RESPONSE TO COMMENT ON CHEN ET AL.

Ultra-Processed Food Consumption and Risk of Type 2 Diabetes: Three Large Prospective U.S. Cohort Studies. Diabetes Care 2023;46:1335–1344

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We have read with interest the letter by Gomes et al. (1) suggesting that methodological artifacts biased some of our analyses on the relationship between ultra-processed food (UPF) subgroups and risk of type 2 diabetes (T2D) (2). We would like to take the opportunity to demonstrate how that is unlikely to be the case.

Potential multicollinearity between total UPF, UPF groups, and UPF subgroups was the first concern. In the main analyses, total UPF intake was quantified using servings/day (Table 2 in our article). In sensitivity analyses, total UPF intake was modeled using four alternative metrics: calories (kcal) from UPF/day, percentage of kcal from UPF/day, percentage of grams from UPF/day, and energy-adjusted servings of UPF/day (Supplementary Table 5 in our article). None of these analyses were affected by multicollinearity, as only total UPF intake was included in the models. We additionally investigated the relationships between nine different UPF groups and T2D risk (Fig. 1 in our article). The groups were simultaneously included in the models, without total UPF intake. Correlation coefficients between intakes of these nine subgroups were considerably low, ranging from −0.02 to 0.35. Finally, we repeated the analyses by expanding three groups (ultra-processed breads and cereals, packaged sweet snacks and desserts, and artificially and sugar-sweetened beverages) into subgroups, including a total of 14 groups and subgroups in the models. Again, the correlations between groups and subgroups were minor, with coefficients ranging from −0.23 to 0.35, suggesting that multicollinearity would not have undermined the reliability of our results.

Concerns with risk of false-positive findings due to multiple testing in group/subgroup analyses were also raised. UPF groups/subgroups with a significant relationship with T2D risk had *P* values <0.0001. The only exceptions were yogurt and dairy-based desserts and ultra-processed dark breads and whole-grain breads, for which the *P* value was 0.005. Setting statistical significance to 0.006 (i.e., 0.05/9 comparisons) to account for multiple testing would still allow for these results to be considered significant or marginally significant. As mentioned in the article, the inverse associations between T2D risk and packaged sweet snacks and desserts as well as packaged savory snacks remain unclear, and residual confounding cannot be ruled out.

Third, it was highlighted that non-UPF consumption was similar across quintiles of UPF intake, and, as a result, the use of servings/day instead of proportional contribution of non-UPF to total energy introduced confounding. In fact, we repeated all our analyses using four alternative metrics for UPF, including with proportional contribution to total energy as well as by controlling for non-UPF intake rather than total energy (Supplementary Tables 5 and 6). The consistency in our findings across multiple metrics and approaches underscores the confidence in our original results.

Fourth, the letter offers suggestions for isocaloric replacement analyses. Our article did not include such analyses, although we could certainly consider substitution analyses in future research.

Overall, we are confident in our conclusions that are supported by the data. Our study supports the recommendations of limiting total UPF consumption, especially those associated with a higher risk of T2D.

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