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

The Harvard community has made this article openly available. **Please share** how this access benefits you. Your story matters

<table>
<thead>
<tr>
<th>Citation</th>
<th>Sun, Qi, Rob M. van Dam, Walter C. Willett, and Frank B. Hu. 2009. Prospective Study of Zinc Intake and Risk of Type 2 Diabetes in Women. Diabetes Care 32(4): 629-634.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Published Version</td>
<td>doi:10.2337/dc08-1913</td>
</tr>
<tr>
<td>Citable link</td>
<td><a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:4891660">http://nrs.harvard.edu/urn-3:HUL.InstRepos:4891660</a></td>
</tr>
<tr>
<td>Terms of Use</td>
<td>This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at <a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA">http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA</a></td>
</tr>
</tbody>
</table>
Prospective Study of Zinc Intake and Risk of Type 2 Diabetes in Women

Qi Sun, MD, ScD1
Rob M. van Dam, PhD1,2
Walter C. Willett, MD, DrPH1,2,3
Frank B. Hu, MD, PhD1,2,3

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) 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.

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...
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 amount of that food and then summing 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 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 χ² 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).
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 polysaturated 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 quintiles 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 intake ($P_{interaction} = 0.13$ 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) ($P_{trend} = 0.03$). 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>
<thead>
<tr>
<th>Table 1—Age-standardized characteristics by quintile (Q) of total and dietary zinc intake in the Nurses’ Health Study at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intake of zinc (mg/day)</strong></td>
</tr>
<tr>
<td>Q1</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>Total zinc intake</td>
</tr>
<tr>
<td>Demography</td>
</tr>
<tr>
<td>Age (year)</td>
</tr>
<tr>
<td>Physical activity (MET/hr)*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>Current smoker (%)</td>
</tr>
<tr>
<td>Postmenopausal (%)</td>
</tr>
<tr>
<td>Postmenopausal hormone use (%)†</td>
</tr>
<tr>
<td>Hypertension (%)</td>
</tr>
<tr>
<td>High cholesterol (%)</td>
</tr>
<tr>
<td>Family history of diabetes (%)</td>
</tr>
<tr>
<td>Diet</td>
</tr>
<tr>
<td>Trans fat (% of total calories)</td>
</tr>
<tr>
<td>Saturated fat (% of total calories)</td>
</tr>
<tr>
<td>Polysaturated fat (% of total calories)</td>
</tr>
<tr>
<td>Alcohol (g/day)</td>
</tr>
<tr>
<td>Cereal fiber (mg/day)</td>
</tr>
<tr>
<td>Magnesium (mg/day)</td>
</tr>
<tr>
<td>Caffeine (mg/day)</td>
</tr>
<tr>
<td>Glycemic load</td>
</tr>
<tr>
<td>Heme iron (mg/day)</td>
</tr>
<tr>
<td>Red meat (servings/day)</td>
</tr>
<tr>
<td>Fish (servings/week)</td>
</tr>
<tr>
<td>Chicken (servings/week)</td>
</tr>
<tr>
<td>Dairy products (servings/day)</td>
</tr>
<tr>
<td>Fruits and vegetables (servings/day)</td>
</tr>
<tr>
<td>Whole grains (g/day)‡</td>
</tr>
<tr>
<td>Multivitamin supplement user (%)</td>
</tr>
<tr>
<td>Zinc supplement user (%)</td>
</tr>
</tbody>
</table>

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

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

*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 (25 per day, or missing), alcohol intake (0.0–4.9, 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-saturated fat ratio, and intakes of red meat, heme iron, whole grains, trans fat, magnesium, and caffeine. ¶Zinc intake from supplement use (in terriles) was further adjusted when modeling the associations for dietary zinc intake.

### 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*

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

*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 insulino-
mimetic effects, including attenuating hy-
parglycemia and increasing lipogenesis, 
when these complexes were orally or in-
trapertionally administered 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 trans-
duction (18) and improved binding of in-
sulin 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 dis-
mutase (CuZnSOD) (19,20), by compet-
ing with redox-active transitional metals, 
such as iron (19,20), or by stimulating 
extression of metallothionein (21), a free-
radical scavenger (22).

Despite this evidence, human data re-
grading this association are sparse (9,10). 
To our knowledge, the current study pro-
vided the first prospective epidemiologic 
data suggesting an inverse association be-
tween zinc intake and risk of type 2 dia-
betes. In the U.S. diet, the primary 
ources of zinc include cereals, meats, and 
dairy products, as well as supplements 
(23). In the current analysis, the magni-
tude of associations for the highest quint-
tile 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 sup-
plementation 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 supple-
ments 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 recom-
ended 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 in-
take levels are adequate, additional zinc 
intake from supplements may not confer 
urther benefits (11).

In the current study, a higher dietary 
zinc-to-heme iron ratio was significantly 
associated with a lower diabetes risk. Al-
though it is clear that nonheme iron can 
inhibit inorganic zinc absorption, few 
studies have examined the interplay be-
tween 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 inor-
ganic nonheme iron (24), may inhibit di-
etary zinc absorption but has weaker 
effects on highly bioavailable supplemental 
zinc absorption. Another possible 
mechanism for zinc-heme iron interac-
tion 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 fur-
ther stopped updating the dietary data 
after report of chronic diseases that might 
change the diet of the participants. By cal-
culating the cumulative average of dietary 
intakes, we minimized the measurement 
errors caused by change of diet over time 
(17). Several limitations are worth discus-
sion as well. Although we adjusted for a 
multitude of established and potential 
ifestyle and dietary confounders, we can-
nnot entirely exclude the possibility that 
residual confounding may explain the ob-
served associations. In addition, despite 
that the FFQs were validated against mul-
tiple diet records, assessment of zinc in-
take was still inevitably subject to some 
measurement error. However, since the 
intakes of zinc were assessed prospec-
tively, such measurement error is more 
likely to be random and thus attenu-
ate 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 gen-
eralized 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 partici-
pants 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), pro-
bably because the cumulative averages re-
duce measurement errors and also reflect 
long-term diet.

In summary, the current study pro-
vided 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 con-
firm these findings.

Acknowledgments—This work was sup-
pported by research grants DK58845, 
CA87969, and HL60712 from the National 
Institutes of Health. Q. S. is supported by a Post-
doctoral Fellowship from the Unilever 
Corporate Research. F. B. H. is a recipient of the 
American Heart Association Established In-
vestigator Award.

No potential conflicts of interest relevant to 
this article were reported.

References
2. Taylor CG: Zinc, the pancreas, and diae-
betes: insights from rodent studies and fu-
ture directions. Biomdelts 18:305–312, 2005
3. Arquilla ER, Packer S, Tarmas W, Miy-
amoto S: The effect of zinc on insulin me-
4. Simon SF, Taylor CG: Dietary zinc sup-
plementation attenuates hyperglycemia in 
db/db mice. Exp Biol Med (Maywood) 226: 
43–51, 2001
5. Begin-Heick N, Daire-Scott M, Rowe J, 
Heick HM: Zinc supplementation attenu-
ates insulin secretory activity in pancre-
atic islets of the ob/ob mouse. Diabetes 34: 
170–184, 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 
7. Fugono J, Fujimoto K, Yashu H, Kawabe 
K, Yoshikawa Y, Koijima 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, Coutard C, Rossini E, 
Halimi S, Favier A, Blache D: Zinc pre-
vents the structural and functional prop-
erties 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: Ef-
fect 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. 
15. Willett WC: Nutritional Epidemiology, New York, Oxford University Press, 1998
Am J Epidemiol 149:531–540, 1999
22. Bremner I, Beattie JH: Metallothionein and the trace minerals. 
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
JAMA 291:711–717, 2004
26. Diabetes Care, volume 32, number 4, April 2009

Zinc intake and type 2 diabetes in women