Author’s response to reviews

Title: Prospective association between ultra-processed food consumption and incident depressive symptoms in the French NutriNet-Santé cohort

Authors:

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Version: 1 Date: 14 Dec 2018

Author’s response to reviews:

Dear Doctor Recchioni,

Please find attached the revised version of our manuscript BMED-D-18-01380 entitled, “Prospective association between ultra-processed food consumption and incident depressive symptoms in the French NutriNet-Santé cohort” which has been extensively modified in line with the Reviewers’ comments. Changes can be seen in the revised version, highlighted in yellow.

Below you will find our point-by-point reply.

We hope that our revised manuscript is now suitable for publication.

Thank you for your consideration.
Yours sincerely,

Moufidath Adjibade

RESPONSE TO BMC Medicine

Manuscript No.: BMED-D-18-01380

Title of Paper: Prospective association between ultra-processed food consumption and incident depressive symptoms in the French NutriNet-Santé cohort

Point-to-point reply

General note

We appreciate the comments made by the Reviewers and believe that their consideration has substantially improved our manuscript. Based on the Reviewers’ suggestions, we have extensively revised our manuscript so as to address the points raised.

Reviewer #1: This is an interesting paper that explores the relationship between Ultra-processed food consumption and incident depressive symptoms.

The authors offer a rigorous methodology and the topic is of great interest, but I do have some concerns regarding the following aspects:

We thank the reviewer for this positive evaluation of our work.

- Inclusion criteria are not clearly stated, except for presence of depressive symptoms and the use of antidepressants. Were those the only exclusion criteria or were there additional criteria, such as the presence of a cognitive impairment?

In this study, the presence of a cognitive impairment was not considered. Only the absence of availability of valid dietary data (at least 3 dietary records during the first two years of follow-up, no under-reporting of food consumption) and reporting of depression or treatment with antidepressants during the food data collection) were considered as exclusion criteria.

Besides, inclusion criteria were:

- Have received at least twice the CES-D questionnaire (included between 2009 and 2012; the CES-D questionnaire is sent to all participants included in the cohort every two years after inclusion);

- Have completed at least two of these questionnaires;
Do not present depressive symptoms at the first CES-D assessment.

We have now better clarified the inclusion and exclusion criteria of the study. The paragraph now reads as follows:

“The inclusion criteria in this study were: 1) have received at least twice the CES-D questionnaire (included between 2009 and 2012), 2) completed at least two of these questionnaires, and 3) not present depressive symptoms at the first CES-D assessment. Among the participants who met these criteria (n=35,782), we excluded participants without valid dietary data (participants with less than 3 dietary records during the first two years of follow-up and under-reporters) and the participants who had reported depression or treatment with antidepressants during the dietary data collection. Thus, a final study sample of 26,730 participants was obtained (Figure 1).” (Methods section - Statistical analysis, page 9, lines 194-201)

How the age is distributed within the study sample should be described. Older people may experience a cognitive deficit which has been often observed to be associated with depressive symptoms. Unless subjects with reduced cognitive functions have been excluded from the analyses, cognitive status should be accounted for in the analysis, especially in an older population.

This study included participants aged 18-86 years, with a mean age of 47.3 (SD=14.2) years.

The following figure shows the distribution of age in our study sample.

We entirely agree that cognitive impairment may be an important confounding factor. In the NutriNet-Santé cohort, cognitive deficits data are not available. However, subjective memory complaints were measured concomitantly with the depressive symptoms scale using the French version of the validated self-administered Cognitive Difficulties Scale (CDS) [1, 2]. We have now presented an additional model that takes into account this data.

The new main results are presented below:

<table>
<thead>
<tr>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
<th>P-trendContinuous a</th>
<th>P b</th>
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<tbody>
<tr>
<td>UPF, range</td>
<td>0%-10%</td>
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<td>19%-76%</td>
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<tr>
<td>UPF, median (IQR)</td>
<td>7% (3%)</td>
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</tr>
<tr>
<td>n</td>
<td>6,682</td>
<td>6,683</td>
<td>6,683</td>
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<td>26,730</td>
</tr>
<tr>
<td>Number of cases</td>
<td>491</td>
<td>459</td>
<td>557</td>
<td>714</td>
<td>2,221</td>
</tr>
<tr>
<td>Person years</td>
<td>21,597</td>
<td>21,097</td>
<td>20,468</td>
<td>19,918</td>
<td>83,080</td>
</tr>
<tr>
<td>Model</td>
<td>1 (ref)</td>
<td>Hazard Ratio (95% CI)</td>
<td>Hazard Ratio (95% CI)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1c</td>
<td>0.90 (0.79; 1.02)</td>
<td>1.07 (0.94; 1.21)</td>
<td>1.31 (1.16; 1.47)</td>
<td></td>
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<tr>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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<tr>
<td>2d</td>
<td>0.91 (0.80; 1.04)</td>
<td>1.09 (0.96; 1.23)</td>
<td>1.30 (1.15; 1.47)</td>
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<tr>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
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</tr>
<tr>
<td>3e</td>
<td>0.91 (0.80; 1.04)</td>
<td>1.08 (0.95; 1.23)</td>
<td>1.29 (1.13; 1.47)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4f</td>
<td>0.92 (0.81; 1.04)</td>
<td>1.09 (0.97; 1.24)</td>
<td>1.31 (1.16; 1.48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5g</td>
<td>0.88 (0.77; 1.00)</td>
<td>1.00 (0.88; 1.13)</td>
<td>1.13 (1.00; 1.28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.14 (1.09; 1.20)</td>
<td>&lt;0.0001</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6h</td>
<td>0.88 (0.78; 1.00)</td>
<td>1.06 (0.94; 1.20)</td>
<td>1.27 (1.13; 1.44)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are hazard ratios (95% confidence intervals). CDS Cognitive Difficulties Scale; CES-D Center for Epidemiologic Studies Depression Scale; IQR Interquartile Range; UPF Proportion of ultra-processed food intake

a Hazard ratios for 10% increase in the proportion of ultra-processed food intake

b P for continuous variable

c Adjusted for age, sex and body mass index

d Adjusted for all variables in model 1 + marital status, educational level, occupational categories, household income per consumption unit, residential area, number of 24h-dietary records, inclusion month, energy intake without alcohol, alcohol intake, smoking status and physical activity (main model)

e Adjusted for all variables in model 2 + dietary patterns derived from the factor analysis (“Healthy” and “Western” dietary pattern) and intakes of lipids, sodium, and carbohydrates
f Adjusted for all variables in model 2 + health events during follow-up (cancer, Type 2 diabetes, hypertension and cardiovascular events)

g Adjusted for all variables in model 2 + use of antidepressants during follow-up and the baseline CES-D score

h Adjusted for all variables in model 2 + CDS score

The different sections have been modified accordingly.

Abstract:

“After accounting for a wide range of potential confounders, an increased risk of depressive symptoms was observed with an increased %UPF in the diet. In the main model adjusted for sociodemographic characteristics, body mass index and lifestyle factors, the estimated hazard ratio for a 10% increase in UPF was 1.21 (95% confidence interval= 1.15-1.27).” (Abstract - Results, page 2, lines 38-42)

Methods section:

“In addition, subjective memory complaints were measured concomitantly with depressive symptoms scale using the French version of the validated self-administered Cognitive Difficulties Scale (CDS) [1, 2].” (Methods section - Covariates, page 8, lines 189-191)

And

“The first model was adjusted for age, sex, and BMI (continuous variable). The second model (main model) was additionally adjusted for marital status, educational level, occupational categories, monthly household income per consumption unit, residential area, energy intake without alcohol, number of 24h records and inclusion month, smoking status, alcohol consumption and physical activity. Four additional models were also performed to account for a) PCA-extracted dietary patterns and intake of carbohydrates, lipids and salt); b) health events occurring during follow-up (cancer, type 2 diabetes and cardiovascular diseases); c) baseline CES-D score (continuous variable) and use of antidepressants during the follow-up and d) CDS score (continuous variable).” (Methods section - Statistical analysis, page 10, lines 221-229)
Results section:

“In the main model adjusted for sociodemographic and lifestyle data, a strong and linear relationship was observed between %UPF in the diet and the risk of incident depressive symptoms. A 10% increase in %UPF in the diet was associated with a 21% (95%CI= 15%-27%) higher risk of depressive symptoms. Further adjustment for dietary patterns and dietary intakes (carbohydrates, lipids and sodium), health events or the CDS score did not substantially modify the association. However, after accounting for the use of antidepressants during follow-up and the baseline value for the CES-D score, the association was attenuated but remained significant (HR for a 10% increase in UPF in the diet= 1.14, 95%CI= 1.09-1.20). The proportional hazards assumption was evaluated using martingale residues and the assumption was acceptable (P=0.12 for the main model). The dose-response association between %UPF and incident depressive symptoms using Restricted Cubic Spline was also presented in Supplemental Figure 1 (p<0.0001 for the overall association).” (Results section, page 12, lines 271-282)

- Why the authors did not stratify their population by age instead of controlling for this factor? This would have made your study population less heterogeneous and possibly allowed different conclusions for different age groups.

As requested, we have now conducted age-stratified analyses (2 subgroups defined using the median value). Please see below.

<table>
<thead>
<tr>
<th>Age &lt; 49 years</th>
<th>Age ≥ 49 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>13,110 13,620</td>
</tr>
<tr>
<td>Number of cases</td>
<td>1349 872</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Age &lt; 49 years</th>
<th>Age ≥ 49 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI)</td>
<td>P</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Model 1b</td>
<td>1.22 (1.15; 1.29)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model 2c</td>
<td>1.19 (1.12; 1.27)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model 3d</td>
<td>1.23 (1.15; 1.32)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model 4e</td>
<td>1.19 (1.13; 1.27)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model 5f</td>
<td>1.14 (1.07; 1.21)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model 6g</td>
<td>1.20 (1.13; 1.28)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
a Hazard ratios for 10% increase in the proportion of ultra-processed food intake

b Adjusted for sex and body mass index

c Adjusted for all variables in model 1 + marital status, educational level, occupational categories, household income per consumption unit, residential area, number of 24h-dietary records, inclusion month, energy intake without alcohol, alcohol intake, smoking status and physical activity (main model)

d Adjusted for all variables in model 2 + dietary patterns derived from the factor analysis (“Healthy” and “Western” dietary pattern) and intakes of lipids, sodium, and carbohydrates

e Adjusted for all variables in model 2 + health events during follow-up (cancer, Type 2 diabetes, hypertension and cardiovascular events)

f Adjusted for all variables in model 2 + use of antidepressants during follow-up and the baseline CES-D score

g Adjusted for all variables in model 2 + CDS score

In order to avoid our manuscript to become too long and complex, only the results of the main model (model 2) were presented in the revised version of the manuscript.

Figure 2 Association between ultra-processed food intake and incident depressive symptoms in population subgroups

Results section have been modified accordingly.

“On the other hand, when considering the ratio of energy intake to energy needs, a significant interaction with %UPF was detected (P=0.04). Hence, analysis stratified according to this ratio (while using the sex-specific EI/BMR median value as cut-off: 1.34 for men and 1.32 for
women) were performed (Figure 2). The association between %UPF and the risk of depressive symptoms was stronger in participants with low energy intakes compared to their needs than their counterparts (HR for a 10% increase in UPF in the diet= 1.23, 95%CI=1.15-1.31 versus 1.19, 95%CI= 1.10-1.28; main model). Similarly, in the stratified analyses according to sex, age (using the median value), BMI (<25 vs. ≥ 25), comorbid conditions and factor loading for the « Healthy » pattern (using the sex-specific median value as cut-off: 0.04 for men and -0.11 for women), stronger associations were observed in the subgroups of women, participants aged ≥ 49 years, participants with a chronic disease, participants with a BMI value ≥ 25, and participants with a lower value for the factor loading of the « Healthy » pattern, compared to their respective counterparts (Figure 2). However, the estimated HR were similar in the subgroups and no significant interaction was observed (P value for the interaction term was 0.49 for sex, 0.46 for age, 0.59 for BMI, 0.88 for comorbidities and 0.18 for the factor loading of the « healthy » dietary pattern). In addition, in the stratified analyses according to the baseline CES-D score (using the sex-specific median value as cut-off: 6 for men and 8 for women) the association between %UPF and the risk of depressive symptoms was significant only among participants with a higher baseline CES-D score (P value for the interaction term was 0.13).” (Methods section, pages 12-13, lines 283-302)

- The area where the population comes from should be specified

The NutriNet-Santé cohort included volunteers from all regions of France. This information has now been clearly mentioned in the revised version of the manuscript.

The sentence now reads as follows:

“Details on the design and method have been previously described [3]. Participants are adult volunteers (aged ≥18 years) recruited from the general population (all regions of France) with access to Internet by a vast multimedia campaign.” (Methods section, page 4, lines 92-94)

Reviewer #2: The authors reported a positive association between the proportion of UPF (%UPF) in diet and incident depressive symptoms. The conclusion was drawn from a large prospective cohort. Although the paper concerns an interesting topic, I have some concerns:

1. It is unclear why so many subjects did not complete 2 CES-D questionnaire assessments (N=84,094). If possible, could the authors make some comparison of baseline characteristics between the excluded and included populations? Could the authors report how many subjects among them have completed the first assessment, then compare these participants with those who had at least 2 assessments?

Baseline characteristics of included participants and those excluded from eligible population were presented and compared in Supplemental Table 3.
As requested, we have now compared participants who completed 1 CES-D questionnaire with those who completed 2 CES-D questionnaires. Please see below.

Supplemental Table 2 Comparison of participants who completed one CES-D questionnaire to those who completed it at least two during follow-up, NutriNet-Santé study a

Baseline characteristics

<table>
<thead>
<tr>
<th>1 completed CES-D questionnaire</th>
<th>At least 2 completed CES-D questionnaires</th>
<th>P b</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>24,154</td>
<td>40,831</td>
</tr>
<tr>
<td>Age, y</td>
<td>42.2 ± 14.5</td>
<td>47.3 ± 14.1</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male</td>
<td>4,803 (19.9)</td>
<td>9,820 (24.0)</td>
</tr>
<tr>
<td>Female</td>
<td>19,351 (80.1)</td>
<td>31,011 (76.0)</td>
</tr>
<tr>
<td>Marital status, n (%)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Living alone</td>
<td>4,516 (18.7)</td>
<td>6,122 (15.0)</td>
</tr>
<tr>
<td>Cohabiting</td>
<td>17,315 (71.7)</td>
<td>30,194 (73.9)</td>
</tr>
<tr>
<td>Separated/Divorced/Widowed</td>
<td>2,323 (9.6)</td>
<td>4,515 (11.1)</td>
</tr>
<tr>
<td>Educational level, n (%)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&lt; High school diploma</td>
<td>4,610 (19.1)</td>
<td>8,440 (20.7)</td>
</tr>
<tr>
<td>High school diploma</td>
<td>4,084 (16.9)</td>
<td>6,469 (15.8)</td>
</tr>
<tr>
<td>University level</td>
<td>15,460 (64.0)</td>
<td>25,922 (63.5)</td>
</tr>
<tr>
<td>Occupational categories, n (%)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Never-employed/other activity</td>
<td>1,327 (5.5)</td>
<td>1,351 (3.3)</td>
</tr>
<tr>
<td>Self-employed</td>
<td>1,493 (6.2)</td>
<td>2,192 (5.4)</td>
</tr>
<tr>
<td>Employee</td>
<td>7,473 (30.9)</td>
<td>10,657 (26.1)</td>
</tr>
<tr>
<td>Intermediate profession</td>
<td>6,231 (25.8)</td>
<td>11,676 (28.6)</td>
</tr>
<tr>
<td>Managerial staff</td>
<td>7,630 (31.6)</td>
<td>14,955 (36.6)</td>
</tr>
</tbody>
</table>
Household income per consumption unit, n (%) <0.0001
Not answered 2,943 (12.2) 4,120 (10.1)
< 1200 euros 4,333 (17.9) 5,476 (13.4)
1200-1800 euros 6,163 (25.5) 9,674 (23.7)
1800-2700 euros 5,558 (23.0) 10,266 (25.1)
≥ 2700 euros 5,157 (21.4) 11,295 (27.7)

Residential area, n (%) <0.0001
Rural 5,182 (21.4) 8,917 (21.8)
Urban 18,972 (78.6) 31,914 (78.2)

Smoking status, n (%) <0.0001
Former smoker 7,942 (32.9) 14,897 (36.5)
Current smoker 4,189 (17.3) 5,283 (12.9)
Never-smoker 12,023 (49.8) 20,651 (50.6)

Physical activity c, n (%) <0.0001
Low 6,750 (27.9) 10,118 (24.8)
Moderate 5,907 (24.5) 9,691 (23.7)
High 11,497 (47.6) 21,022 (51.5)

Body mass index d, n (%) <0.0001
Underweight 1,260 (5.2) 1,940 (4.8)
Normal weight 15,335 (63.5) 26,225 (64.2)
Overweight 5,095 (21.1) 9,178 (22.5)
Obesity 2,464 (10.2) 3,488 (8.5)

Prevalence of chronic diseases e, n (%) 1,068 (4.4) 4,420 (10.9) <0.0001

Baseline CES-D score 12.4 ± 9.4 10.9 ± 8.7 <0.0001

CES-D Center for Epidemiologic Studies Depression Scale
a Values are means ± standard deviation or numbers (percentages) as appropriate

b P-values are based on T-test or chi-square test

c Physical activity was classified as low (< 30 minutes of physical activity; equivalent to brisk walking/day), moderate (30-60 min) and high (≥ 60 min)

d Body mass index (BMI) was classified as underweight (BMI < 18.5), normal weight (18.5 < BMI < 25), overweight (25 ≤ BMI < 30) and obesity (BMI ≥ 30)

e Incident cases of cancer, Type 2 diabetes, hypertension and cardiovascular diseases

In summary, compared to those who completed at least 2 CES-D questionnaires, participants who completed 1 CES-D questionnaire were younger, less physically active and more likely to be women, current smoker or living alone. They were also more likely to have a BMI value ≥30, a slightly higher baseline CES-D score, a household income per unit consumption < 1,800 or not having provided their income, and less likely to be managerial staff or to have an intermediate profession, or a chronic disease.

These findings are now presented in the Supplemental Table 2.

We have also added this sentence at the beginning of the results section.

“In the NutriNet-santé cohort, participants who completed only 1 CES-D questionnaire (n=24,154), compared to those who completed it at least 2 during follow-up (n=40,831) were younger, less physically active and more likely to be women, current smoker or living alone. They were also more likely to have a BMI value ≥30, a slightly higher baseline CES-D score, a household income per unit consumption < 1,800 or not having provided their income, and less likely to have a chronic disease, an intermediate profession or to be managerial staff (Supplemental Table 2).” (Results section, page 11, lines 249-255)

Perhaps subjects that completed the first but not the second assessment is more likely to have depressive symptoms. The authors should also describe this study limitation in the Discussion/limitation section.
Please see the following comment.

2. The survey included volunteers who might be more interested in health issues and all questionnaires and diet records were web-based self-administered, which may be associated with selection bias.

We have now mentioned these limitations in the revised version of the manuscript. The new paragraph reads as follows:

“Third, participants of the NutriNet-Santé study were volunteers in a nutrition-related cohort and thus more interested in nutritional issues and healthy lifestyles than the general population. In particular, their consumption of UPF may be lower than in the general population which may have led to an underestimation of the associations investigated in our study. In addition, excluding participants who completed only one CES-D questionnaire and participants with depressive symptoms at baseline might have resulted in excluding those most likely to have depressive symptoms. Similar analysis in this specific population should deserve further investigations. All this might have led to a selection bias and thus a potential bias in the risk estimates. As a result, any generalization of our findings should be done with caution.”
(Discussion section, page 17, lines 398-407)

3. Table 1 (baseline characteristics) revealed that CES-D scale is strongly associated with the quartiles of ultra-processed food consumption. Therefore, baseline CES-D scale should be adjusted in the final model.

Our main analysis strategy was to conduct a prospective study by identifying people without depressive symptoms. As requested by the reviewer, we have now considered the first CES-D score in an additional model.

The new main results are presented below:

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<td>714</td>
<td>2,221</td>
</tr>
<tr>
<td>Model</td>
<td>Hazard Ratio (95% CI)</td>
<td>p-value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1c</td>
<td>0.90 (0.79; 1.02)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2d</td>
<td>0.91 (0.80; 1.04)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3e</td>
<td>0.91 (0.80; 1.04)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4f</td>
<td>0.92 (0.81; 1.04)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5g</td>
<td>0.88 (0.77; 1.00)</td>
<td>1.14 (1.09; 1.20)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6h</td>
<td>0.88 (0.78; 1.00)</td>
<td>1.06 (0.94; 1.20)</td>
<td>1.27 (1.13; 1.44)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Values are hazard ratios (95% confidence intervals). CDS Cognitive Difficulties Scale; CES-D Center for Epidemiologic Studies Depression Scale; IQR Interquartile Range; UPF Proportion of ultra-processed food intake.

**a** Hazard ratios for 10% increase in the proportion of ultra-processed food intake

**b** P for continuous variable

**c** Adjusted for age, sex and body mass index

**d** Adjusted for all variables in model 1 + marital status, educational level, occupational categories, household income per consumption unit, residential area, number of 24h-dietary records, inclusion month, energy intake without alcohol, alcohol intake, smoking status and physical activity (main model)
Adjusted for all variables in model 2 + dietary patterns derived from the factor analysis (“Healthy” and “Western” dietary pattern) and intakes of lipids, sodium, and carbohydrates

Adjusted for all variables in model 2 + health events during follow-up (cancer, Type 2 diabetes, hypertension and cardiovascular events)

Adjusted for all variables in model 2 + use of antidepressants during follow-up and the baseline CES-D score

Adjusted for all variables in model 2 + CDS score

The different sections have been modified accordingly.

Abstract:

“After accounting for a wide range of potential confounders, an increased risk of depressive symptoms was observed with an increased %UPF in the diet. In the main model adjusted for sociodemographic characteristics, body max index and lifestyle factors, the estimated hazard ratio for a 10% increase in UPF was 1.21 (95% confidence interval= 1.15-1.27).” (Abstract - Results, page 2, lines 38-42)

Methods section:

“In addition, subjective memory complaints were measured concomitantly with depressive symptoms scale using the French version of the validated self-administered Cognitive Difficulties Scale (CDS) [1, 2].” (Methods section - Covariates, page 8, lines 189-191)

And

“The first model was adjusted for age, sex, and BMI (continuous variable). The second model (main model) was additionally adjusted for marital status, educational level, occupational categories, monthly household income per consumption unit, residential area, energy intake without alcohol, number of 24h records and inclusion month, smoking status, alcohol consumption and physical activity. Four additional models were also performed to account for a)
PCA-extracted dietary patterns and intake of carbohydrates, lipids and salt); b) health events occurring during follow-up (cancer, type 2 diabetes and cardiovascular diseases); c) baseline CES-D score (continuous variable) and use of antidepressants during the follow-up and d) CDS score (continuous variable).” (Methods section - Statistical analysis, page 10, lines 221-229)

Results section:

“In the main model adjusted for sociodemographic and lifestyle data, a strong and linear relationship was observed between %UPF in the diet and the risk of incident depressive symptoms. A 10% increase in %UPF in the diet was associated with a 21% (95%CI= 15%-27%) higher risk of depressive symptoms. Further adjustment for dietary patterns and dietary intakes (carbohydrates, lipids and sodium), health events or the CDS score did not substantially modify the association. However, after accounting for the use of antidepressants during follow-up and the baseline value for the CES-D score, the association was attenuated but remained significant (HR for a 10% increase in UPF in the diet= 1.14, 95%CI= 1.09-1.20). The proportional hazards assumption was evaluated using martingale residues and the assumption was acceptable (P=0.12 for the main model). The dose-response association between %UPF and incident depressive symptoms using Restricted Cubic Spline was also presented in Supplemental Figure 1 (p<0.0001 for the overall association).” (Results section, page 12, lines 271-282)

4. In introduction, the reasons why did the author study the association between UPF and depressive symptoms is not enough. What is the study basis of the hypothesize?

The present study is based on the fact that some western or pro-inflammatory diets are characterized by a high consumption of UPF, while these diets have been associated with an increased risk of developing depression [4–6].

Indeed, the UPF contain food additives and other molecules resulting from the transformation, which may amongst others cause alterations of the gut microbiota [7], involved in the physiopathology of mental disorders, including depression [8].

The investigation of the association between UPF consumption and the risk of depression is therefore a relevant question. However, to date, no study has explored the effect of UPF consumption on the risk of depression.

We have now revised the Introduction section as follows:

“On the opposite, a western dietary pattern or pro-inflammatory diet characterized among other things by more processed foods has been associated with poor mental health [4, 5, 9]. Previous studies that reported associations between these diets and depression considered nutritional
characteristics of the diet, and interaction within the food matrix. However some of those diets integrate a large part of ultra-processed food (UPF) (i.e. industrial recipes that are practical, ready to eat and palatable [10]) which consumption has drastically increased over the past decades [11, 12]. For instance, a recent American study reported that, between 2007-2012, about 60% of the overall energy intake was provided by UPF [13]. In the French NutriNet-Santé study, UPF contributed to 35.9% of the daily energy intake and the proportion of UPF (%UPF) in the diet has been associated with a poor overall quality of the diet [14].

While processing ensures improvement of food availability, digestibility, short-term safety, transportability, and storage life [15], UPF are often energy-dense, mostly very rich in fat, sugar and salt and poor in micronutrients, thus they may have a potential deleterious role on health. Beyond their unfavorable nutritional composition, they also contain other components generated during transformation such as neo-formed molecules produced during heating, food additives used in manufacturing and molecules migrated from packaging, some of which might have a detrimental role for gut microbiota [16], involved in the development of several diseases characterized by an inflammatory component (including depression) [17]. The investigation of the association between UPF consumption and health is therefore important.

Recent studies on the link between UPF consumption and health have shown a positive association between UPF consumption and obesity [18], hypertension [19], metabolic disorders [20] and cancer [21]. To date, no study has focused on mental disorders.

The purpose of the present study was thus to investigate for the first time the prospective association between %UPF in the diet and the risk of depressive symptoms using the data of the NutriNet-Santé cohort study.” (Introduction section - Statistical analysis, pages 3-4, lines 62-86)

5. The authors should provide detailed inclusion and exclusion criteria. For example, whether baseline chronic diseases, such as hypertension, diabetes, CVD and cancer were excluded or not, which may affect the incident depressive symptoms.

In this study, only the absence of availability of valid dietary data (at least 3 dietary records during the first two years of follow-up, no under-reporting of food consumption) and reporting of depression or treatment with antidepressants during the food data collection were considered as exclusion criteria.

Besides, inclusion criteria were:

- Have received at least twice the CES-D questionnaire (included between 2009 and 2012 ; the CES-D questionnaire is sent to all participants included in the cohort every two years after inclusion) ;

- Have completed at least two of these questionnaires;

- Do not present depressive symptoms at the first CES-D assessment.
We have now detailed the inclusion and exclusion criteria of the study.

The paragraph now reads as follows:

“The inclusion criteria in this study were: 1) have received at least twice the CES-D questionnaire (included between 2009 and 2012), 2) completed at least two of these questionnaires, and 3) not present depressive symptoms at the first CES-D assessment. Among the participants who met these criteria (n=35,782), we excluded participants without valid dietary data (participants with less than 3 dietary records during the first two years of follow-up and under-reporters) and the participants who had reported depression or treatment with antidepressants during the dietary data collection. Thus, a final study sample of 26,730 participants was obtained (Figure 1).” (Methods section - Statistical analysis, page 9, lines 194-201)

6. page 10 and 11, lines 237-243: "The first model (main model) was adjusted for age, sex, marital status, educational level, occupational categories, monthly household income per consumption unit, residential area, energy intake without alcohol, number of 24h records and inclusion month, smoking status, alcohol consumption, physical activity and BMI (continuous variable). Three additional models were created to also account for a) PCA-extracted dietary patterns, or b) nutrient intakes, namely carbohydrates, lipids and salt intakes or c) for health events occurring during follow-up (cancer, type 2 diabetes and cardiovascular diseases).” Is baseline health status adjusted?

In this cohort, health events reported at inclusion were considered as prevalent and only incident cases of major health events (cancer and some cardiovascular diseases) were validated by the medical committee. Thus, prevalent cases of major health events were not considered in our models.

7. Over a mean follow-up of 5.4 years, are there any lifestyle changes (including dietary, smoking, drinking, etc) among participants during follow-up?

We acknowledge that updating the exposure variable of interest is of high importance, but in the present study a strictly prospective design was used, consisting of using baseline exposure among participants without depressive symptoms to estimate the risk of developing depressive symptoms during the follow-up.

8. The prevalence of depressive symptoms is higher in males than in females. In the present study, is there a difference between males and females?

In this study, the prevalence of depressive symptoms was slightly higher among men than among women. We identified 573 incident cases of depressive symptoms (9.0%) among men and 1648 cases (8.1%) among women (p =0.02).
We have now mentioned these findings in the revised version.

“During follow-up (mean= 5.4, SD= 1.13 years), a total of 2,221 incident cases of depressive symptoms (9.0% in men and 8.1% in women; p=0.02) were identified.” (Methods section – Statistical analysis, page 11, lines 259-261)

9. Page 7, line 150-151: "validated against blood and urinary biomarkers [24]" It seems that only urinary biomarkers were mentioned in reference 24. Please clarify.

We thank the reviewer to point out this missing reference. Self-reported intake of fish, fruit and vegetables in the NutriNet-Santé study was also validated, but against biomarkers (plasma beta carotene, vitamin C, and n-3 polyunsaturated fatty acids) [22].

We have now added this reference in the revised version.

“The NutriNet-Santé web-based self-administered 24-hour dietary records have also been validated against blood and urinary biomarkers [23, 22].” (Methods section – Dietary data and UPF assessment, page 6, lines 125-127)

10. Page 11, lines 242 and 243: "c) for health events occurring during follow-up (cancer, type 2 diabetes and cardiovascular diseases).”; Table 1: "b Incident cases of cancer, Type 2 diabetes, and cardiovascular diseases". The incidence rate (34.6–44.0%) of chronic diseases is fairly high in this study. Please explain in detail.

We thank the reviewer to point out this mistake. We have now corrected it in the revised version.

Baseline characteristics

<table>
<thead>
<tr>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
<th>P-trend 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPF, range</td>
<td>0%-10%</td>
<td>10%-14%</td>
<td>14%-19%</td>
<td>19%-76%</td>
</tr>
<tr>
<td>n</td>
<td>6,682</td>
<td>6,683</td>
<td>6,683</td>
<td>6,682</td>
</tr>
<tr>
<td>Chronic diseases e, n (%)</td>
<td>741 (11.1)</td>
<td>724 (10.9)</td>
<td>683 (10.2)</td>
<td>559 (8.4)</td>
</tr>
</tbody>
</table>

e Incident cases of cancer, Type 2 diabetes, hypertension and cardiovascular diseases

11. Table 3 - Can the authors present the age, sex and BMI-adjusted model before the multivariate model?

As suggested by the reviewer, we have also presented an adjusted model for age, sex and BMI (Model 1). Please see below.
<table>
<thead>
<tr>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
<th>P-trend</th>
<th>Continuous b</th>
<th>P c</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPF, range</td>
<td>0%-10%</td>
<td>10%-14%</td>
<td>14%-19%</td>
<td>19%-76%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>6,682</td>
<td>6,683</td>
<td>6,683</td>
<td>6,682</td>
<td>26,730</td>
<td></td>
</tr>
<tr>
<td>Model 1d</td>
<td>1 (ref)</td>
<td>0.90 (0.79; 1.02)</td>
<td>1.07 (0.94; 1.21)</td>
<td>1.31 (1.16; 1.47)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.23 (1.17; 1.29)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2e</td>
<td>1 (ref)</td>
<td>0.91 (0.80; 1.04)</td>
<td>1.09 (0.96; 1.23)</td>
<td>1.30 (1.15; 1.47)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.21 (1.15; 1.27)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are hazard ratios (95% confidence intervals).

b Hazard ratios for 10% increase in the proportion of ultra-processed food intake

c P for continuous variable

d Adjusted for age, sex and body mass index

e Adjusted for all variables in model 1 + marital status, educational level, occupational categories, household income per consumption unit, residential area, number of 24h-dietary records, inclusion month, energy intake without alcohol, alcohol intake, smoking status and physical activity (main model)

12. Page 15, line 344-345: "more 370 scientific papers than" a typo, should be "more than 370 scientific papers"

We have corrected the sentence.

“However, a recent review based on more than 370 scientific papers reported that data are currently insufficient to conclude [24].” (Discussion section, page 16, lines 366-367)

13. A statistic test of the model's significance is also useful for demonstration. The authors need to assess the proportional hazards assumption, and report the result in the "Statistical Analysis" section.

As suggested by the reviewer, we have now reported the result of the proportional hazards assumption in the revised version of the manuscript.

The added sentences read as follows.

“The proportional hazards assumption was evaluated using martingale residues and the assumption was acceptable (P=0.12 for the main model).” (Results section, page 12, lines 279-280)
14. Please provide more detail on what cardiovascular diseases was included. Information on hypertension and hyperlipidemia would add much value to the paper.

The cases of cardiovascular diseases considered and validated in this study included incident cases of strokes, myocardial infarctions and acute coronary syndromes. Other health events were self-reported as well as specific treatment use.

This information has now been added in the Methods section.

The sentence now reads as follows:

“Prevalent and incident cases of cancer and cardiovascular diseases (strokes, myocardial infarctions and acute coronary syndromes) were self-reported during follow-up; incident cases were validated by a medical committee based on medical records (diagnosis, hospitalization, radiological reports, electrocardiograms, etc.), and a link was made with medico-administrative databases of the French National Health insurance. Type 2 diabetes and hypertension were self-reported or identified using specific medication.” (Methods section - Covariates, page 8, lines 183-189)

15. No interactions with chronic diseases and BMI were observed?

P-value for interaction was 0.88 for chronic diseases and 0.59 for BMI. However we have performed subgroups analyses. Please see below.

Stratified analyses according to body mass index

\[
\begin{align*}
\text{BMI} &< 25 \\
\text{BMI} &\geq 25 \\
\text{n} &
\end{align*}
\]

\[
\begin{align*}
\text{Number of cases} &
\end{align*}
\]

\[
\begin{align*}
\text{HR (95\% CI) a} &
\end{align*}
\]

\[
\begin{align*}
\text{P} &
\end{align*}
\]

\[
\begin{align*}
\text{HR (95\% CI) a} &
\end{align*}
\]

\[
\begin{align*}
\text{P} &
\end{align*}
\]

\[
\begin{align*}
\text{Model 1b} &
\end{align*}
\]

\[
\begin{align*}
1.24 (1.16; 1.31) &<0.0001 \\
1.22 (1.12; 1.33) &<0.0001 \\
\end{align*}
\]

\[
\begin{align*}
\text{Model 2c} &
\end{align*}
\]

\[
\begin{align*}
1.22 (1.15; 1.29) &<0.0001 \\
1.19 (1.09; 1.30) &0.0001 \\
\end{align*}
\]

\[
\begin{align*}
\text{Model 3d} &
\end{align*}
\]

\[
\begin{align*}
1.24 (1.16; 1.33) &<0.0001 \\
1.17 (1.07; 1.29) &0.001 \\
\end{align*}
\]

\[
\begin{align*}
\text{Model 4e} &
\end{align*}
\]

\[
\begin{align*}
1.22 (1.15; 1.30) &<0.0001 \\
1.19 (1.09; 1.30) &<0.0001 \\
\end{align*}
\]

\[
\begin{align*}
\text{Model 5f} &
\end{align*}
\]

\[
\begin{align*}
1.15 (1.08; 1.22) &<0.0001 \\
1.14 (1.04; 1.24) &0.01 \\
\end{align*}
\]

\[
\begin{align*}
\text{Model 6g} &
\end{align*}
\]

\[
\begin{align*}
1.22 (1.15; 1.30) &<0.0001 \\
1.19 (1.09; 1.30) &0.0001 \\
\end{align*}
\]
Values are hazard ratios (95% confidence intervals). CDS Cognitive Difficulties Scale; CES-D Center for Epidemiologic Studies Depression Scale; IQR Interquartile Range; UPF Proportion of ultra-processed food intake

a Hazard ratios for 10% increase in the proportion of ultra-processed food intake

b Adjusted for age and sex

c Adjusted for all variables in model 1 + marital status, educational level, occupational categories, household income per consumption unit, residential area, number of 24h-dietary records, inclusion month, energy intake without alcohol, alcohol intake, smoking status and physical activity (main model)

d Adjusted for all variables in model 2 + dietary patterns derived from the factor analysis (“Healthy” and “Western” dietary pattern) and intakes of lipids, sodium, and carbohydrates

e Adjusted for all variables in model 2 + health events during follow-up (cancer, Type 2 diabetes, hypertension and cardiovascular events)

f Adjusted for all variables in model 2 + use of antidepressants during follow-up and the baseline CES-D score

g Adjusted for all variables in model 2 + CDS score

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI) a</th>
<th>P</th>
<th>HR (95% CI) a</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1b</td>
<td>1.26 (1.07; 1.48)</td>
<td>0.01</td>
<td>1.23 (1.17; 1.30)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model 2c</td>
<td>1.25 (1.06; 1.47)</td>
<td>0.01</td>
<td>1.21 (1.15; 1.28)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model 3d</td>
<td>1.26 (1.06; 1.49)</td>
<td>0.01</td>
<td>1.23 (1.16; 1.30)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model 5e</td>
<td>1.12 (0.95; 1.32)</td>
<td>0.18</td>
<td>1.15 (1.10; 1.22)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model 6f</td>
<td>1.22 (1.03; 1.43)</td>
<td>0.02</td>
<td>1.22 (1.15; 1.28)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Stratified analyses according to comorbidities

Participants with chronic diseases

Participants without chronic diseases

n 2707 23939

Number of cases 238 1975
Values are hazard ratios (95% confidence intervals). CDS Cognitive Difficulties Scale; CES-D Center for Epidemiologic Studies Depression Scale; IQR Interquartile Range; UPF Proportion of ultra-processed food intake

a Hazard ratios for 10% increase in the proportion of ultra-processed food intake

b Adjusted for age, sex and body mass index

c Adjusted for all variables in model 1 + marital status, educational level, occupational categories, household income per consumption unit, residential area, number of 24h-dietary records, inclusion month, energy intake without alcohol, alcohol intake, smoking status and physical activity (main model)

d Adjusted for all variables in model 2 + dietary patterns derived from the factor analysis (“Healthy” and “Western” dietary pattern) and intakes of lipids, sodium, and carbohydrates

e Adjusted for all variables in model 2 + use of antidepressants during follow-up and the baseline CES-D score

f Adjusted for all variables in model 2 + CDS score

In order to avoid our manuscript to become too long and complex, only the results of the main model (model 2) were presented in the revised version of the manuscript.

Figure 2 Association between ultra-processed food intake and incident depressive symptoms in population subgroups

Results section have been modified accordingly.

“On the other hand, when considering the ratio of energy intake to energy needs, a significant interaction with %UPF was detected (P=0.04). Hence, analysis stratified according to this ratio (while using the sex-specific EI/BMR median value as cut-off: 1.34 for men and 1.32 for women) were performed (Figure 2). The association between %UPF and the risk of depressive symptoms was stronger in participants with low energy intakes compared to their needs than their counterparts (HR for a 10% increase in UPF in the diet= 1.23, 95%CI=1.15-1.31 versus 1.19, 95%CI= 1.10-1.28; main model). Similary, in the stratified analyses according to sex, age (using the median value), BMI (<25 vs. ≥ 25), comorbid conditions and fator loading for the « Healthy » pattern (using the sex-specific median value as cut-off: 0.04 for men and -0.11 for women), stronger associations were observed in the subgroups of women, participants aged ≥ 49 years, participants with a chronic disease, participants with a BMI value ≥ 25, and participants with a lower value for the factor loading of the « Healthy » pattern, compared to their respective
counterparts (Figure 2). However, the estimated HR were similar in the subgroups and no significant interaction was observed (P value for the interaction term was 0.49 for sex, 0.46 for age, 0.59 for BMI, 0.88 for comorbidities and 0.18 for the factor loading of the « healthy » dietary pattern). In addition, in the stratified analyses according to the baseline CES-D score (using the sex-specific median value as cut-off: 6 for men and 8 for women) the association between %UPF and the risk of depressive symptoms was significant only among participants with a higher baseline CES-D score (P value for the interaction term was 0.13).” (Methods section, pages 12-13, lines 283-302)

16. Because dementia is frequently associated with symptoms of depression, and the quality of the questionnaire was also affected by dementia, please consider excluding subjects with dementia in the final model.

We agree with the Reviewer regarding this important comment. Nevertheless, we cannot perform this sensitivity analysis because of validated data on the diagnosis of dementia are not available in this cohort study. However, subjective memory complaints were measured using the French version of the validated self-administered Cognitive Difficulties Scale (CDS) [1, 2]. As mentioned above, we have now presented an additional model that takes into account this data.

Reviewer #3:

Nice manuscript. Very interesting results and good methodology.

We thank the reviewer for this positive evaluation of our work.

Abstract: please mention the number of repeated 24 recalls and the proportion of men and women in the cohort.

We have now mentioned such information.

The new sentence reads as follows:

“The proportion of UPF in the diet was computed for each subject using the NOVA classification applied to dietary intakes collected by repeated 24h records (mean=8; SD=2.3).” (Abstract – Methods section, page 2, lines 32-34)

Methods: a simple table with the list of UPF is needed

In this study, more than 3,000 food items were evaluated using the NOVA classification and approximately 1,100 were classified as ultra-processed foods. It would therefore be difficult to provide a table with the list of ultra-processed foods.
Briefly, the UPF category includes packaged sweet and savory snacks, sodas and sweetened drinks, manufactured desserts, instant soups and noodle kits, prepared/reconstituted/transformed meat using nitrite preservatives (other than salt), packaged breads, ready-to-eat meals (cookies, confectionary, ice-cream, soft drinks etc.) and poultry and fish nuggets.

This information has now been better detailed in the methods section.

The paragraph now reads as follows:

“UPF are manufactured food products containing numerous ingredients as well as additives such as hydrogenated oils, non-sugar sweeteners, modified starch, flavoring agents, emulsifiers, humectants, colors, and other additives used for cosmetic purpose. This food category includes among others: mass-produced packaged breads and buns; breakfast "cereals", and "energy" bars; sweet or savory packaged snacks; Carbonated and "energy" drinks; sweet fruit-based desserts with added sugars, artificial flavours and texturizing agents; flavoured milk drinks and cocoa drinks; industrial cookies, pastries, cakes, and cake mixes; confectionery (ice-cream, chocolate, candies); meat and chicken extracts and "instant" sauces; margarines and spreads; cooked seasoned vegetables with ready-made sauces; ready-to-heat products (powdered and packaged "instant" soups, noodles and desserts, pre-prepared pies, pasta and pizza dishes, poultry and fish "nuggets", burgers, hot dogs, and other reconstituted meat products).” (Methods section – Classification of the level of processing, page 7, lines 157-165)

References: please add PMID: 29031185 (perhaps it can replace one of the older meta-analyses)

You can consider also the pro-inflammatory aspects. Please check: PMID: 30319085

Suggested references have been added.

“ On the opposite, a western dietary pattern or pro-inflammatory diet characterized among other things by more processed foods has been associated with poor mental health [4, 5, 9]. ”

(Introduction section, page 3, lines 62-63)

Results:

Please correct the typo "were was" in lines 271-272

Corrected

Lines 294-298 should be considerably expanded (see below) with further sensitivity analyses

The sensitivity analyses suggested by the Reviewer were conducted (according to sex, age, baseline levels of CES-D and baseline adherence to a high-quality dietary pattern).

Please see below.
Discussion

Please consider PMID: 21835082

This study has now been considered in the Discussion section.

The added sentence reads as follows:

“An increased risk of depression was also observed among the participants included in the Seguimiento Universidad de Navarra - University of Navarra Follow-up (SUN) Project, who were in the highest quintile of fast food (hamburgers, sausages, pizza) and processed pastries (muffins, doughnuts, croissants) compared with those in the lowest quintile (HRquintiles 5 vs. quintiles 1=1.37, 95%CI= 1.02-1.83) [25].” (Discussion section, page 15, lines 340-345)

Table 1,

please specify the units of measurement for "UPF, range"

In this study, we considered the proportion (in percentage) of UPF in the diet. There is no unit for this variable.

In the revised version of the manuscript, we have now written « % UPF ».

Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>% UPF, range</td>
<td>0%-10%</td>
<td>10%-14%</td>
<td>14%-19%</td>
<td>19%-76%</td>
</tr>
</tbody>
</table>

please correct the typo separated // separated

Corrected

Please clarify the superscript "3" used for physical activity, what is low / moderate or high physical activity? Please include cut-offs

please include the cut-off points for BMI

We have now added these information as footnotes in table 1 as follows.

Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
<th>P-trend b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical activity, n (%) c</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Low</td>
<td>1212 (18.1)</td>
<td>1473 (22.1)</td>
<td>1682 (25.2)</td>
<td>2014 (30.1)</td>
<td></td>
</tr>
</tbody>
</table>
Moderate   1478 (22.1)  1612 (24.1)  1660 (24.8)  1614 (24.2)
High     3992 (59.8)  3598 (53.8)  3341 (50.0)  3054 (45.7)

Body mass index d, n (%)   0.001
Underweight   294 (4.4)   276 (4.1)   272 (4.1)   350 (5.2)
Normal weight   4517 (67.6)  4459 (66.7)  4417 (66.1)  4323 (64.7)
Overweight   1448 (21.7)  1477 (22.1)  1522 (22.8)  1414 (21.2)
Obesity     423 (6.3)    471 (7.1)    472 (7.0)    595 (8.9)

c Physical activity was classified as low (<30 minutes of physical activity; equivalent to brisk walking / day) or moderate/high physical activity (≥30 minutes of physical activity; equivalent to brisk walking / day)

d Body mass index was classified as underweight (BMI <18.5), normal weight (18.5≥ BMI <25), overweight (25≥ BMI <30) or obese (BMI ≥30)

Table 2
Please clarify the meaning of the last row "Fats"

This food group includes sauces and added fats.

We have now mentioned it in the revised version of the manuscript.

Table 3
Please include the number of persons-years follow-up in each category

This has been added

Sensitivity analyses, you may include a forest plot with sensitivity analyses (highest vs. lowest quintiles of UPF) including the following analyses:

Please repeat the main fully-adjusted analysis but additionally adjusting for baseline CES-D scores

We have now considered the baseline CES-D score in an additional model. Please see below.

<table>
<thead>
<tr>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
<th>P-trendContinuous b</th>
<th>P c</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPF, range</td>
<td>0%-10%</td>
<td>10%-14%</td>
<td>14%-19%</td>
<td>19%-76%</td>
<td></td>
</tr>
<tr>
<td>UPF, median (IQR)</td>
<td>7% (3%)</td>
<td>12% (2%)</td>
<td>16% (2%)</td>
<td>23% (8%)</td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>---------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>6,682</td>
<td>6,683</td>
<td>6,683</td>
<td>6,682</td>
<td>26,730</td>
</tr>
<tr>
<td>Number of cases</td>
<td>491</td>
<td>459</td>
<td>557</td>
<td>714</td>
<td>2,221</td>
</tr>
<tr>
<td>Person years</td>
<td>21,597</td>
<td>21,097</td>
<td>20,468</td>
<td>19,918</td>
<td>83,080</td>
</tr>
</tbody>
</table>

**Model 1d**
- 1 (ref) 0.90 (0.79; 1.02)
- 1.07 (0.94; 1.21)
- 1.31 (1.16; 1.47)
- <0.0001

**Model 2e**
- 1 (ref) 0.91 (0.80; 1.04)
- 1.09 (0.96; 1.23)
- 1.30 (1.15; 1.47)
- <0.0001

**Model 3f**
- 1 (ref) 0.91 (0.80; 1.04)
- 1.08 (0.95; 1.23)
- 1.29 (1.13; 1.47)
- <0.0001

**Model 4g**
- 1 (ref) 0.92 (0.81; 1.04)
- 1.09 (0.97; 1.24)
- 1.31 (1.16; 1.48)
- <0.0001

**Model 5h**
- 1 (ref) 0.88 (0.77; 1.00)
- 1.00 (0.88; 1.13)
- 1.13 (1.00; 1.28)
- 0.01
- 1.14 (1.09; 1.20)
- <0.0001

**Model 6i**
- 1 (ref) 0.88 (0.78; 1.00)
- 1.06 (0.94; 1.20)
- 1.27 (1.13; 1.44)
- <0.0001

---

a Values are hazard ratios (95% confidence intervals). CDS Cognitive Difficulties Scale; CES-D Center for Epidemiologic Studies Depression Scale; IQR Interquartile Range; UPF Proportion of ultra-processed food intake.

b Hazard ratios for 10% increase in the proportion of ultra-processed food intake.

c P for continuous variable.

d Adjusted for age, sex and body mass index.
e Adjusted for all variables in model 1 + marital status, educational level, occupational categories, household income per consumption unit, residential area, number of 24h-dietary records, inclusion month, energy intake without alcohol, alcohol intake, smoking status and physical activity (main model)

f Adjusted for all variables in model 2 + dietary patterns derived from the factor analysis (“Healthy” and “Western” dietary pattern) and intakes of lipids, sodium, and carbohydrates

g Adjusted for all variables in model 2 + health events during follow-up (cancer, Type 2 diabetes, hypertension and cardiovascular events)

h Adjusted for all variables in model 2 + use of antidepressants during follow-up and the baseline CES-D score

i Adjusted for all variables in model 2 + CDS score

The different sections have been modified accordingly.

Abstract:
“After accounting for a wide range of potential confounders, an increased risk of depressive symptoms was observed with an increased %UPF in the diet. In the main model adjusted for sociodemographic characteristics, body max index and lifestyle factors, the estimated hazard ratio for a 10% increase in UPF was 1.21 (95% confidence interval= 1.15-1.27).” (Abstract - Results, page 2, lines 38-42)

Methods section:
“In addition, subjective memory complaints were measured concomitantly with depressive symptoms scale using the French version of the validated self-administered Cognitive Difficulties Scale (CDS) [1, 2].” (Methods section - Covariates, page 8, lines 189-191)

And
“The first model was adjusted for age, sex, and BMI (continuous variable). The second model (main model) was additionally adjusted for marital status, educational level, occupational categories, monthly household income per consumption unit, residential area, energy intake without alcohol, number of 24h records and inclusion month, smoking status, alcohol consumption and physical activity. Four additional models were also performed to account for a) PCA-extracted dietary patterns and intake of carbohydrates, lipids and salt; b) health events occurring during follow-up (cancer, type 2 diabetes and cardiovascular diseases); c) baseline CES-D score (continuous variable) and use of antidepressants during the follow-up and d) CDS score (continuous variable).” (Methods section - Statistical analysis, page 10, lines 221-229)

Results section:

“In the main model adjusted for sociodemographic and lifestyle data, a strong and linear relationship was observed between %UPF in the diet and the risk of incident depressive symptoms. A 10% increase in %UPF in the diet was associated with a 21% (95%CI= 15%-27%) higher risk of depressive symptoms. Further adjustment for dietary patterns and dietary intakes (carbohydrates, lipids and sodium), health events or the CDS score did not substantially modify the association. However, after accounting for the use of antidepressants during follow-up and the baseline value for the CES-D score, the association was attenuated but remained significant (HR for a 10% increase in UPF in the diet= 1.14, 95%CI= 1.09-1.20). The proportional hazards assumption was evaluated using martingale residues and the assumption was acceptable (P=0.12 for the main model). The dose-response association between %UPF and incident depressive symptoms using Restricted Cubic Spline was also presented in Supplemental Figure 1 (p<0.0001 for the overall association).” (Results section, page 12, lines 271-282)

Please include subgroup analyses of the association UPF-depression within dichotomous subgroups of sex, age, baseline levels of CES-D and baseline adherence to a high-quality dietary pattern

Stratified analyses according to sex, age (2 subgroups; median value), baseline adherence to a high-quality dietary pattern and the first CES-D score were performed (2 subgroups; sex-specific median value). Please see below.

\[
\begin{array}{c|c|c}
\text{Stratified analyses according to sex} & \\
\text{Women} & \\
\text{Men} & \\
\hline
n & 20380 & 6350 \\
\hline
\text{Number of cases} & 1648 & 573 \\
\end{array}
\]
<table>
<thead>
<tr>
<th>Model</th>
<th>HR (95% CI) a</th>
<th>P</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1b</td>
<td>1.26 (1.19; 1.33)</td>
<td>&lt;0.0001</td>
<td>1.15 (1.04; 1.27)</td>
<td>0.01</td>
</tr>
<tr>
<td>Model 2c</td>
<td>1.22 (1.16; 1.29)</td>
<td>&lt;0.0001</td>
<td>1.18 (1.06; 1.31)</td>
<td>0.003</td>
</tr>
<tr>
<td>Model 3d</td>
<td>1.22 (1.15; 1.30)</td>
<td>&lt;0.0001</td>
<td>1.20 (1.07; 1.35)</td>
<td>0.001</td>
</tr>
<tr>
<td>Model 4e</td>
<td>1.23 (1.16; 1.30)</td>
<td>&lt;0.0001</td>
<td>1.18 (1.06; 1.31)</td>
<td>0.003</td>
</tr>
<tr>
<td>Model 5f</td>
<td>1.15 (1.09; 1.22)</td>
<td>&lt;0.0001</td>
<td>1.12 (1.00; 1.25)</td>
<td>0.04</td>
</tr>
<tr>
<td>Model 6g</td>
<td>1.22 (1.16; 1.29)</td>
<td>&lt;0.0001</td>
<td>1.18 (1.06; 1.31)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

a Values are hazard ratios for 10% increase in the proportion of ultra-processed food intake (95% confidence intervals). CDS Cognitive Difficulties Scale; CES-D Center for Epidemiologic Studies Depression Scale; IQR Interquartile Range; UPF Proportion of ultra-processed food intake.

b Adjusted for age and body mass index.

c Adjusted for all variables in model 1 + marital status, educational level, occupational categories, household income per consumption unit, residential area, number of 24h-dietary records, inclusion month, energy intake without alcohol, alcohol intake, smoking status and physical activity (main model).

d Adjusted for all variables in model 2 + dietary patterns derived from the factor analysis (“Healthy” and “Western” dietary pattern) and intakes of lipids, sodium, and carbohydrates.

e Adjusted for all variables in model 2 + health events during follow-up (cancer, Type 2 diabetes, hypertension and cardiovascular events).

f Adjusted for all variables in model 2 + use of antidepressants during follow-up and the first CES-D score.
Stratified analyses according to age

<table>
<thead>
<tr>
<th>Age category</th>
<th>n</th>
<th>Number of cases</th>
<th>HR (95% CI) a</th>
<th>P</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 49 years</td>
<td>13,110</td>
<td>1349</td>
<td>1.22 (1.15; 1.29)</td>
<td>&lt;0.0001</td>
<td>1.26 (1.15; 1.38)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age ≥ 49 years</td>
<td>13,620</td>
<td>872</td>
<td>1.19 (1.12; 1.27)</td>
<td>&lt;0.0001</td>
<td>1.26 (1.15; 1.38)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Model 1b: Adjusted for sex and body mass index

Model 2c: Adjusted for all variables in model 1 + marital status, educational level, occupational categories, household income per consumption unit, residential area, number of 24h-dietary records, inclusion month, energy intake without alcohol, alcohol intake, smoking status and physical activity (main model)

Model 3d: Adjusted for all variables in model 2 + dietary patterns derived from the factor analysis ("Healthy" and "Western" dietary pattern) and intakes of lipids, sodium, and carbohydrates

Model 4e: Adjusted for all variables in model 2 + health events during follow-up (cancer, Type 2 diabetes, hypertension and cardiovascular events)

Model 5f: Adjusted for all variables in model 2 + CDS score

Model 6g: Adjusted for all variables in model 2 + CDS score

a Values are hazard ratios for 10% increase in the proportion of ultra-processed food intake (95% confidence intervals). CDS Cognitive Difficulties Scale; CES-D Center for Epidemiologic Studies Depression Scale; IQR Interquartile Range; UPF Proportion of ultra-processed food intake
f Adjusted for all variables in model 2 + use of antidepressants during follow-up and the first CES-D score

g Adjusted for all variables in model 2 + CDS score

\[
\text{Stratified analyses according to baseline adherence to a high-quality dietary pattern}
\]

Fator loading for the « Healthy » pattern < 0.04 for men and -0.11 for women
Fator loading for the « Healthy » pattern ≥ 0.04 for men and -0.11 for women

\[
n \quad 13365 \quad 13365
\]

Number of cases \quad 1280 \quad 941

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI) a</th>
<th>P</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1b</td>
<td>1.24 (1.17; 1.32)</td>
<td>&lt;0.0001</td>
<td>1.18 (1.07; 1.30)</td>
<td>0.001</td>
</tr>
<tr>
<td>Model 2c</td>
<td>1.23 (1.16; 1.30)</td>
<td>&lt;0.0001</td>
<td>1.18 (1.07; 1.31)</td>
<td>0.001</td>
</tr>
<tr>
<td>Model 3d</td>
<td>1.22 (1.15; 1.30)</td>
<td>&lt;0.0001</td>
<td>1.18 (1.07; 1.31)</td>
<td>0.001</td>
</tr>
<tr>
<td>Model 4e</td>
<td>1.23 (1.16; 1.31)</td>
<td>&lt;0.0001</td>
<td>1.19 (1.08; 1.31)</td>
<td>0.001</td>
</tr>
<tr>
<td>Model 5f</td>
<td>1.16 (1.10; 1.24)</td>
<td>&lt;0.0001</td>
<td>1.12 (1.02; 1.24)</td>
<td>0.02</td>
</tr>
<tr>
<td>Model 6g</td>
<td>1.23 (1.16; 1.31)</td>
<td>&lt;0.0001</td>
<td>1.16 (1.05; 1.28)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

a Values are hazard ratios for 10% increase in the proportion of ultra-processed food intake (95% confidence intervals). CDS Cognitive Difficulties Scale; CES-D Center for Epidemiologic Studies Depression Scale; IQR Interquartile Range; UPF Proportion of ultra-processed food intake

b Adjusted for age, sex and body mass index

c Adjusted for all variables in model 1 + marital status, educational level, occupational categories, household income per consumption unit, residential area, number of 24h-dietary records, inclusion month, energy intake without alcohol, alcohol intake, smoking status and physical activity (main model)
d Adjusted for all variables in model 2 + dietary patterns derived from the factor analysis (“Western” dietary pattern) and intakes of lipids, sodium, and carbohydrates

e Adjusted for all variables in model 2 + health events during follow-up (cancer, Type 2 diabetes, hypertension and cardiovascular events)

f Adjusted for all variables in model 2 + use of antidepressants during follow-up and the first CES-D score

g Adjusted for all variables in model 2 + CDS score

Stratified analyses according to the first CES-D score

First CES-D score < 6 for men and 8 for women

First CES-D score ≥ 6 for men and 8 for women

n 12544 14186

Number of cases 327 1894

<table>
<thead>
<tr>
<th>Model</th>
<th>HR (95% CI) a</th>
<th>P</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1b</td>
<td>1.06 (0.92; 1.24)</td>
<td>0.41</td>
<td>1.19 (1.13; 1.25)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model 2c</td>
<td>1.07 (0.92; 1.24)</td>
<td>0.36</td>
<td>1.18 (1.12; 1.24)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model 3d</td>
<td>1.15 (0.98; 1.35)</td>
<td>0.08</td>
<td>1.19 (1.12; 1.26)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model 4e</td>
<td>1.08 (0.93; 1.25)</td>
<td>0.33</td>
<td>1.18 (1.12; 1.24)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model 5f</td>
<td>1.07 (0.92; 1.24)</td>
<td>0.41</td>
<td>1.17 (1.11; 1.23)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model 6g</td>
<td>1.08 (0.93; 1.25)</td>
<td>0.33</td>
<td>1.18 (1.12; 1.25)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

a Values are hazard ratios for 10% increase in the proportion of ultra-processed food intake (95% confidence intervals). CDS Cognitive Difficulties Scale; CES-D Center for Epidemiologic Studies Depression Scale; IQR Interquartile Range; UPF Proportion of ultra-processed food intake

b Adjusted for age, sex and body mass index
c Adjusted for all variables in model 1 + marital status, educational level, occupational categories, household income per consumption unit, residential area, number of 24h-dietary records, inclusion month, energy intake without alcohol, alcohol intake, smoking status and physical activity (main model)

d Adjusted for all variables in model 2 + dietary patterns derived from the factor analysis ("Healthy" and "Western" dietary pattern) and intakes of lipids, sodium, and carbohydrates

e Adjusted for all variables in model 2 + health events during follow-up (cancer, Type 2 diabetes, hypertension and cardiovascular events)

f Adjusted for all variables in model 2 + use of antidepressants during follow-up

g Adjusted for all variables in model 2 + CDS score

In order to avoid our manuscript to become too long and complex, only the results of the main model (model 2) were presented in the revised version of the manuscript.

Figure 2 Association between ultra-processed food intake and incident depressive symptoms in population subgroups

Results section have been modified accordingly.

“On the other hand, when considering the ratio of energy intake to energy needs, a significant interaction with %UPF was detected (P=0.04). Hence, analysis stratified according to this ratio (while using the sex-specific EI/BMR median value as cut-off: 1.34 for men and 1.32 for women) were performed (Figure 2). The association between %UPF and the risk of depressive symptoms was stronger in participants with low energy intakes compared to their needs than their counterparts (HR for a 10% increase in UPF in the diet= 1.23, 95%CI=1.15-1.31 versus 1.19, 95%CI= 1.10-1.28; main model). Similarly, in the stratified analyses according to sex, age (using the median value), BMI (<25 vs. ≥ 25), comorbid conditions and factor loading for the « Healthy » pattern (using the sex-specific median value as cut-off: 0.04 for men and -0.11 for women), stronger associations were observed in the subgroups of women, participants aged ≥ 49 years, participants with a chronic disease, participants with a BMI value ≥ 25, and participants
with a lower value for the factor loading of the « Healthy » pattern, compared to their respective counterparts (Figure 2). However, the estimated HR were similar in the subgroups and no significant interaction was observed (P value for the interaction term was 0.49 for sex, 0.46 for age, 0.59 for BMI, 0.88 for comorbidities and 0.18 for the factor loading of the « healthy » dietary pattern). In addition, in the stratified analyses according to the baseline CES-D score (using the sex-specific median value as cut-off: 6 for men and 8 for women) the association between %UPF and the risk of depressive symptoms was significant only among participants with a higher baseline CES-D score (P value for the interaction term was 0.13).” (Methods section, pages 12-13, lines 283-302)

Please repeat the analyses after excluding cases occurring during a short follow-up period (those that occurred in the first 1-2 years) because they may have been subclinical cases at inception (to exclude reverse causality bias).

In the present study, only the second and third assessments of the depressive symptomatology were used to identify incident cases of depressive symptoms because all participants with depressive symptoms at the first assessment were excluded from the study. In addition, CES-D assessment was repeated every two years, thus very early “cases” were not identified.

We have now better clarified this in the revised version.

The new version reads as follows:

“The inclusion criteria in this study were: 1) have received at least twice the CES-D questionnaire (included between 2009 and 2012), 2) completed at least two of these questionnaires, and 3) not present depressive symptoms at the first CES-D assessment. Among the participants who met these criteria (n=35,782), we excluded participants without valid dietary data (participants with less than 3 dietary records during the first two years of follow-up and under-reporters) and the participants who had reported depression or treatment with antidepressants during the dietary data collection. Thus, a final study sample of 26,730 participants was obtained (Figure 1).” (Methods section - Statistical analysis, page 9, lines 194-201)

Please repeat the analyses but considering as cases only those who (according to CES-D) had depressive symptoms during follow-up AND also used antidepressant treatment during follow-up (the number of cases will be substantially reduced) but the increased specificity will reinforce your conclusions.

As requested by the Reviewer, only participants who had depressive symptoms and who used antidepressants during follow-up were considered as cases in a sensitivity analyse.

The results have been presented in Supplemental Table 7.
Supplemental Table 7 Association between ultra-processed food intake and incident depressive symptoms (considering as cases, only the participants who had depressive symptoms and also reported antidepressant treatment during follow-up), NutriNet-Santé study

<table>
<thead>
<tr>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
<th>P-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPF_EI, range</td>
<td>0%-24%</td>
<td>24%-31%</td>
<td>31%-39%</td>
<td>39%-83%</td>
</tr>
<tr>
<td>UPF_EI, median (IQR)</td>
<td>19% (6%)</td>
<td>27% (3%)</td>
<td>35% (4%)</td>
<td>46% (9%)</td>
</tr>
<tr>
<td>n</td>
<td>6,682</td>
<td>6,683</td>
<td>6,683</td>
<td>6,682</td>
</tr>
<tr>
<td>Number of cases</td>
<td>27</td>
<td>22</td>
<td>28</td>
<td>36</td>
</tr>
<tr>
<td>Model 1d</td>
<td>1 (ref)</td>
<td>0.80 (0.45; 1.41)</td>
<td>1.01 (0.59; 1.72)</td>
<td>1.32 (0.78; 2.21)</td>
</tr>
<tr>
<td></td>
<td>1.44 (1.19; 1.76)</td>
<td>0.0002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2e</td>
<td>1 (ref)</td>
<td>0.86 (0.48; 1.51)</td>
<td>1.09 (0.63; 1.87)</td>
<td>1.39 (0.82; 2.37)</td>
</tr>
<tr>
<td></td>
<td>1.43 (1.18; 1.73)</td>
<td>0.0003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 3f</td>
<td>1 (ref)</td>
<td>0.87 (0.49; 1.54)</td>
<td>1.11 (0.64; 1.94)</td>
<td>1.45 (0.83; 2.54)</td>
</tr>
<tr>
<td></td>
<td>1.51 (1.22; 1.85)</td>
<td>0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 4g</td>
<td>1 (ref)</td>
<td>0.81 (0.45; 1.43)</td>
<td>1.07 (0.62; 1.84)</td>
<td>1.38 (0.81; 2.35)</td>
</tr>
<tr>
<td></td>
<td>1.43 (1.18; 1.74)</td>
<td>0.0003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 5h</td>
<td>1 (ref)</td>
<td>0.81 (0.46; 1.42)</td>
<td>1.01 (0.59; 1.74)</td>
<td>1.21 (0.71; 2.07)</td>
</tr>
<tr>
<td></td>
<td>1.36 (1.12; 1.65)</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 6i</td>
<td>1 (ref)</td>
<td>0.83 (0.47; 1.46)</td>
<td>1.07 (0.62; 1.84)</td>
<td>1.36 (0.80; 2.32)</td>
</tr>
<tr>
<td></td>
<td>1.42 (1.17; 1.72)</td>
<td>0.0004</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Values are hazard ratios (95% confidence intervals). CDS Cognitive Difficulties Scale; CES-D Center for Epidemiologic Studies Depression Scale; IQR Interquartile Range; UPF Proportion of ultra-processed food intake

b Hazard ratios for 10% increase in the proportion of ultra-processed food intake
c P for continuous variable

d Adjusted for age, sex and body mass index

e Adjusted for all variables in model 1 + marital status, educational level, occupational categories, household income per consumption unit, residential area, number of 24h-dietary records, inclusion month, energy intake without alcohol, alcohol intake, smoking status and physical activity (main model)

f Adjusted for all variables in model 2 + dietary patterns derived from the factor analysis (“Healthy” and “Western” dietary pattern) and intakes of lipids, sodium, and carbohydrates

g Adjusted for all variables in model 2 + health events during follow-up (cancer, Type 2 diabetes, hypertension and cardiovascular events)

h Adjusted for all variables in model 2 + baseline CES-D score

i Adjusted for all variables in model 2 + CDS score

Indeed, depressive symptoms are not systematically treated, which could explain the small number of observed cases.

The different sections have also been modified accordingly.

Methods section:

“We also repeated the analyses by considering as cases, only the participants who had depressive symptoms during follow-up (according to CES-D score) and also reported antidepressant treatment during follow-up.” (Methods section - Sensitivity analyses, page 11, lines 243-245)
Results section:

“In addition, the analyses considering as cases only participants who had depressive symptoms and also used antidepressant treatment during follow-up showed stronger associations (Supplemental Table 6). However, the associations were not significant when the %UPF was modeled as quartiles, mainly due to low statistical power because of the small number of cases (n=113 cases). In the main model, the estimated HR for the analysis with a 10% increase in UPF consumption was 1.43 (95%CI= 1.18-1.73).” (Results section - Sensitivity analyses, pages 13-14, lines 310-316)

You can accommodate here the sensitivity analyses that you did: using other CES-D cut-offs (a) 16 or b) 19).

Please add a spline figure to graphically represent the dose-response pattern, the HRs and the 95% confidence intervals across the full range of values of UPF intake

The graphical dose-response association between %UPF and the risk of depressive symptoms has now been presented in Supplemental Figure 2.

Supplemental Figure 1 Dose-response association between ultra-processed food intake and incident depressive symptoms using Restricted Cubic Spline

The following sentence has been added in the Results section:

The dose-response association between %UPF and incident depressive symptoms using Restricted Cubic Spline was also presented in Supplemental Figure 1 (p<0.0001 for the overall association).

References


