RESPONSE TO COMMENT ON GALVEZ-FERNANDEZ ET AL.

Urinary Zinc and Incident Type 2 Diabetes: Prospective Evidence From the Strong Heart Study. Diabetes Care 2022;45:2561–2569

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We thank very much Yang et al. (1) for their interest in our article that was recently published in *Diabetes Care* (2). To address the question about potential confounding by alcohol drinking, waist-to-hip ratio, blood pressure, and lipids, we have conducted a sensitivity analysis including the variables proposed. Notice that alcohol drinking and waist-to-hip ratio could be actual confounders, as they could influence metal exposure and excretion. Blood pressure and lipids could be considered mediators as metal exposure could influence blood pressure and lipid levels, although blood pressure and metabolic state could also influence urinary excretion of metals, including zinc. In the updated sensitivity analyses adding these four additional variables, we found very similar associations between urinary zinc and incident type 2 diabetes mellitus (T2DM), as in the main models in the original publication.

Regarding the comparison of the findings for the Strong Heart Study (SHS) and the Strong Heart Family Study (SHFS) for the association between urinary zinc levels and T2DM, we argue that the findings are largely consistent in the direction of the association, although they differ in statistical power, with a statistically significant association in the SHS and a nonsignificant association in the SHFS. This is the first study to assess the association between urinary zinc levels and incident T2DM in two cohorts with different ages. The SHS has an older population (median age 53.9 years vs. 35.9 years in the SHFS) with lower estimated glomerular filtration rate, estimated by the Chronic Kidney Disease Epidemiology Collaboration formula (100.4 vs. 118.7 mL/min/1.73 m^2), and higher fasting plasma glucose levels (101 vs. 93 mg/dL) compared with participants from the SHFS. We hypothesized that a younger population presents other compensatory mechanisms that regulate zinc metabolism. However, as these results are novel, more epidemiological studies would be necessary to support this hypothesis. Similarly, we do not have a clear explanation for the stronger association between urinary zinc and T2DM in participants with lower BMI in the SHFS but among participants with higher BMI in the SHS. Again, this could be related to age, kidney function, and metabolic state differences across both cohorts, although we cannot discard unstable findings in interaction analyses in studies due to the limited number of events in some of the strata.

We have conducted additional analyses for the possible interaction of urinary zinc with incident T2DM by urinary arsenic, selenium, and cadmium. We found no evidence of a possible interaction for any of these metals.

Following the suggestions of Yang et al. (1), we estimated the prevalence ratio using Poisson regression with robust standard error for the association of urinary zinc with prediabetes, finding consistent results.

Finally, we appreciate the authors' suggestion about considering mediation models to evaluate metal mixtures and T2DM. This was beyond the scope of the current article, which had urinary zinc as its main focus. We agree, however, that mixture analysis can yield important novel information regarding the connection of metal exposure and metabolism with incident T2DM, and we aim to consider those strategies in future studies.

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

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