

**** Comments from the external peer reviewers****

→ We would like to sincerely thank the Editor and Reviewer for their valuable comments and suggestions in this second revision. All of them have been carefully taken into account. We believe that they truly contribute to further improve the quality, the overall presentation and the clarity of our manuscript. Below, please find a point by point description of how each comment was addressed in the manuscript.

Reviewer: 1

Recommendation:

Comments:

The authors try to clarify what is ultra-processed food; however, the definition is still not clear and hard to distinguish with those of not ultra-processed food.

→ We have further elaborated the definition of ultra-processed food in the Methods section of the revised manuscript (page 8) to help the reader understand the classification and distinguish between the ultra-processed categories and the other classes for which definition and examples have been given as well. This section now reads:

“All food and beverage items of the NutriNet-Santé composition table were categorized into one of the four food groups in NOVA, a food classification system based on the extent and purpose of industrial food processing¹⁻³. This study primarily focused on the “ultra-processed foods” NOVA group. This group includes mass-produced packaged breads and buns, sweet or savoury packaged snacks, industrialized confectionery and desserts, sodas and sweetened beverages, meat balls, poultry and fish nuggets and other reconstituted meat products transformed with addition of preservatives other than salt (e.g nitrites), instant noodles and soups, frozen or shelf-stable ready meals, and other food products made mostly or entirely from sugar, oils, and fats and other substances not commonly used in culinary preparations such as hydrogenated oils, modified starches, and protein isolates. Industrial processes notably include hydrogenation, hydrolysis, extruding, moulding, reshaping, and pre-processing by frying. Flavouring agents, colours, emulsifiers, humectants, non-sugar sweeteners and other cosmetic additives are often added to these products to imitate sensorial properties of unprocessed or minimally processed foods and their culinary preparations or to disguise undesirable qualities of the final product. The ultra-processed food group is defined by opposition to the other NOVA groups: “unprocessed or minimally processed foods” (fresh, dried, grounded, chilled, frozen, pasteurized or fermented staple foods such as fruits, vegetables, pulses, rice, pasta, eggs, meat, fish or milk), “processed culinary ingredients” (salt, vegetable oils, butter, sugar and other substances extracted from foods and used in kitchens to transform unprocessed or minimally processed foods into culinary preparations) and “processed foods” (canned vegetables with added salt, sugar-coated dry fruits, meat products only preserved by salting, cheeses and freshly made unpackaged breads, and other products manufactured with the addition of salt, sugar or other substances of the “processed culinary ingredients” group). As previously described⁴, home-made and artisanal food preparations were identified and decomposed using standardized recipes, and the NOVA classification was applied to their ingredients. Precisions and examples are presented in Appendix I.”

We have also provided some concrete examples in the Appendix 1, notably helping the reader understand the distinction between ultra-processed and processed products:

“For instance, fruit compotes with only added sugar are considered as “processed foods”, while flavoured fruit desserts with added sugar, texturizing agents and colorants are considered as “ultra-processed foods”.

Regarding meats, salted-only red or white meats are considered as “processed foods” whereas smoked or cured meats with added nitrites and conservatives, such as sausages and ham are classified as “ultra-processed foods”.

Similarly, canned salted vegetables are considered as “processed foods” whereas industrial cooked or fried seasoned vegetables, marinated in industrial sauces with added flavourings are considered as “ultra-processed foods”.”

Moreover, we have added, as secondary analyses in the Results section page 19, the results of Cox models for associations between the other NOVA categories and cancer risk:

“As a secondary analysis, associations between the proportions of the three other NOVA degrees of food processing and cancer risk were also tested. No significant associations were found between the proportions of “processed culinary ingredients” nor “processed foods” with cancer risk at any location (all $p > 0.05$). However, and consistently with our findings, the consumption of “minimally/unprocessed foods” was associated with lower risks of overall and breast cancers ($HR_{\text{for a 10-point increment in the proportion of unprocessed foods in the diet}} = 0.91 (0.87-0.95)$, $P < .0001$, 2228 cases and 102752 non-cases for overall cancer, $HR = 0.42 (0.19-0.91)$, $P = 0.03$, 739 cases and 81420 non-cases for breast cancer), in multivariable analyses adjusted for model 1 covariates.”

The western dietary pattern was derived from the dietary intake and the dietary lipid, sodium, carbohydrate were also derived from dietary intake. They were both adjusted in model 4.

→ The Western dietary pattern and individual macro-nutrients intakes are two distinct indicators of the nutritional quality of the diet. The Western dietary pattern provides an indicator of the overall diet and was derived from 20 food groups (in g/day), as detailed in Appendix 2. Nutritional intakes (in macro or micronutrients) were not used to derive dietary patterns. Although the Western pattern and macronutrient intakes were associated (which is not prohibited for covariates in a Cox model), they were far from being collinear (which would have introduced instability into the model), as shown by Pearson correlation coefficients with the Western dietary pattern, which were 0.5 for dietary lipids, 0.6 for sodium and 0.40 for carbohydrates. We have added this information in the footnote to Table 2, page 17.

The important point anyway is that results remained very similar across the different adjustments tested (model 1: no adjustment for the Western pattern or macronutrients; model 2: adjustment for the Western pattern; model 3: adjustment for the macronutrients; model 4: adjustment for both), which argues in favor of a high stability of the model.

The author adjusted the fruits and vegetable intake. Fruits and vegetable contributed to 15% of the ultra-processed food. How did the author deal with overlap-consideration?

→ The overlap is very minor here. Indeed, ultra-processed foods contributed to only 15% of total ultra-processed food intake. Besides, the adjustment tested was for total fruit and vegetable

intake (and not only ultra-processed fruits and vegetables), in order to exclude a potential protective effect of fruit and vegetable on cancer risk and thus potential confounding by this factor. We have clarified this point by replacing the term “adjustment for fruit and vegetable consumption” in the results section page 19 by “adjustment for overall fruit and vegetable consumption”, and by replacing the term “Fruits and vegetables” in figure 1 by “Ultra-processed fruits and vegetables”.

This further adjustment for fruit and vegetable intake is not part of the main model and has indeed been tested upon request of a Reviewer during the first revision. It did not modify the findings nor introduced instability into the model.

Since the author added the mediation analysis which is complex. So can you show the detailed table of such results?

→ A Table showing the detailed results of the mediation analyses has been added in Appendix 3.

The author said ” 5% of values were missing and were imputed to the modal value”. How did the author impute? with which method?

→ For all covariates with a very low proportion of missing values (<5%), the latter were replaced by the modal value among the population study (for categorical variables) or to the median (for continuous variables). Corresponding values have been added in the footnote to Table 1, page 14.

Besides, we had tested other methods to deal with missing data, such as multiple imputation⁵ and complete case analysis (i.e. exclusion of participants with at least one missing data for a covariate). The results were very similar: for the multiple imputation analysis: HR_{for a 10-point increment in the proportion of ultraprocessed foods in the diet}=1.11 (1.06-1.17), P<0.0001, 2228 cases and 102752 non-cases for overall cancer, HR=1.11 (1.01-1.21), P=0.02, 739 cases and 81420 non-cases for breast cancer; and for the complete case analysis: HR =1.11 (1.05-1.18), P=0.0003, 1813 cases and 82824 non-cases for overall cancer, HR=1.14 (1.03-1.26), P=0.01, 579 cases and 64642 non-cases for breast cancer. We have added this information in the manuscript page 19.

The author added the sensitivity analysis and stratified analysis, the results is based on which model? which confounders are adjusted?

→ We apologize if this point was not clear. Sensitivity and stratified analyses were all based on the main model, i.e. Model 1. Thus, they were adjusted for the covariates of Model 1, as defined in the Statistical analysis section and in footnotes to table 2. We have clarified this point in the Methods section page 11, and throughout the Results section pages 15, 18 and 19.

In appendix 2, the health pattern the first dominant factor and the western pattern is the second factor. Please specify the variance and proportion explained by each factor, which were extracted from the principal component analysis.

→ The proportions of variance explained by the Healthy and the Western patterns were respectively 10.6% and 7.0%. This information has been added in Appendix 2. This order of

magnitude is similar (and even higher) to the one generally observed in such *a priori* dietary pattern analyses⁶⁻⁸.

We primarily tested the adjustment for the Western pattern because we first wanted to eliminate the hypothesis that the observed associations between ultra-processed food intake and cancer risk was only due to a low overall nutritional quality of the diet among people eating larger amounts of ultra-processed foods. In secondary analyses (already mentioned in the manuscript page 19), we also checked that the results were unchanged after adjustment for the Healthy dietary pattern. As stated previously, none of these adjustments modified the findings.

References

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