimally-adjusted[c] associations		Fully-adjusted[d] associations		#Cases	Minimally-adjusted[c] associations		Fully-adjusted[d] associations		#Cases	Minimally-adjusted[c] associations		Fully-adjusted[d] associations	
		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI
Mineral score, continuous	4,575	0.99	(0.98, 1.00)	1.00	(0.99, 1.01)	6,934	0.98	(0.97, 0.99)	0.99	(0.98, 1.00)	18,407	0.99	(0.98, 0.99)	1.00	(0.99, 1.00)
Mineral Score, quintiles															
1	1,127	1.00	ref	1.00	ref	1,780	1.00	ref	1.00	ref	4,617	1.00	ref	1.00	ref
2	844	0.93	(0.85, 1.02)	0.98	(0.89, 1.07)	1,264	0.89	(0.83, 0.96)	0.96	(0.89, 1.04)	3,388	0.91	(0.88, 0.96)	0.98	(0.93, 1.02)
3	859	0.92	(0.84, 1.01)	0.99	(0.90, 1.09)	1,297	0.87	(0.81, 0.93)	0.96	(0.89, 1.04)	3,441	0.89	(0.85, 0.93)	0.97	(0.92, 1.02)
4	978	0.89	(0.82, 0.97)	1.00	(0.91, 1.10)	1,444	0.82	(0.76, 0.88)	0.93	(0.86, 1.01)	3,860	0.85	(0.81, 0.89)	0.95	(0.90, 1.00)
5	767	0.88	(0.80, 0.96)	1.00	(0.90, 1.12)	1,149	0.81	(0.75, 0.87)	0.93	(0.85, 1.02)	3,101	0.85	(0.81, 0.89)	0.95	(0.90, 1.01)
P-trend		0.003		0.89			<0.0001		0.07			<0.0001		0.06	

Abbreviations: CI, confidence interval; HR, hazards ratio; ref, referent.

[a] From Cox Proportional hazards regression.

[b] Mineral score calculated from food and supplemental intakes of calcium, magnesium, manganese, zinc, selenium, potassium, iodine, iron, copper, phosphorus and sodium as described in the text. A higher score indicates a predominance of putative predominately anti- relative to pro-carcinogenetic minerals.

[c] The covariates in this model are: age, total energy intake.

[d] The covariates in this model are: age, education, family history of cancer, marital status, baseline chronic diseases, hormone replacement therapy, height, BMI category, waist-hip ratio, physical activity, smoking status, alcohol intake, multivitamin intake, calcium supplemental intake, total vitamin e intake, total energy intake, total fat intake, dietary fiber intake, total fruits & vegetables intake, total red & processed meats intake.