



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 read with great interest the study by Chen et al. (1), which adds further robust evidence that dietary patterns based on ultra-processed products (UPP) increase the risk for incident type 2 diabetes (T2D). However, as for the attempt to investigate the associations of specific groups and subgroups of UPP with T2D, here we argue that methodological artifacts may explain the findings on putative protective associations of some UPP groups and subgroups with T2D.

First, the multivariable models have ignored the evident multicollinearity between total UPP, UPP group, and UPP subgroup intake added to models, particularly in food frequency questionnaires studies (2). Multicollinearity can obscure true relationships between exposure and outcome variables. It can lead to unreliable estimates, making it difficult to adequately determine individual associations of each correlated exposure variable (e.g., total UPP, UPP groups, and UPP subgroups) with an outcome of interest (e.g., T2D). Overall, multicollinearity makes it difficult to draw meaningful conclusions about the relationships between variables.

Second, false-positive findings may be inflated in subgroup analyses (3), raising concerns about the validity of statistical

inferences given appropriate adjustments for multiple comparisons were not conducted in the various subgroup analyses (4).

Third, a lack of information on UPP and non-UPP (e.g., fruits, vegetables, and whole grains) serving sizes may impede the interpretability of the subgroup analyses. Considering that non-UPP servings/day were similar across fifths of UPP intake, even if included in the multivariable models, measured as such they would offer no contrast to explain variations on T2D risk. Since the total energy intake increases as UPP intake increases, the proportional contribution of non-UPP (e.g., fruits, vegetables, and whole grains) to total energy may decrease from lower to higher fifths of UPP intake. Such contrast was lost by considering servings/day instead of the caloric share of such non-UPP to factor in their associations with T2D. In addition, collinearity is more pronounced in crude intake (such as servings/day used by the authors) versus density intake (i.e., proportional to energy intake) measures (5).

Fourth, the analyses on the isocaloric replacement of a given UPP subgroup intake falsely assumed that an equivalent amount of energy intake would be evenly

redistributed across all the other foods consumed, regardless of their category or levels of processing. We argue that an equivalent subgroup of non-UPP should have been used as comparators in the isocaloric replacement analyses.

These limitations might explain some of the reported protective associations of groups and subgroups of UPP with T2D. Furthermore, when explaining the putative protective associations of dairy-based desserts, reverse causation was mentioned as a potential explanation, but the same argument was not considered for other groups or subgroups of UPP.

Therefore, we argue that methodological artifacts are likely the most plausible explanation for the findings on the protective associations of UPP subgroups with T2D.

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