Differential association of sugar-sweetened beverages in men and women: is it the sugar or calories?

Dear Sir:

The findings from the recent study by Tasevska et al (1) suggest that there is a difference in response to sugars between women and men. Similar to other cohort studies that found a sex difference for soda intake and stroke risk (2), Tasevska et al reported a significant positive cardiovascular mortality trend with greater intakes of sugar from beverages in women but not in men (1). Although the difference in sex physiology is a plausible explanation for these associations, the consideration for other differences in sex responses is necessary in the interpretation of these analyses.

The authors adjusted for total energy intake in their models. Taking this approach reduces the effect of potential confounding but does not address the underlying limitation of energy intake measurements: underreporting, which may lead to overestimation of the association between exposure and outcome. Although the Diet History Questionnaire used in the study has been validated and shown to have moderate correlations with 24-h recalls for added sugar as assessed (0.68 in men and 0.79 in women) (3), the OPEN (Observing Protein and Energy Nutrition) Biomarker Study reported that the Diet History Questionnaire is still significantly limited by underreporting of energy intake (4). The underreporting of energy intake is concerning because a recent assessment of the validity of self-report dietary intake from 24-h recalls found that more than two-thirds of women have energy estimates that are not physiologically plausible (5). Furthermore, women also tend to underreport their energy intake much more than men (by ~365 kcal/d in women and ~281 kcal/d in men) (5). This inability to provide accurate estimations of energy intake limits our ability to interpret data and may have a significant impact on clinical decisions. Therefore, even when energy intake is adjusted in association models, these association models may not necessarily be free from the confounding effect of energy.

Other lines of high-quality evidence from systematic reviews and meta-analyses of controlled trials have shown excess energy to be an important mediating factor in the effects of fructose on cardiometabolic risk. In a series of Canadian Institutes of Health Research–funded (clinicaltrials.gov identifier NCT01363791) systematic reviews and meta-analyses of controlled feeding trials, we found that fructose in isocaloric exchange for other carbohydrates (energy-matched conditions between the fructose and carbohydrate comparator arms) showed no signal for harm in relation to body weight (6), fasting and postprandial lipids (7), glycemic control (8), insulin (8), blood pressure (9), and uric acid (9) and markers of nonalcoholic fatty liver disease (10). Although there may be a dose threshold for fasting lipids in some subgroup analyses (7), an overall lack of harm is seen even under conditions of fructose overfeeding (positive energy balance) at high doses, as long as the comparison with the carbohydrate comparator remains matched for the excess calories. A consistent signal for harm is only seen in imbalanced, hypercaloric comparisons, in which fructose supplements control diets with excess calories compared with the same control diets alone without the excess calories. In the absence of a clear effect on cardiometabolic risk factors in isocaloric comparisons (especially under conditions of positive energy balance), fructose does not appear to be any worse than other refined carbohydrates. The implication is that the adverse effects seen in the hypercaloric comparisons relate to the excess energy rather than the fructose. Consideration for total energy intake would therefore seem to be essential in understanding whether an association with fructose exists beyond the energy it contributes.

In conclusion, underreporting of energy complicates the interpretation of the association between sugar intake and cardiovascular mortality risk. This issue is especially important when considering the response observed in women because they are more likely to underreport their energy intake than men. To address the issue of energy as a confounding factor, isocaloric randomized controlled trials are needed to isolate the true effect of sugar intake, independent of energy intake, on cardiovascular health.

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Reply to V Ha et al

Dear Sir:

We thank Ha et al for their comments on our findings from the analysis of dietary sugars and mortality risk in a large US cohort study (1). In their letter, Ha et al claim that the positive associations for sugars and cardiovascular vascular disease (CVD) mortality risk in women observed in our study may have been overestimated due to energy underreporting, which is more common in women. First, we would like to clarify that, although we did not find added total sugars from beverages to be positively associated with CVD mortality risk in men, there was a significant increase in risk with greater intake of fructose from beverages in both men (HR for quartile 5 compared with quartile 1: 1.13; 95% CI: 1.05, 1.22; P-trend = 0.001) and women (HR for quartile 5 compared with quartile 1: 1.14; 95% CI: 1.02, 1.28; P-trend = 0.002). Furthermore, in both men and women, there was a borderline increased risk for CVD mortality with high total sugars and fructose intake (P-trend = 0.08–0.09) (Table 2 in reference 1).

Ha et al argue that adjusting for energy intake “reduces the effect of potential confounding variables but does not address the underlying limitation of energy intake measurements: underreporting, which may lead to overestimation of the association between exposure and outcome.” In fact, adjusting for energy intake has been recommended in analyses of nutritional cohort studies as an approach to alleviate measurement error and attenuation of RR estimate in multivariable disease risk models with self-reported dietary variables measured with error (2, 3). We used the nutrient density method to adjust for energy intake, in which total energy and nutrient densities (g/1000 kcal) were entered in the multivariable models. In the Observing Protein and Energy Nutrition (OPEN) study, using the predictive biomarker for total sugars intake, we showed that the disease risk attenuation would be much less severe, albeit still present, when using total sugars density (g/1000 kcal) rather than absolute intake (g/d), as measured by the Diet History Questionnaire (4). Similar to findings for self-reported energy with the use of doubly labeled water (5), we also found that measurement error in self-reported sugars and predicted risk attenuation was greater in women than in men (4). We would, therefore, expect that the risk estimates for sugars observed in our article may have been attenuated and thus underestimated, rather than being overestimated as claimed by Ha et al. More important, to further investigate the Observing Protein and Energy Nutrition possible effect of energy underreporting, the main analyses were re-run after excluding potential energy underreporters identified by the Goldberg cutoffs, which more than halved the sample size and the

REFERENCES
