Prospective Study of Zinc Intake and Risk of Type 2 Diabetes in Women

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OBJECTIVE — The aim of this study is to investigate the intake of zinc in relation to risk of type 2 diabetes in U.S. women.

RESEARCH DESIGN AND METHODS — Dietary intakes of zinc and other nutrients were assessed and updated using a validated food frequency questionnaire from 1980 to 2002 among 82,297 women who were aged 33–60 years at baseline in 1980 and followed up to 2004 in the Nurses' Health Study.

RESULTS — During the 24 years of follow-up, 6,030 incident cases of type 2 diabetes were ascertained. After adjustment of lifestyle and dietary risk factors, the relative risks (RRs) (95% CI) of type 2 diabetes comparing the highest with the lowest quintiles were 0.90 (0.82–0.99) ($P_{trend} = 0.04$) for total zinc intake and 0.92 (0.84–1.00) ($P_{trend} = 0.009$) for dietary zinc intake from food sources, respectively. We further found an inverse association for dietary zinc to heme iron ratio. After multivariate adjustment of covariates, the RRs (95% CI) across quintiles of this ratio were 1.0 (reference), 0.93 (0.86–1.01), 0.86 (0.79–0.94), 0.82 (0.75–0.90), and 0.72 (0.66–0.80), respectively ($P_{trend} < 0.0001$).

CONCLUSIONS — Higher zinc intake may be associated with a slightly lower risk of type 2 diabetes in women. More studies are warranted to confirm this association and to explore potential mechanisms.

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Zinc is an essential trace element that exists in all cells and is required by thousands of proteins for catalytic, structural, or transcriptional functions. Since the 1930s when zinc was first demonstrated to be an integral element of the insulin crystalline structure (1), many studies have been conducted to shed light on the relationship between zinc and insulin action. Animal studies have shown that zinc is able to not only stabilize and prevent the degradation of insulin hexamers (2), a storage form of insulin in β-cells, but also improve the binding of insulin to liver receptors and inhibit the degradation by live plasma membranes (3). In rodent models, zinc supplementation attenuated hyperglycemia and hyperinsulinemia in *ob/ob* and *db/db* mice (4,5). Interestingly, oral or intraperitoneal administration of certain zinc complexes showed insulinomimetic effects in rodent models, including stimulating lipogenesis and attenuating hyperglycemia (6,7). In addition, there is increasing evidence supporting the role of zinc as an antioxidant that could protect insulin and cells from being attacked by free radicals (8).

Despite the evidence from animal studies that zinc intake may have protective effects against type 2 diabetes, few studies in humans have been conducted to examine this relationship. In obese Brazilian women, 4 weeks of zinc supplementation (30 mg/day) significantly improved insulin sensitivity (9). In a cross-sectional analysis, higher dietary zinc intake was associated with a lower prevalence of diabetes and metabolic syndrome in an Indian population (10). However, the hypothesis that dietary zinc intake is associated with a reduced risk of type 2 diabetes has not been examined in a prospective study. Also, it would be useful to examine the associations for supplemental zinc and zinc from food sources separately because the former is more bioavailable than the latter (11). In addition, minerals with similar physical or chemical properties, such as iron and zinc, would compete with each other biologically (12). Several human studies already demonstrated that both inorganic iron and heme iron can inhibit the absorption of zinc (13). Whether iron intakes modify the association of zinc on risk of type 2 diabetes has not been examined in epidemiological studies. Therefore, we used the prospective data with repeated measurements of dietary intake from the Nurses' Health Study to evaluate the long-term zinc intake in relation to risk of type 2 diabetes and to examine the potential iron and zinc interactions.

RESEARCH DESIGN AND METHODS

— The Nurses' Health Study is an ongoing prospective cohort study conducted in U.S. registered female nurses. The study design was described in detail elsewhere (14). Briefly, a list of names and addresses of 238,026 registered nurses who lived in 1 of 11 states and fulfilled the eligibility criteria (married female) were obtained in 1972 from the American Nurses' Association. Of these eligible women, 65,613 (27.6%) were either unreachable by mail or already deceased. Of the remaining 172,413 women, 121,701 (70.6%) completed baseline questionnaires about their lifestyle and medical history. Follow-up questionnaires were sent to participating nurses biennially to update the information of lifestyle risk factors and disease occurrence. Up to 2004, the follow-up rate was >95% in the Nurses' Health Study.

For the current analysis, we used 1980 as the study baseline when the first food frequency questionnaire (FFQ) was

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administered. Exclusion criteria include *1*) a history of diabetes, cancer (except nonmelanoma skin cancer), or cardiovascular disease at baseline; *2*) >10 items of the 1980 FFQ were missing; and/or *3*) total energy intake <500 kcal/day or >3,500 kcal/day. We excluded participants with major chronic diseases at baseline based on considerations that these participants may have changed their diet because of the diagnosis of chronic diseases. In addition, the study hypothesis was to examine zinc and diabetes relationship among relatively healthy participants rather than people with these chronic diseases; the association may be different between people with and without chronic diseases. After these exclusions, 82,297 participants were available for analysis. The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard School of Public Health.

Dietary assessment

In 1980, a 61-item FFQ was sent to participants to inquire about their dietary intakes. Similarly, expanded FFQs were administered every 2–4 years since 1980. The FFQs used in the Nurses' Health Study were designed to inquire about food consumption in the previous year. For each food item, a standard portion size was specified and the participants were asked how often, on average, they consumed foods of that specified amount. There were nine possible coding responses, ranging from "never or less than once per month" to "six or more times per day." Multivitamin and zinc supplement use were assessed in the 1980 questionnaire and in all biennial follow-up questionnaires. Zinc intake from food sources was calculated by multiplying the frequency of consumption of each food by the zinc composition in the specified amount of that food and then summing up the zinc intake from each food item. The food composition database was primarily based on the U.S. Department of Agriculture sources. When estimating the total zinc intake, supplementation use was taken into account as well. The FFQs have been validated against multiple food records and showed reasonable correlations for most nutrients (15). The Pearson correlation coefficient between the FFQ and two 1-week diet record assessments of zinc intake was 0.67 in a validation study among 127 health professionals (16). In the current analysis, we adjusted nutrient intakes, except for alcohol intake, for total energy intake using the residual method (15).

Assessment of type 2 diabetes

Women who reported a diagnosis of type 2 diabetes in the biennial follow-up questionnaires were sent supplementary questionnaires inquiring about symptoms, diagnostic tests, and treatment for the purpose of confirmation. Consistent with the criteria of the National Diabetes Data Group, diagnosed cases required *1*) an elevated glucose concentration (fasting plasma glucose ≥7.8 mmol/l, random plasma glucose ≥11.1 mmol/l, or plasma glucose ≥11.1 mmol/l after an oral glucose load) and at least one symptom related to diabetes (excessive thirst, polyuria, weight loss, or hunger); *2*) no symptoms but elevated glucose concentrations on two occasions; and *3*) treatment with insulin or oral hypoglycemic medication. For cases of type 2 diabetes identified after 1998, the cutoff point used for fasting plasma glucose concentrations was lowered to 7.0 mmol/l, according to the American Diabetes Association criteria.

The self-report of diagnosis of type 2 diabetes has been proven to be accurate in a validation study. Of a random sample of 62 nurses reporting type 2 diabetes, 61 (98%) were confirmed after their medical records were reviewed by an endocrinologist blinded to the supplementary questionnaire information. Women with the diagnosis of type 1 diabetes were excluded from the current analysis. Deaths were identified by reports from next of kin, postal authorities, or by searching the National Death Index. At least 98% of deaths among the Nurses' Health Study participants were identified.

Statistical analysis

Each participant's person-years of follow-up were counted from the date of returning 1980 FFQ to June 2004, the date of death, or the date of diagnosis of type 2 diabetes, whichever came first. We used Cox proportional hazard regressions to estimate the relative risks (RRs) for total and dietary zinc intake in relation to the risk of type 2 diabetes. To control as finely as possible for confounding by age and calendar time, we stratified the analysis jointly by age in months at start of follow-up and calendar year of the current questionnaire cycle. The time scale for the analysis was then measured as months since the start of the current questionnaire cycle. Women were categorized into quintiles according to the intake of total or dietary zinc. To examine the proportional hazard assumption of Cox regressions, we constructed interaction terms between dietary zinc intake and calendar year and used likelihood ratio tests to assess the significance of these interaction terms. Likelihood ratio tests are based on the difference of −2 log likelihood of models with and without interaction terms and follow the χ^2 distribution with the degree of freedom equal to the number of parameters of interaction terms. *P* values for the interaction terms were 0.48 for total zinc analysis and 0.30 for dietary zinc analysis, indicating that the proportional hazard assumption was not violated.

To minimize the impact of random measurement errors of dietary assessment and to better represent long-term diet, we calculated the cumulative averages of nutrient intakes from baseline to the censoring events. These cumulative averages were treated as time-varying covariates. To avoid systematic errors in dietary assessment due to the biased recall after occurrence of chronic diseases that may change usual dietary habit, we stopped updating diet when a participant reported a diagnosis of hypertension, hypercholesterolemia, cardiovascular disease, peptic ulcer, or cancer and then carried forward the cumulative averages of dietary intakes before the occurrence of these diseases to represent long-term diet for later follow-up (17).

In the multivariate analysis, we adjusted for age, BMI, family history of diabetes (among first-degree relatives), smoking, alcohol intake, menopausal status, postmenopausal hormone use, multivitamin use, physical activity, total energy intake, glycemic load, polyunsaturated-to-saturated fat intake ratio, and intakes of red meat, heme iron, whole grains, *trans* fat, magnesium, and caffeine. Likelihood ratio tests were used to evaluate the significance of potential interactions between zinc and iron intakes. We further examined the associations for zinc–to–total iron and zinc–to–heme iron ratios.

Tests for trends were conducted by assigning the median value to each quintile and modeling this value as a continuous variable. All *P* values were two sided. Ninety-five percent CIs were calculated for relative risks. Data were analyzed with the Statistical Analysis Systems software package, version 9.1 (SAS Institute, Cary, NC).

Table 1—*Age-standardized characteristics by quintile (Q) of total and dietary zinc intake in the Nurses' Health Study at baseline*

	Total zinc intake			Dietary zinc intake		
	Q1	Q3	Q5	Q1	Q3	Q5
Intake of zinc (mg/day)	2.7	5.4	16.2	2.7	5.0	10.7
Demography						
Age (year)	45.8	46.1	46.1	45.8	46.0	46.1
Physical activity (MET/hr)*	3.2	3.4	3.3	3.2	3.4	3.4
BMI (kg/m^2)	23.9	24.3	24.1	23.9	24.3	24.1
Current smoker (%)	32.9	26.3	30.8	32.8	26.3	30.8
Postmenopausal (%)	30.9	30.8	30.6	30.9	30.8	30.8
Postmenopausal hormone use (%)†	30.3	31.3	31.6	31.1	31.0	29.6
Hypertension (%)	15.2	14.5	13.8	15.3	14.8	13.8
High cholesterol (%)	5.0	4.9	4.2	5.0	5.0	4.1
Family history of diabetes (%)	24.0	24.3	24.1	24.1	24.7	23.1
Diet						
Trans fat (% of total calories)	2.6	2.2	2.0	2.6	2.3	1.9
Saturated fat (% of total calories)	15.9	15.1	16.7	15.9	15.1	16.5
Polyunsaturated fat (% of total calories)	5.8	5.3	4.8	5.8	5.4	4.7
Alcohol (g/day)	7.5	6.2	6.4	7.5	6.3	6.3
Cereal fiber (mg/day)	1.9	2.6	2.8	1.9	2.5	2.8
Magnesium (mg/day)	257.5	304.0	298.4	258.0	300.8	301.1
Caffeine (mg/day)	363.7	406.9	415.7	362.9	402.9	420.7
Glycemic load	86.5	86.1	83.8	86.4	86.4	83.8
Heme iron (mg/day)	1.8	1.5	1.4	1.9	1.5	1.4
Red meat (servings/day)	1.7	1.3	1.3	1.7	1.4	1.2
Fish (servings/week)	0.9	1.3	1.1	0.9	1.2	1.2
Chicken (servings/week)	1.2	1.9	1.9	1.2	1.9	2.0
Dairy products (servings/day)	1.0	2.0	2.0	1.0	1.9	2.1
Fruits and vegetables (servings/day)	3.5	4.2	3.9	3.6	4.2	3.9
Whole grains (g/day)‡	9.0	12.0	11.7	9.0	12.0	11.6
Multivitamin supplement user (%)	24.6	32.9	46.8	27.9	34.9	36.3
Zinc supplement user (%)	0.4	2.5	23.1	4.8	6.7	7.1

*MET/hr denotes metabolic equivalent hours. †Among postmenopausal women. ‡Whole-grain intake data were based on 1984 FFQ assessment.

RESULTS — During the 24 years of follow-up, we identified and confirmed 6,030 cases of incident type 2 diabetes. Women in the higher quintiles of either total or dietary zinc intake were slightly older and less likely to have a history of hypertension and hypercholesterolemia (Table 1). Higher zinc intake was also associated with higher intakes of cereal fiber, caffeine, chicken, and dairy products and lower intakes of alcohol, glycemic load, red meat, and polyunsaturated and *trans* fat. At baseline, on average, 6.3% of the women reported use of supplements that contained zinc (including both multivitamin and zinc-specific supplement use). In 2004, the proportion of use of zinc-containing supplements increased to 48.6%, mostly due to the increased use of multivitamins that contain zinc. Women in the higher quintiles of dietary zinc intake were also more likely to use zinc supplements than did those in the lower quintiles.

In age-adjusted analysis, intake of total zinc, but not dietary zinc from food sources, was significantly associated with a lower risk of type 2 diabetes (Table 2). After adjustment for nondietary risk factors, including age, BMI, smoking, and other covariates, highest quintiles of both total and dietary zinc intake were significantly associated with an ~20% lower risk of type 2 diabetes. After further adjustment for dietary risk factors, the associations were attenuated but remained statistically significant. When we examined the associations for dietary zinc intake, we further adjusted for the zinc intakes from supplements. In comparison with women in the lowest quintile, women in the highest quintiles of total and dietary zinc intakes had a 10% (95% CI 1–8) (P_{trend} = 0.04) and an 8% (0–16) (P_{trend} = 0.009) lower risk of type 2 diabetes, respectively. Zinc intake from supplement use was associated with the risk of type 2 diabetes only among women with the lowest dietary zinc intake levels. Among women in the lowest tertile for dietary zinc intake, the RRs (95% CI) for the tertiles of supplemental zinc intake were 1.0 (reference), 1.02 (0.87–1.21), and 0.86 (0.74–0.99), respectively (P_{trend} = 0.009). In contrast, among women in the higher tertiles of dietary zinc intake, supplemental zinc intake was not associated with the risk of type 2 diabetes. The corresponding RRs (95% CI) for supplemental zinc intake tertiles were 1.0 (reference), 1.14 (0.98–1.33), and 1.05 (0.92–1.19) (P_{trend} = 0.78). Similarly, dietary zinc intake was more strongly associated with a lower risk of type 2 diabetes among those with low zinc intakes from supplements. The RRs (95% CI) for the highest tertile of dietary zinc intake were 0.84 (0.75–0.95) (P_{trend} = 0.007) or 1.0 (0.87–1.16) (P_{trend} = 0.98) among women in the lowest or highest tertile of supplemental zinc intake levels, respectively.

Although we did not find significant interactions between zinc and heme iron intakes ($P_{interaction}$ = 0.13 for total zinc and 0.07 for dietary zinc, respectively), zinc–to–heme iron ratios, especially dietary zinc–to–heme iron ratio, were significantly associated with a lower risk of type 2 diabetes after multivariate adjustment for covariates (Table 3). Because these ratios are significantly correlated with heme iron intake (correlation coefficients = −0.30 for total zinc–to–heme iron ratio and −0.50 for dietary zinc–to–heme iron ratio, respectively), associations of these ratios might be strongly influenced by the positive association between heme iron intake and risk of type 2 diabetes. To examine the robustness of these associations, we conducted a sensitivity analysis with further adjustment for heme iron intake. The association for dietary zinc–to–heme iron ratio was attenuated but remained significant after such adjustment. The RR for highest quintile versus lowest quintile was 0.75 (95% CI 0.66–0.85) (P_{trend} < 0.0001). In contrast, the association for total zinc–to–heme iron ratio was somewhat weaker. The RR for highest quintile versus lowest quintile was 0.87 (0.78–0.96) (P_{trend} = 0.05). We did not find any significant interaction between zinc and total iron or for zinc/total iron ratios.

We conducted several sensitivity analyses to examine the robustness of the

Table 2—*RRs and 95% CIs for type 2 diabetes during 24 years of follow-up by quintile (Q) of zinc intake in the Nurses' Health Study

Intake	Q1	Q2	Q3	Q4	Q5	P_{trend}†
Total zinc (mg/day)	4.9 (<6.0)	7.7 (6.0–8.6)	9.4 (8.7–10.3)	11.4 (10.4–13.3)	18.0 (>13.3)	—
n of diabetes onsets	1,208	1,256	1,258	1,202	1,106	—
Person-years	335,665	365,448	410,141	361,592	367,857	—
Age adjusted	1.0	0.96 (0.89–1.04)	0.91 (0.84–0.99)	0.92 (0.85–1.00)	0.83 (0.77–0.90)	<0.0001
Age and nondietary factors adjusted‡	1.0	0.93 (0.86–1.01)	0.83 (0.77–0.90)	0.86 (0.79–0.93)	0.82 (0.75–0.89)	<0.0001
Age, nondietary, and dietary factors adjusted§	1.0	0.97 (0.90–1.06)	0.88 (0.81–0.96)	0.92 (0.84–1.00)	0.90 (0.82–0.99)	0.04
Dietary zinc (mg/day)	5.0 (<6.0)	7.3 (6.0–8.0)	8.7 (8.1–9.3)	9.9 (9.4–10.6)	11.6 (>10.6)	—
n of diabetes onsets	1,179	1,228	1,140	1,240	1,243	—
Person-years	340,219	376,260	363,931	387,481	372,811	—
Age adjusted	1.0	0.95 (0.88–1.03)	0.89 (0.82–0.97)	0.95 (0.88–1.03)	1.00 (0.92–1.08)	0.08
Age and nondietary factors adjusted‡	1.0	0.95 (0.88–1.03)	0.85 (0.78–0.92)	0.83 (0.77–0.90)	0.83 (0.77–0.90)	<0.0001
Age, nondietary, and dietary factors adjusted§¶	1.0	1.01 (0.93–1.10)	0.92 (0.84–1.00)	0.91 (0.83–0.99)	0.92 (0.84–1.00)	0.009

*For the intake level at each quintile, values were expressed as median (range). †*P* values for trends were conducted by assigning the median value to each quintile and modeling this value as a continuous variable. ‡Nondietary factors included BMI (<21, 21–22.9, 23–24.9, 25–26.9, 27.0–29.9, 30.0–32.9, 33–34.9, 35–39.9, or ≥40 kg/m^2), family history of diabetes (yes, no), smoking status (never, past, current with cigarette use of 1–14, 15–24, or ≥25 per day, or missing), alcohol intake (0, 0.1–4.9, 5.0–14.9, or ≥15.0 g/day), menopausal status (yes, no), postmenopausal hormone use (never, past, or current user), multivitamin use (yes, no), and physical activity (<3, 3–8, 9–17, 18–27, or ≥27 MET/week). §Dietary factors included total energy (kcal) and quintiles of glycemic load, polyunsaturated-to-saturated fat ratio, and intakes of red meat, heme iron, whole grains, *trans* fat, magnesium, and caffeine. ¶Zinc intake from supplement use (in tertiles) was further adjusted when modeling the associations for dietary zinc intake.

observed associations. The observed associations between zinc intake and type 2 diabetes risk were somewhat weaker when we *1*) used baseline diet only, *2*) censored participants after they developed chronic diseases, or *3*) continued updating diet after participants developed chronic diseases.

CONCLUSIONS — In this prospective cohort study, we found a modest inverse association between zinc intake and risk of type 2 diabetes in U.S. women after adjustment of established and potential confounders. In addition, a higher zinc–to–heme iron ratio was associated with a significantly lower risk of type 2 diabetes.

The close relationship between zinc and insulin action was first documented by Scott (1) in early 1930s, when zinc was found to be an integral component of crystalline insulin. Over the years, studies have shown that zinc ions play important roles in the biosynthesis, storage, and action of insulin (2). Interestingly, certain

Table 3—*RRs and 95% CIs for type 2 diabetes during 24 years of follow-up by quintile (Q) of zinc–to–heme iron ratio in the Nurses' Health Study

	Q1	Q2	Q3	Q4	Q5	P_{trend}†
Total zinc to heme iron	2.9 (<5.0)	6.4 (5.0–7.5)	8.6 (7.6–9.9)	11.5 (10.0–14.3)	20.6 (>14.3)	—
n of diabetes onsets	1,430	1,333	1,237	1,050	980	—
Person-years	338,715	366,796	379,268	377,332	378,035	—
Age adjusted	1.0	0.85 (0.79–0.92)	0.77 (0.71–0.83)	0.64 (0.59–0.69)	0.59 (0.54–0.64)	<0.0001
Age and nondietary factors adjusted‡	1.0	0.85 (0.79–0.92)	0.82 (0.75–0.88)	0.75 (0.69–0.81)	0.74 (0.68–0.81)	<0.0001
Age, nondietary, and dietary factors adjusted‡	1.0	0.87 (0.80–0.94)	0.85 (0.78–0.92)	0.79 (0.72–0.86)	0.81 (0.74–0.89)	0.0002
Dietary zinc to heme iron	2.9 (<4.7)	6.1 (4.7–7.0)	7.8 (7.1–8.7)	9.7 (8.8–10.9)	13.1 (>10.9)	—
n of diabetes onsets	1,403	1,410	1,252	1,114	851	—
Person-years	337,433	367,450	374,909	381,295	379,060	—
Age adjusted	1.0	0.92 (0.85–0.99)	0.79 (0.74–0.86)	0.69 (0.64–0.75)	0.52 (0.48–0.57)	<0.0001
Age and nondietary factors adjusted‡	1.0	0.91 (0.85–0.98)	0.83 (0.77–0.90)	0.78 (0.72–0.85)	0.67 (0.61–0.73)	<0.0001
Age, nondietary, and dietary factors adjusted‡§	1.0	0.93 (0.86–1.01)	0.86 (0.79–0.94)	0.82 (0.75–0.90)	0.72 (0.66–0.80)	<0.0001

*Value of the ratios were expressed as median (range). †*P* values for trends were conducted by assigning the median value to each quintile and modeling this value as a continuous variable. ‡The variables included in the multivariable models can be found in the footnotes to Table 2, except heme iron intake. §Zinc intake from supplement use was further adjusted when modeling the associations for dietary zinc–to–heme iron ratio.

zinc complexes, per se, showed insulinomimetic effects, including attenuating hyperglycemia and increasing lipogenesis, when these complexes were orally or intraperitoneally administrated to mice (6,7). Studies on mechanisms underlying the effects of zinc on insulin signaling are limited. But current evidence suggested that enhancement of tyrosine kinase phosphorylation in insulin signal transduction (18) and improved binding of insulin to its receptor may be involved (3). Another line of evidence indicated that zinc could act as an antioxidant as well. Zinc may protect insulin and β-cells from being attacked by free radicals by playing a structural role of antioxidant enzymes, such as copper, zinc, and superoxide dismutase (CuZnSOD) (19,20), by competing with redox-active transitional metals, such as iron (19,20), or by stimulating expression of metallothionein (21), a free-radical scavenger (22).

Despite this evidence, human data regarding this association are sparse (9,10). To our knowledge, the current study provided the first prospective epidemiologic data suggesting an inverse association between zinc intake and risk of type 2 diabetes. In the U.S. diet, the primary sources of zinc include cereals, meats, and dairy products, as well as supplements (23). In the current analysis, the magnitude of associations for the highest quintile was similar for total and dietary zinc intake despite the fact that the median level of the former was nearly twice as high as the latter, indicating that zinc supplementation may not further decrease the risk of type 2 diabetes in people with high dietary zinc intake. Indeed, in the current analysis, zinc intake from supplements was associated with a lower risk of type 2 diabetes only among those who had low levels of dietary zinc intake and vice versa. The average intake levels in our participants have reached the recommended dietary allowance, which is 8 mg/day for women (11). The bioavailability of zinc is higher for zinc supplements than for zinc from foods, but when dietary intake levels are adequate, additional zinc intake from supplements may not confer further benefits (11).

In the current study, a higher dietary zinc–to–heme iron ratio was significantly associated with a lower diabetes risk. Although it is clear that nonheme iron can inhibit inorganic zinc absorption, few studies have examined the interplay between heme iron and organic zinc in foods (13). It is possible that heme iron, for which absorption is through separate pathways and is less regulated than inorganic nonheme iron (24), may inhibit dietary zinc absorption but has weaker effects on highly bioavailable supplemental zinc absorption. Another possible mechanism for zinc-heme iron interaction is that zinc may compete with iron ions for chelation by the organic ligand cysteine and thus inhibit the production of hydroxyl radicals in human body (20). Heme iron contributes to high body iron stores, which has been demonstrated to be a risk factor for type 2 diabetes (25).

One of the strengths of this prospective study design was that dietary data were collected before the occurrence of disease so that disease status could not influence the self-report of diet. We further stopped updating the dietary data after report of chronic diseases that might change the diet of the participants. By calculating the cumulative average of dietary intakes, we minimized the measurement errors caused by change of diet over time (17). Several limitations are worth discussion as well. Although we adjusted for a multitude of established and potential lifestyle and dietary confounders, we cannot entirely exclude the possibility that residual confounding may explain the observed associations. In addition, despite that the FFQs were validated against multiple diet records, assessment of zinc intake was still inevitably subject to some measurement error. However, since the dietary intakes of zinc were assessed prospectively, such measurement error is more likely to be random and thus attenuate the true associations. Because the vast majority of participants in the current study were white nurses, it is important to examine whether the results can be generalized to women of other ethnicities or professions in future studies. Finally, we observed these significant associations only after using cumulative average of diet and stopping diet updates after participants developed chronic diseases. Our previous analyses have shown that the use of cumulative averages yielded stronger estimates than the use of baseline diet only or simply updated diet (17), probably because the cumulative averages reduce measurement errors and also reflect long-term diet.

In summary, the current study provided novel evidence that zinc intake may be associated with a lower risk of type 2 diabetes in U.S. women. Our results also suggest that a diet with high zinc–to–heme iron ratio is significantly associated with lower risk of type 2 diabetes. These findings are considered preliminary, and, thus, further studies are warranted to confirm these findings.

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References

1. Scott DA: Crystalline insulin. *Biochem J* 28:1592–1602, 1934
2. Taylor CG: Zinc, the pancreas, and diabetes: insights from rodent studies and future directions. *Biometals* 18:305–312, 2005
3. Arquilla ER, Packer S, Tarmas W, Miyamoto S: The effect of zinc on insulin metabolism. *Endocrinology* 103:1440–1449, 1978
4. Simon SF, Taylor CG: Dietary zinc supplementation attenuates hyperglycemia in db/db mice. *Exp Biol Med (Maywood)* 226: 43–51, 2001
5. Begin-Heick N, Dalpe-Scott M, Rowe J, Heick HM: Zinc supplementation attenuates insulin secretory activity in pancreatic islets of the ob/ob mouse. *Diabetes* 34: 179–184, 1985
6. Adachi Y, Yoshida J, Kodera Y, Kiss T, Jakusch T, Enyedy EA, Yoshikawa Y, Sakurai H: Oral administration of a zinc complex improves type 2 diabetes and metabolic syndromes. *Biochem Biophys Res Commun* 351:165–170, 2006
7. Fugono J, Fujimoto K, Yasui H, Kawabe K, Yoshikawa Y, Kojima Y, Sakurai H: Metallokinetic study of zinc in the blood of normal rats given insulinomimetic zinc(II) complexes and improvement of diabetes mellitus in type 2 diabetic GK rats by their oral administration. *Drug Metab Pharmacokinet* 17:340–347, 2002
8. Faure P, Lafond JL, Coudray C, Rossini E, Halimi S, Favier A, Blache D: Zinc prevents the structural and functional properties of free radical treated-insulin. *Biochim Biophys Acta* 1209:260–264, 1994
9. Marreiro DN, Geloneze B, Tambascia MA, Lerario AC, Halpern A, Cozzolino SM: Effect of zinc supplementation on serum leptin levels and insulin resistance of obese women. *Biol Trace Elem Res* 112: 109–118, 2006
10. Singh RB, Niaz MA, Rastogi SS, Bajaj S, Gaoli Z, Shoumin Z: Current zinc intake and risk of diabetes and coronary artery disease and factors associated with insulin

resistance in rural and urban populations of North India. *J Am Coll Nutr* 17:564–570, 1998
11. Maret W, Sandstead HH: Zinc requirements and the risks and benefits of zinc supplementation. *J Trace Elem Med Biol* 20:3–18, 2006
12. Hill CH, Matrone G: Chemical parameters in the study of in vivo and in vitro interactions of transition elements. *Fed Proc* 29:1474–1481, 1970
13. Solomons NW: Competitive interaction of iron and zinc in the diet: consequences for human nutrition. *J Nutr* 116:927–935, 1986
14. Rosenberg L, Hennekens CH, Rosner B, Belanger C, Rothman KJ, Speizer FE: Oral contraceptive use in relation to nonfatal myocardial infarction. *Am J Epidemiol* 111:59–66, 1980
15. Willett WC: *Nutritional Epidemiology*, New York, Oxford University Press, 1998
16. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC: Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. *Am J Epidemiol* 135: 1114–1126 [discussion 1127–1136], 1992
17. Hu FB, Stampfer MJ, Rimm E, Ascherio A, Rosner BA, Spiegelman D, Willett WC: Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. *Am J Epidemiol* 149:531–540, 1999
18. Mooney RA, Bordwell KL: Differential dephosphorylation of the insulin receptor and its 160-kDa substrate (pp160) in rat adipocytes. *J Biol Chem* 267:14054–14060, 1992
19. Bettger WJ: Zinc and selenium, site-specific versus general antioxidation. *Can J Physiol Pharmacol* 71:721–724, 1993
20. Bray TM, Bettger WJ: The physiological role of zinc as an antioxidant. *Free Radic Biol Med* 8:281–291, 1990
21. Blain D, Kubow S, Chan HM: Zinc pretreatment inhibits isotretinoin teratogenicity and induces embryonic metallothionein in CD-1 mice. *J Nutr* 128: 1239–1246, 1998
22. Bremner I, Beattie JH: Metallothionein and the trace minerals. *Annu Rev Nutr* 10: 63–83, 1990
23. Walsh CT, Sandstead HH, Prasad AS, Newberne PM, Fraker PJ: Zinc: health effects and research priorities for the 1990s. *Environ Health Perspect* 102 (Suppl. 2):5–46, 1994
24. Andrews NC: Disorders of iron metabolism. *N Engl J Med* 341:1986–1995, 1999
25. Jiang R, Manson JE, Meigs JB, Ma J, Rifai N, Hu FB: Body iron stores in relation to risk of type 2 diabetes in apparently healthy women. *JAMA* 291:711–717, 2004