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Journal:	*BMJ*
Manuscript ID	BMJ-2018-047977
Article Type:	Research
BMJ Journal:	BMJ
Date Submitted by the Author:	14-Nov-2018
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Keywords:	cohort, mortality, processed food, epidemiology, public health

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Word count: 3437

ABSTRACT

OBJECTIVES: Ultra-processed foods (UPFs) consumption has increased in the past decade**.** The main aim of the study was to evaluate the association between UPFs consumption and higher risk of all-cause mortality.

DESIGN: We evaluated the association between UPFs consumption and the risk of mortality in a dynamic, prospective Spanish cohort of university graduates, the "Seguimiento Universidad de Navarra" (SUN) cohort.

SETTING: The SUN project. A prospective, dynamic and multipurpose cohort formed by Spanish university graduates, 1999-2018 followed-up every 2 years.

PARTICIPANTS: We used data from 19,897 participants followed-up between December 1999 and February 2014 for a median of 10.4 years, with a retention rate of 90.9%.

INTERVENTIONS: We categorized all foods and drinks items of the FFQ into one of the four food groups of NOV*A*, a food classification system based on the extent and purpose of industrial food processing. We adjusted UPFs consumption for energy intake using the residuals method. Participants were classified according to their energy-adjusted UPFs consumption into quartiles. Cox proportional hazards models were fitted to estimate adjusted hazards ratio (HR) and 95% confidence intervals (CI) for all-cause mortality.

MAIN OUTCOME MEASURES: All-cause mortality.

RESULTS: We registered 335 deaths in 200,417 persons-years of follow-up. Participants in the highest quartile of UPFs consumption had a higher risk for all-cause mortality compared to those in the lowest quartile (multivariable adjusted HR=1.62; 95% CI 1.13-2.32) with a significant dose-response trend (p for linear trend=0.005). For each additional serving of UPFs consumption, mortality relatively increased by 9% (HR=1.09; 95% CI 1.02-1.17).

CONCLUSIONS: UPFs consumption was associated with an increased risk for all-cause mortality in a prospective cohort of Spanish middle-aged adult university graduates. Further longitudinal studies are needed to confirm our results.

TRIAL REGISTRATION: ClinicalTrials.gov identifier: NCT02669602.

KEYWORDS: cohort, mortality, processed food, epidemiology, public health

INTRODUCTION

Nutrition has been widely recognized as one of the crucial drivers of chronic diseases.[1] Dietary habits influence many risk factors for cardiometabolic health, including type 2 diabetes, stroke and heart disease, which are among the leading global causes of death.

Collectively, risk factors for ill health associated with consumption of a poor-quality diet pose substantial health and economic burdens. In fact, worldwide studies have shown that dietary factors are one of the main causes of the global burden of disease (measured as disability adjusted life years).[2]

UPFs are industrial formulations made mostly or entirely from substances derived from foods and additives with little, if any, intact food.[3] They are convenient (durable, ready-to-eat or heat), hyper-palatable (extremely tasty) and highly profitable food products (very low-cost ingredients) designed to displace all other food groups with the aid of an attractive packaging and intensive marketing.[4]

Throughout the last decades, availability and consumption of ultra-processed food (UPF), characterized by a low nutritional quality and a high energy density, has increased dramatically in many countries.[5,6] The percentage of UPF consumption has almost tripled between 1990 and 2010 (from 11.0 to 31.7% of daily energy intake),[7] in parallel with increases in added sugars content.

Foods were first classified according to their degree of processing in 2010 using the NOV*A* system, which was updated in 2016.[3] Studies based on NOV*A* have shown an exponential growth in UPF consumption. Negative nutritional attributes of UPF (high content of bad quality fat, added sugar and salt, along with a low vitamin density and fiber content) produce a direct harm. Furthermore, they are coupled with an indirect harm related to their ability to displace the healthy consumption of unprocessed or minimally processed foods and freshly prepared meals.

The beneficial effects of dietary patterns based on fresh or minimally processed food on mortality are well-known. Conversely, several studies have described the detrimental effects of higher UPF consumption. In the French NutriNet-Santé cohort, authors found significant associations between a higher consumption of UPFs and an increased risk of cancer[8] and irritable bowel syndrome.[9] In addition, early ultra-processed product consumption was found related with a higher incidence of dyslipidemia in Brazilian children[10] and a higher risk of overweight, obesity[11] and hypertension[12] in a Spanish cohort. However, to our knowledge, no study has yet evaluated the association between UPF consumption and all-cause mortality. Therefore, we aimed to assess the relationship between UPFs consumption and mortality in the Seguimiento Universidad de Navarra (SUN) cohort.

METHODS

Study Population

The SUN project is a prospective, dynamic and multipurpose cohort formed by Spanish university graduates. Its design, objectives and methods have been previously described.[13] Briefly, the recruitment started in December 1999 and is permanently open (i.e., the SUN cohort was designed as a dynamic cohort). The participants are followed up every 2 years and the information is gathered through mailed or web-based questionnaires. The Institutional Review Board (IRB) of the University of Navarra approved the protocol. The methods used to obtain consent of participants conformed to the principles embodied in the Declaration of Helsinki. The SUN project was registered at clinicaltrials.gov (NCT02669602).

We considered only participants recruited before March 2014 (n=22,335) in order to warrant that they may have the opportunity to respond to the 2-year follow-up questionnaire and therefore ensure a minimum follow-up of 2 years. We excluded 444 with total daily energy intake out of percentiles 1 and 99, and 1,994 participants lost to follow-up (retention rate: 90.9%). Finally, data from 19,897 participants remained available for the analyses **(Figure 1)**.

Dietary assessment

Diet exposure was assessed at baseline with a 136-item semi-quantitative FFQ previously validated and repeatedly reevaluated in Spain.[14,15] Frequencies of consumption were measured in 9 categories (ranging from never or almost never to >6 servings/d), and the FFQ included a typical portion size for each item. Daily food consumption was estimated by multiplying the portion size by the consumption frequency for each food item.

We categorized all foods and drinks items of the FFQ into one of the four food groups of NOV*A*, a food classification system based on the extent and purpose of industrial food processing.[3] The first group includes "unprocessed or minimally processed foods", that are fresh or processed in ways that did not add substances such as salt, sugar, oils, or fats and infrequently contain additives. Processes used are aimed to extend life, allow storage for long use, and facilitate or diversify preparation (freezing, drying, and pasteurization). Examples in this group are fruits and vegetables, grains (cereals), flours, nuts and seeds, fresh and pasteurized milk, natural yogurt with no added sugar or artificial sweeteners, meat and fish, tea, coffee, spices, and herbs. The second group contains "processed culinary ingredients". These are substances obtained from foods of the first group or from nature and may contain additives to preserve the original properties (e.g. salt, sugar, honey, vegetable oils, butter, lard, and vinegar). The third group is "processed foods" made with the addition of substances such as salt, sugar, or oil and the use of processes such as smoking, curing, or fermentation. Examples of foods in this group are canned or bottled vegetables and legumes, fruits in syrup, canned fish, cheeses, freshly made bread, and salted or sugared nuts and seeds. The fourth group is "ultra-processed foods and drink products", made predominantly or entirely from

industrial substances and contain little or no whole foods. These products are ready to eat, drink, or heat, i.e. carbonated drinks, sausages, biscuits (cookies), candy (confectionery), fruit yogurts, instant packaged soups and noodles, sweet or savory packaged snacks, and sugared milk and fruit drinks. This study focused on this last NOV*A* group and assessed it as the relevant exposure.

The frequency of UPFs consumption was estimated by the sum of the food items from the fourth group in the FFQ (a total of 34 items). The sample was divided into quartiles according to total consumption (servings/d). **Supplemental table 1** shows the classification of FFQ foods according to NOV*A*. Total energy, macronutrient, fiber, alcohol intake, consumption of fruits, vegetables, fast-food, fried-food, processed meat, unprocessed meat, and sugar-sweetened beverages was assessed with the use of a validated FFQ.[14,15] Adherence to a Mediterranean dietary pattern was evaluated with the use of the well-known score proposed by Trichopoulou *et al.*[16]

Outcome assessment

The primary outcome was all-cause mortality. Most deaths, more than 85% of them, were identified from reports by the next of kin, work's associates and postal authorities because we have a continuous contact with participants. Deaths are confirmed by a review of medical records (with permission of the next of kin). In order to confirm the rest of deaths, we checked at least once a year both the Spanish National Death Index and the National Statistics Institute. The positive predictive value for these sources of information regarding fatal events was very high, expected to be around 100%.

We consider that the follow-up ascertainment for the deceased participants was complete taking into account the combination of all these sources of information. The follow-up for each participant was calculated from date of returning the baseline questionnaire to date of death or date of returning the last follow-up questionnaire, whichever came first.

Assessment of other variables

The baseline questionnaire also collected information on the following variables: sex, age, marital status, educational status, smoking status, physical activity, television watching, nap sleep, diet and dietary habits, and snacking between main meals. Physical activity was evaluated with the use of a validated 17-item questionnaire.[17] Data on self-reported anthropometric characteristics was also gathered at baseline. A validation study with a subsample of the cohort showed enough validity to be used in epidemiological studies.[18] Nowadays in clinical practice, the most used tool to detect underweight, overweight and obesity in middle-aged adults is the body mass index (BMI). Therefore, we calculated BMI, defined as the body weight in kilograms divided by height in square meters (BMI=kg/m^2).

Statistical analysis

We used inverse probability weighting to adjust for age and sex the comparisons of the means or proportions of baseline variables according to quartiles of UPFs consumption. UPFs consumption was adjusted for total energy intake using the residuals method and subsequently categorized in quartiles. Quartiles were labeled as "low" (quartile 1), "low-medium" (quartile 2), "medium-high" (quartile 3) and "high UPFs consumption" (quartile 4). No missing data were found for this variable of interest.

To assess the association between energy-adjusted quartiles of UPFs consumption at baseline and all-cause mortality, we fitted Cox regression models with age as the underlying time variable (birth date as origin), and date of death or date when completing the last follow-up questionnaire for survivors as exit time. We estimated hazard ratios (HRs) for each of the 3 upper quartiles and their 95% confidence intervals (CIs), using the lowest quartile as the reference category.

Potential confounders included as covariates in multivariable models were age, sex, marital status married (yes/no), body mass index (linear and quadratic term), total energy intake (kilocalories/day, continuous), smoking status (never smoked, active smoker, former smoker), family history of cardiovascular disease (CVD; dichotomous), alcohol consumption (g/d, continuous), CVD, cancer or diabetes at baseline (yes/no), hypertension at baseline (yes/no), self-reported hypercholesterolemia at baseline (yes/no), depression at baseline (yes/no), education level (no graduate, graduate, postgraduate, doctorate), snacking (yes/no), following a special diet at baseline (yes/no), physical activity (quartiles). Results were stratified by recruitment period (1999-2000, 2001, 2002-2003, 2004, 2005-2007, 2008-2014), deciles of age, television viewing (dichotomous, cut-off: ≥3 h/day) and four categories of a sedentary index defined as the sum of television viewing (h/d), computer use (h/d) and driving (h/d). In case of missing values, we considered participants as if they did not present the condition.

Tests of linear trends across categorical quartiles of UPFs were conducted, assigning the median value to each category, and considering them as continuous variables. We verified the proportionality of hazards with a test based on Schoenfeld residuals, obtaining a non-significant result (p=0.114), suggesting that the proportionality assumption was met.

To determine the contribution of each food group to the between-person variance in UPFs consumption,[19] we constructed a series of nested least-squares linear regression models after stepwise-selection regression analyses. The additional contribution of a given food group was reflected in the change in the cumulative R^2. To assess the contribution of each food group to the total UPFs consumption, we calculated the ratio between the servings of each food group divided by the total servings of UPFs consumption and multiplying by 100.

We used Kaplan-Meier curves, with inverse probability weighting to adjust for confounding (using the above-mentioned confounders), to describe all-cause mortality according to baseline quartiles of UPFs consumption. To simplify the graph, we merged quartiles 1 and 2 (low and low-medium consumption).

The potential non-parametrical non-linear association between UPF consumption and all-cause mortality was calculated with restricted cubic splines with 3 knots. Tests for non-linearity used the likelihood ratio test, comparing the model with only the linear term to the model with the linear and the cubic spline terms.

Additionally, we conducted subgroup and sensitivity analyses by rerunning all the models under different a priori established assumptions: 1) including only men; 2) including only women; 3) excluding participants with prevalent hypertension; 4) using percentiles 5 and 95 as limits for allowable total energy intake; 5) using the energy limits proposed by Willett,[19] 6) excluding participants with prevalent cardiovascular disease or cancer; 7) excluding participants with special diets at baseline; 8) including only participants aged ≥45 years at recruitment; 9) including only participants aged <55 years at recruitment; 10) including only participants aged <65 years at recruitment; 11) excluding deaths from injuries; 12) excluding cardiovascular deaths; 13) excluding cancer deaths; 14) excluding early deaths (those occurring in the 2 first years); 15) excluding late deaths (occurred after 10-year follow-up or longer); 16) additionally adjusting for having gained 3 kg or more before baseline; 17) additionally adjusting for coffee consumption and for a quadratic term for alcohol consumption; 18) additionally adjusting for the consumption of all fried foods.

All p-values<0.05 were deemed as statistically significant. All analyses were performed using STATA version 15.0 (StataCorp, College Station, TX, USA).

RESULTS

A total of 7,786 men and 12,111 women were included in this analysis. The mean age of participants at baseline was 37.6 years (SD±12.3). They were followed-up during a median of 10.4 years and we observed 335 deaths during 200,417 person-years of follow-up. **Table 1** shows baseline characteristics of participants according to quartiles of total UPFs consumption adjusted for sex and age.

Participants in the fourth quartile of UPFs foods (high consumption), on average had higher BMI. They were more likely to be current smokers, to have a higher level of university education, a family history of CVD, cancer, diabetes, hypertension, hypercholesterolemia, prevalent CVD and depression. In addition, they consumed more between-meal snacks, watched television and used computer for longer periods, were more prone to be sedentary and sleep a nap, and exhibited higher total fat intake but lower protein and carbohydrate intake than those in the lowest quartile.

Moreover, on average, as expected, they consumed more fast food, fried foods, processed meats, and sugar-sweetened beverages. In contrast, they showed the poorest consumption of vegetables, fruits, olive oil, alcohol and total fiber. In addition, adherence to the Mediterranean diet tended to be progressively lower across successive quartiles of ultra-processed foods consumption (i.e., the higher the consumption of ultra-processed foods, the lower the adherence to the Mediterranean diet), with a correlation coefficient r=-0.39 between the score of adherence to the Mediterranean diet and UPF

consumption.

Processed meats, biscuits and cookies, sugar-sweetened beverages, and pastries were among the major contributors to UPF consumption variability **(Table 2)**. Regarding the respective quantities of UPFs provided by each source of UPF, processed meats, sugar-sweetened beverages, dairy products, and French fries were among the major contributors to UPF consumption quantity **(Table 3)**.

The main cause of death in the participants of the SUN cohort was cancer (164 deaths). Among deceased participants, their mean age at death was 58.0 years (SD±15.6). Those participants in the highest quartile of UPF consumption had a 62% relatively higher risk of all-cause death compared to those in the lowest quartile (multivariable adjusted HR=1.62; 95% CI 1.13-2.32) with a significant dose-response trend (p for trend=0.005) **(Table 4; Figure 2)**. For each additional serving of UPF consumption, all-cause mortality relatively increased by 9% (adjusted HR=1.09; 95% CI 1.02-1.17).

We calculated the p for interaction between ultra-processed foods consumption (quartiles) and age (dichotomous, 45 years old or less and older than 45 years old) or sex, using the likelihood-ratio test. The a priori selection of these 2 interactions was based on previous literature. None of them was statistically significant (p=0.658 for age; p=0.912 for sex).

Sensitivity analyses were conducted by repeating the multivariable-adjusted Cox regression models in different scenarios comparing the highest to the lowest quartile of UPFs. All point estimates showed associations between UPFs consumption and higher mortality. Results did not substantially change in any of these alternative scenarios, suggesting that the direct association between UPF consumption and mortality was robust **(Figure 3; Supplemental Table 2)**. However, some associations became non-significant under the following scenarios: including only women; excluding prevalent hypertension at baseline; including only participants age at recruitment <55 years, and excluding late deaths (more than 10 years). Conversely, the association grew stronger after excluding prevalent cardiovascular disease or cancer.

Finally, the restricted cubic spline analysis with 3 knots and adjusted for the same potential confounding factors suggested that the consumption of 5 or more servings/d of UPFs (which corresponds to consumption in the highest quartile) was associated with a significantly higher risk of all-cause mortality (Figure 4).

DISCUSSION

To our knowledge, this is the first prospective epidemiological study reporting an association between UPFs consumption and all-cause mortality. We evidenced that a high consumption of UPFs (≥5 servings/day) was significantly associated with 62% higher risk of mortality. Moreover, each additional serving of UPF was associated with a statistically significant 9% higher risk of all-cause mortality.

The NOV*A* classification was used to identify four different groups of foods according to their degree of processing. The fourth group constituted the exposure that we assessed and included UPF and drink products, which tend to be nutritionally unbalanced as a result of several industrial processes. These foods are economically profitably because they increase the shelf-life and sales of these food products, but they decrease their nutritional quality, are characterized by a high energy density, low content of fiber and micronutrients, and high amounts of added or free sugars, sodium, saturated fat and chemical additives.[4]

In the last decades, the intake of ready-to-eat, to-drink or to-heat "fast" and "convenient" products has dramatically increased in all countries, regardless of their economical level, which might have contributed to the global increased rates of overall cancer,[8] dyslipidemia,[10] obesity[11] and hypertension[12].

Two recent prospective French studies using data of NutriNet-Santé cohort evaluated the relationship between UPF consumption and the risk of overall cancer and gastrointestinal disorders. Their results showed a positive association between increased UPF consumption and overall cancer risk and breast cancer risk,[8] and irritable bowel syndrome.[9] Moreover, previous results in the SUN cohort found that UPF consumption was associated with a higher risk of overweight, obesity and hypertension.[11,12] These findings seem to be in line with ours, and consistently evidence the adverse effects related to UPF consumption.

Other findings from a large national cross-sectional study, the United Kingdom National Diet and Nutrition Survey, showed that diets rich in unprocessed foods and lower in UPFs are associated with a healthier food profile, although no association was found for body weight.[20] Several studies have reported other adverse effects related to UPF consumption. In the framework of the US National Health and Nutrition Examination Survey (NHANES), authors reported a strong inverse association between UPF consumption and urinary concentrations of phytoestrogens.[21] Other longitudinal study performed among US pregnant women suggested that the percent of total calorie intake coming from UPF may be a useful predictor of gestational weight gain and neonatal body fat.[22]

A study in the United States that analyzed household's availability of UPFs showed that 61% of total purchased dietary energy was derived from UPFs.[23] Another cross-sectional study using data from NHANES showed that UPFs represented 57.9% of energy intake and that 90% of this amount was derived from added sugars.[24] In the same line, results from the 2004 Pelotas (Brazil) Birth Cohort Study showed that 40.3% of total daily energy intake in 6 year-old children came from UPFs.[25]

Altogether, these results support the non-salutary effects of UPFs, which currently represent a significant portion of the calories consumed in many countries. In line with the cited evidences, our findings reinforce the existing evidence regarding the dramatically negative impact of UPFs on the overall incidence of chronic diseases and all-cause mortality.

Some strengths of this study are its prospective and dynamic design, the use of validated methods, the adjustment for a wide array of potential confounders, the long follow-up period, the good retention rate (91% overall), and the use of a variety of sensitivity analyses supporting the robustness of results. Although this study was based on self-reported data, we can assume high quality data as all participants are highly motivated university graduates, which adds validity to the information derived from their questionnaires and reduces the potential for misclassification bias. Another strength of the present study is its novelty. To the best of our knowledge, this is the first longitudinal study to evaluate the relationship between UPF consumption and all-cause mortality.

However, we should also mention some limitations. Firstly, the FFQ was not specifically designed to collect data regarding this new classification of UPF consumption. Moreover, using servings of UPF as an indicator for UPF consumption, due to the methodology, might lead to some degree of misclassification. Other limitation is the limited external validity of our findings, as the cohort was not representative of the general population. Nevertheless, in analytical epidemiology, cohorts are usually non-representative and therefore generalization of these results must be based on biological mechanisms rather than on statistical representativeness. Finally, the number of observed deaths was small, and we acknowledge that some analyses can be underpowered, especially in cause-specific mortality subgroups.

In conclusion, our results suggest that an increased UPF consumption was associated with a higher risk of all-cause mortality. The improvement of eating habits based on minimally processed food, which is a key aspect of the Mediterranean diet and has been shown to protect against chronic disease[26] and all-cause mortality[27–30], and at the same time the discouragement of UPFs consumption, should be promoted as an important health-policy action to improve global public health.

Acknowledgments

We sincerely thank all the participants of the SUN cohort. We are indebted for their invaluable support to the project answering biannually our questionnaires.

Author Contribution

AR-C, MAM-G, MB-R contributed to the conception and design of the work. AR-C, IA-A, MAM-G, and MB-R contributed to the data analyses, CF-A and RDM contributed to the data acquisition and interpretation of the data, MAM-G, and MB-R contributed to the funding of the project, AR-C and CG-D drafted the manuscript. AR-C, MAM-G, IA-A, RDM, CF-A, CG-D, MB-R critically revised and corrected the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work ensuring integrity and accuracy.

Role of funding source

The SUN Project has been supported by the Spanish Government-Instituto de Salud

Carlos III, and the European Regional Development Fund (FEDER) (RD 06/0045, PI14/01798, PI14/01764, PI17/01795), the Navarra Regional Government, and the University of Navarra. The funding sources had no role in the design, execution, analyses, and interpretation of the data or decision to submit the results of this study.

Declaration of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

Ethical approval

The protocol was written in accordance with the principles of the Declaration of Helsinki, was approved by the Institutional Review Boards at all study sites and was registered at ClinicalTrials.gov (NCT02669602).

Transparency declaration

MB-R (the guarantor) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing: No additional data available.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Foods with formulation made mostly or entirely from substances derived from food and additives, with little, if any, intact "real" food are called ultra-processed foods (UPFs).
- Based on prospective cohorts the consumption of UPFs have been found related to higher risk of developing cancer risk, irritable bowel syndrome, obesity, and hypertension in adult populations.
- However, to date, no studies have assessed the association between consumption of UPFs and mortality.

WHAT THIS STUDY ADDS

- In this prospective study of 19,897 middle-aged participants, a higher consumption of UPFs (5 or more servings/day) was independently associated with a 62% increased risk for all-cause mortality. Each additional serving of UPFs consumption/day increased mortality risk in 9%.
- These findings suggest that the warning increasing consumption of UPFs may drive to an increasing global public health burden.

REFERENCES

1. Mozaffarian D. Dietary and Policy Priorities for Cardiovascular Disease, Diabetes, and Obesity – A Comprehensive Review Dariush. *Circulation* 2016;133:187-225. doi:10.1161/CIRCULATIONAHA.115.018585
2. Gakidou E, Afshin A, Abajobir AA, et al. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017;390:1345-422. doi:10.1016/S0140-6736(17)32366-8
3. Monteiro CA, Cannon G, Levy R, et al. Food classification . Public health. *Public Heal J World Public Heal Nutr* 2016;7:28-38.
4. Moubarac JC, Martins APB, Claro RM, et al. Consumption of ultra-processed foods and likely impact on human health. Evidence from Canada. *Public Health Nutr* 2013;16:2240-8. doi:10.1017/S1368980012005009
5. Moodie R, Stuckler D, Monteiro C, et al. Profits and pandemics: Prevention of harmful effects of tobacco, alcohol, and ultra-processed food and drink industries. *Lancet* 2013;381:670-9. doi:10.1016/S0140-6736(12)62089-3
6. Monteiro CA, Moubarac JC, Cannon G, et al. Ultra-processed products are becoming dominant in the global food system. *Obes Rev* 2013;14:21-8. doi:10.1111/obr.12107
7. Latasa, P., Louzada, M.L.D.C, Martinez-Steele, E., et al. Added sugars and ultra-processed foods in Spanish households (1990-2010). *Eur J Clin Nutr* 2018;72:1404-12. doi:10.1038/s41430-017-0039-0
8. Fiolet T, Srour B, Sellem L, et al. Consumption of ultra-processed foods and cancer risk: results from NutriNet-Santé prospective cohort. *BMJ* 2018;360:k322. doi:10.1136/bmj.k322
9. Schnabel L, Buscail C, Sabate JM, et al. Association Between Ultra-Processed Food Consumption and Functional Gastrointestinal Disorders: Results From the French NutriNet-Santé Cohort. *Am J Gastroenterol* 2018;113:1217-28. doi:10.1038/s41395-018-0137-1
10. Rauber F., Campagnolo P.D.B., Hoffmanc D.J. VMR. Consumption of ultra-processed food products and its effects on children's lipid profiles: A longitudinal study. *Nutr Metab Cardiovasc Dis* 2015;25:116-22. doi:10.1016/j.numecd.2014.08.001
11. De Deus Mendonça R, Pimenta AM, Gea A, et al. Ultraprocessed food consumption and risk of overweight and obesity: The University of Navarra Follow-Up (SUN) cohort study. *Am J Clin Nutr* 2016;104:1433-40. doi:10.3945/ajcn.116.135004
12. De Deus Mendonça R, Souza Lopes AC, Pimenta AM, et al. Ultra-processed food

consumption and the incidence of hypertension in a mediterranean cohort: The seguimiento universidad de navarra project. *Am J Hypertens* 2017;30:358-66. doi:10.1093/ajh/hpw137

13. Seguí-Gómez M, de la Fuente C, Vázquez Z, et al. Cohort profile: The "Seguimiento Universidad de Navarra" (SUN) study. *Int J Epidemiol* 2006;35:1417-22. doi:10.1093/ije/dyl223
14. Martín-Moreno, J.M., Boyle, P., Gorgojo, et al. Development and validation of a food frequency questionnaire in Spain. *Int J Epidemiol* 1993;22:512–9.
15. De La Fuente-Arrillaga C, Vzquez Ruiz Z, Bes-Rastrollo M, et al. Reproducibility of an FFQ validated in Spain. *Public Health Nutr* 2010;13:1364-72. doi:10.1017/S1368980009993065
16. Trichopoulou, A., Costacou, T., Bamia, C., et al. Adherence to a Mediterranean diet and survival in a Greek population. *N Engl J Med* 2003;348:2599-608. doi:10.1056/NEJMoa1110039
17. Martínez-González MA, López-Fontana C, Varo JJ, et al. Validation of the Spanish version of the physical activity questionnaire used in the Nurses' Health Study and the Health Professionals' Follow-up Study. *Public Health Nutr* 2005;8:920-7. doi:10.1079/PHN2005745
18. Bes-Rastrollo M, Pérez-Valdivieso, J.R., Sánchez-Villegas, et al. Validación del peso e índice de masa corporal auto-declarados de los participantes de una cohorte de graduados universitarios. *Rev Esp Obes* 2005;3:352-8.
19. Willett W. *Nutritional Epidemiology*. 3rd ed. New York: Press, Oxford University; 2013.
20. Adams J, White M. Characterisation of UK diets according to degree of food processing and associations with socio-demographics and obesity: Cross-sectional analysis of UK National Diet and Nutrition Survey (2008-12). *Int J Behav Nutr Phys Act* 2015;12. doi:10.1186/s12966-015-0317-y
21. Steele EM, Monteiro CA. Association between dietary share of ultra-processed foods and urinary concentrations of phytoestrogens in the US. *Nutrients* 2017;9:209. doi:10.3390/nu9030209
22. Rohatgi KW, Tinius RA, Cade WT, et al. Relationships between consumption of ultra-processed foods, gestational weight gain and neonatal outcomes in a sample of US pregnant women. *PeerJ* 2017;5:e4091. doi:10.7717/peerj.4091
23. Poti JM, Mendez MA, Ng SW, et al. Is the degree of food processing and convenience linked with the nutritional quality of foods purchased by US households? *Am J Clin Nutr* 2015;101:1251-62. doi:10.3945/ajcn.114.100925
24. Steele EM, Baraldi LG, Da Costa Louzada ML, et al. Ultra-processed foods and added sugars in the US diet: Evidence from a nationally representative cross-sectional study. *BMJ Open* 2016;6:1-8. doi:10.1136/bmjopen-2015-009892

25. Bielemann RM, Santos LP, Costa C dos S, et al. Early feeding practices and consumption of ultraprocessed foods at 6 y of age: Findings from the 2004 Pelotas (Brazil) Birth Cohort Study. *Nutrition* 2018;47:27-32. doi:10.1016/j.nut.2017.09.012

26. Estruch R, Ros E, Salas-Salvadó J, et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. *N Engl J Med* 2018;368:1279-90. doi: 10.1056/NEJMoa1800389

27. Martinez-Gonzalez MA, Guillen-Grima F, De Irala J, et al. The Mediterranean Diet Is Associated with a Reduction in Premature Mortality among Middle-Aged Adults. *J Nutr* 2012;142:1672-8. doi:10.3945/jn.112.162891

28. Chen G-C, Zhang R, Martínez-González MA, et al. Nut consumption in relation to all-cause and cause-specific mortality: a meta-analysis 18 prospective studies. *Food Funct* 2017:3893-905. doi:10.1039/C7FO00915A

29. Reedy J, Krebs-Smith SM, Miller PE, et al. Higher diet quality is associated with decreased risk of all-cause, cardiovascular disease, and cancer mortality among older adults. *J Nutr* 2014;144:881-9. doi:10.3945/jn.113.189407

30. Alvarez-Alvarez I, Zazpe I, Pérez de Rojas J, et al. Mediterranean diet, physical activity and their combined effect on all-cause mortality: The Seguimiento Universidad de Navarra (SUN) cohort. *Prev Med* 2018;106:45-52. doi:10.1016/j.ypmed.2017.09.021

Table 1. Age and sex-adjusted* baseline characteristics of participants according to their consumption of ultra-processed foods in the SUN Project[1] (1999-2014).

	Quartiles of energy-adjusted ultra-processed food consumption			
Characteristics	**Q1 (<2 serv/d)**	**Q2 (2-<3 servs/d)**	**Q3 (3-<5 servs/d)**	**Q4 (>=5 servs/d)**
n	4975	4974	4974	4974
UPFs, servings/day	2.2 (1.2)	2.8 (1.2)	3.6 (1.3)	5.9 (2.4)
Baseline BMI, Kg/m^2	23.3 (3.42)	23.5 (3.5)	23.6 (3.7)	23.8 (3.7)
Marital status, %				
Married	50.8	50.4	50.0	49.6
Educational status, %				
Graduate	84.6	82.0	81.1	80.9
Postgraduate	6.6	8.0	8.3	8.3
Doctorate	8.8	10.3	10.6	10.9
Smoking status, %				
Current	23.0	24.2	24.8	28.3
Former	26.5	25.6	24.3	24.1
Family history of CVD, %	13.5	13.9	13.7	15.9
Cancer at baseline, %	3.5	3.2	3.4	4.4
Diabetes at baseline, %	2.0	1.8	2.1	2.3
Hypertension at baseline, %	18.8	19.9	19.7	22.7
Hypercholesterolemia at baseline, %	17.3	17.0	17.2	17.8
Cardiovascular disease at baseline, %	1.5	1.5	1.6	2.4
Depression at baseline, %	10.8	11.2	12.0	13.4
Special diet at baseline, %	8.5	8.4	8.2	7.2
Between-meal snacking, %	29.5	30.9	33.8	42.4
Television viewing (>=3h/d), %	6.9	7.3	8.2	10.5
Computer use, h/d	2.0 (1.9)	2.1 (1.9)	2.1 (1.9)	2.2 (2.0)
Driving, h/d	0.9 (1.1)	0.9 (1.1)	0.9 (1.1)	0.9 (1.1)
Sedentary index[2], h/d	4.5 (2.8)	4.6 (2.8)	4.7 (2.6)	4.9 (2.8)
Sleeping siesta, h/d	0.3 (0.7)	0.3 (0.8)	0.3 (0.8)	0.4 (0.8)
Physical activity, MET-h/wk	30.8 (27.6)	27.1 (23.0)	25.5 (22.0)	25.2 (23.8)
Adherence to the Mediterranean diet (0-9 score)	5.1 (1.7)	4.3 (1.7)	3.8 (1.7)	3.6 (1.7)

Total energy intake, kcal/d	2799 (764.3)	2338 (693.1)	2299 (714.7)	2632 (873.0)
Macronutrients, % energy				
Carbohydrate intake	44.6 (7.9)	42.9 (7.3)	42.8 (7.0)	43.6 (7.5)
Protein intake	18.1 (3.4)	18.6 (3.3)	18.3 (3.1)	16.9 (3.1)
Fat intake	35.3 (7.2)	36.4 (6.4)	37.0 (6.0)	37.5 (6.5)
SFAs	11.5 (3.4)	12.3 (3.0)	12.8 (3.0)	13.2 (3.2)
MUFAs	15.6 (4.1)	15.8 (3.7)	15.7 (3.4)	15.6 (3.5)
PUFAs	5.0 (1.6)	5.1 (1.5)	5.3 (1.5)	5.4 (1.7)
Total dietary fiber intake, g/d	37.9 (17.1)	28.6 (11.5)	26.0 (11.0)	26.5 (12.7)
Alcohol consumption, g/d	7.5 (12.0)	6.6 (9.5)	6.0 (9.5)	7.3 (12.3)
Olive oil consumption, g/d	22.5 (17.5)	15.9 (13.2)	13.2 (11.9)	12.7 (12.1)
Fruits consumption, servings/d	4.3 (3.2)	2.9 (2.0)	2.5 (1.8)	2.4 (1.9)
Vegetables consumption, servings/d	3.5 (2.2)	2.8 (1.4)	2.5 (1.3)	2.4 (1.5)
Fast-food consumption[3], servings/d	0.1 (0.1)	0.2 (0.2)	0.2 (0.2)	0.2 (0.2)
Fried food consumption, servings/d	0.5 (0.7)	0.5 (0.6)	0.5 (0.6)	0.6 (0.7)
Red meat consumption, servings/d	0.6 (0.4)	0.6 (0.3)	0.5 (0.3)	0.5 (0.3)
Processed meat consumption [4], servings/d	0.3 (0.3)	0.4 (0.3)	0.4 (0.4)	0.5 (0.5)
SSB consumption, servings/d	0.1 (0.2)	0.2 (0.3)	0.3 (0.4)	0.8 (1.2)
Low-fat dairy products consumption, servings/d	0.5 (1.5)	0.4 (0.8)	0.4 (0.8)	0.4 (0.9)
High-fat dairy products consumption, servings/d	0.6 (1.1)	0.5 (0.8)	0.4 (0.7)	0.4 (0.7)
Sodium intake, mg/d	4103 (2032)	3783 (2116)	4053 (2578)	4909(4248)
Potassium intake, mg/d	6122(2187)	4887 (1544)	4560 (1516)	4630 (1721)
Calcium intake, mg/d	1531(661)	1242 (480)	1176 (473)	1246(518)
Magnesium intake, mg/d	527(166)	421 (125)	398 (124)	421 (149)
Phosphorous intake, mg/d	2346 (729)	1953 (560)	1869 (563)	1970(641)
Caffeine intake, mg/d	40.9 (39.2)	40.2 (37.0)	40.0 (36.2)	52.0 (49.0)

*Adjusted through inverse probability weighting

UPF: Ultra-processed Food; BMI: Body mass Index; SSB: Sugar-sweetened beverage consumption; MET: Metabolic Equivalent of task; SFAs: Saturated Fat Acid; MUFAs: Monounsaturated Fat Acids; PUFAs:Polyunsaturated fatty acids; serv: serving; d: day

[1] All values are means (SDs) unless otherwise indicated.

[2] Sum of television viewing (h/d), computer use (h/d) and driving (h/d)

[3] Sum of hamburgers, sausages and pizza

[4] Sum of sausages, hamburgers and ham

Table 2. Main sources of variability in the group of ultra-processed foods[1].

	R^2	Cumulative R^2
Processed meat[2]	0.26	
Cookies[3]	0.18	0.44
Sugar-sweetened beverages	0.17	0.60
Pastries[4]	0.10	0.70
Breakfast cereals	0.07	0.77
Artificially sugared beverages	0.05	0.86
Fried foods	0.04	0.81
Dairy products[5]	0.03	0.89
Margarine	0.02	0.91
French fries	0.02	0.93
Mayonnaise	0.01	0.94
Ready to eat soups and purées	0.01	0.95

[1]Cumulative R^2 values were determined with the use of nested regression analyses after a stepwise selection.
[2]Includes ham, sausages, chorizo, salami, mortadella, and hamburgers.
[3]Includes biscuits and chocolate cookies.
[4]Includes muffins, doughnuts, croissants or other pastries, and confectionery.
[5]Includes custard, ice cream, milkshakes, and *petit suisse*.

Table 3. Percentage of each food contributing to the total amount of ultra-processed foods.

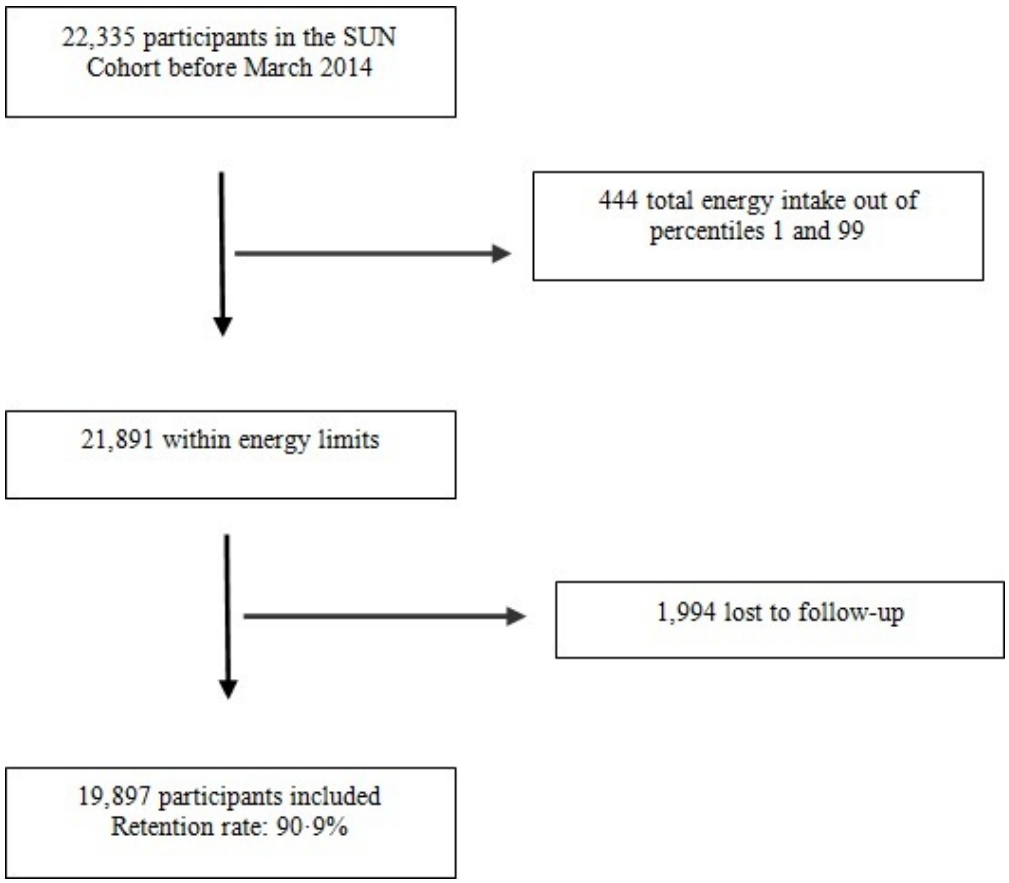
Food Groups	Contribution
Processed meats[1]	15%
Sugar-sweetened beverages	15%
Dairy products[2]	12%
French fries	11%
Pastries[3]	10%
Cookies[4]	8%
Ready to eat soups and purées	6%
Fried foods	6%
Artificially sugared beverages	5%
Breakfast cereals	3%
Pizza	2%
Liquors	2%
Margarine	1%
Mayonnaise	1%

[1]Includes ham, sausages, chorizo, salami, mortadella, and hamburgers.
[2]Includes custard, ice cream, milkshakes, *petit suisse*.
[3]Includes muffins, doughnuts, croissants or other pastries, and confectionery.
[4]Includes biscuits and chocolate cookies.

Table 4. Cox proportional HRs and 95% CIs for all-cause mortality of ultra-processed foods consumption categories[1].

	Quartiles of ultra-processed foods consumption				
	Q1	**Q2**	**Q3**	**Q4**	**p for trend**
	(<2 servs/day)	**(2-<3 servs/day)**	**(3-<5 servs/day)**	**(>=5 servs/day)**	
Total deaths					
N	4975	4974	4974	4974	
Person/years	49817	50310	49956	50334	
Deaths	108	74	80	73	
Unadjusted	1.00 (reference)	1.02 (0.75, 1.37)	1.38 (1.03, 1.85)	1.78 (1.30, 2.43)	<0.001
Age- and sex-adjusted	1.00 (reference)	0.99 (0.73, 1.35)	1.28 (0.93, 1.75)	1.71 (1.21, 2.41)	0.002
Multivariable-adjusted[2]	1.00 (reference)	0.98 (0.71,1.36)	1.26 (0.90,1.75)	1.61 (1.13,2.31)	0.007
Multivariable-adjusted[3]	1.00 (reference)	1.03 (0.74, 1.43)	1.35 (0.97,1.88)	1.62 (1.13, 2.32)	0.005
Cardiovascular deaths					
N	4867	4892	4894	4896	
Person/years	49245	49941	49474	49893	
Deaths	22	20	14	15	
Unadjusted	1.00 (reference)	1.37 (0.74, 2.53)	1.43 (0.73, 2.76)	1.86 (0.90, 3.83)	0.089
Age- and sex- adjusted	1.00 (reference)	1.04 (0.54, 2.00)	1.33 (0.62, 2.87)	2.08 (0.96, 4.52)	0.173
Multivariable-adjusted[2]	1.00 (reference)	0.87 (0.41, 1.84)	1.13 (0.45, 2.82)	2.10 (0.94, 4.69)	0.099
Multivariable-adjusted[3]	1.00 (reference)	0.76 (0.32, 1.81)	1.12 (0.45, 2.75)	2.21 (0.94, 5.20)	0.095
Cancer deaths					
N	4867	4892	4894	4896	
Person/years	49518	50019	49689	49987	
Deaths	62	33	40	29	
Unadjusted	1.00 (reference)	0.78 (0.51, 1.20)	1.26 (0.85, 1.86)	1.36 (0.85,2.18)	0.135
Age- and sex- adjusted	1.00 (reference)	0.80 (0.52, 1.23)	1.03 (0.68, 1.56)	1.36 (0.82, 2.27)	0.204
Multivariable-adjusted[2]	1.00 (reference)	0.79 (0.51, 1.23)	1.01 (0.65, 1.57)	1.23 (0.71, 2.11)	0.497
Multivariable-adjusted[3]	1.00 (reference)	0.85 (0.54, 1.34)	1.10 (0.71, 1.69)	1.25 (0.72, 2.16)	0.394

[1] All values are HRs; 95% CIs in parentheses unless otherwise indicated.
[2]Adjusted for age (underlying time variable), sex, marital-status, physical activity (quartiles), smoking status (never smoked, active smoker, former smoker), snacking (dichotomous), following a special diet at baseline (dichotomous), body mass index (linear and quadratic terms), total energy intake (continuous), alcohol consumption (continuous), and education level (continuous) stratified by recruitment period, deciles of age, sedentary index[4], and television viewing (>=3h/d).
[3]Adjusted for age (underlying time variable), sex, marital-status, physical activity (quartiles), smoking status (never smoked, active smoker, former smoker), snacking (dichotomous), following a special diet at baseline (dichotomous), body mass index (linear and quadratic terms), total energy intake (continuous), alcohol consumption (continuous), family history of CVD (dichotomous), diabetes at baseline (dichotomous), hypertension at baseline (dichotomous), self-reported hypercholesterolemia at baseline (dichotomous), CVD at baseline (dichotomous), cancer at baseline (dichotomous), depression at baseline (dichotomous) and education level (continuous) stratified by recruitment period, deciles of age, sedentary index[4], and television viewing (>=3h/d).
[4]Sum of television viewing (h/d), computer use (h/d) and driving (h/d).



Flow chart

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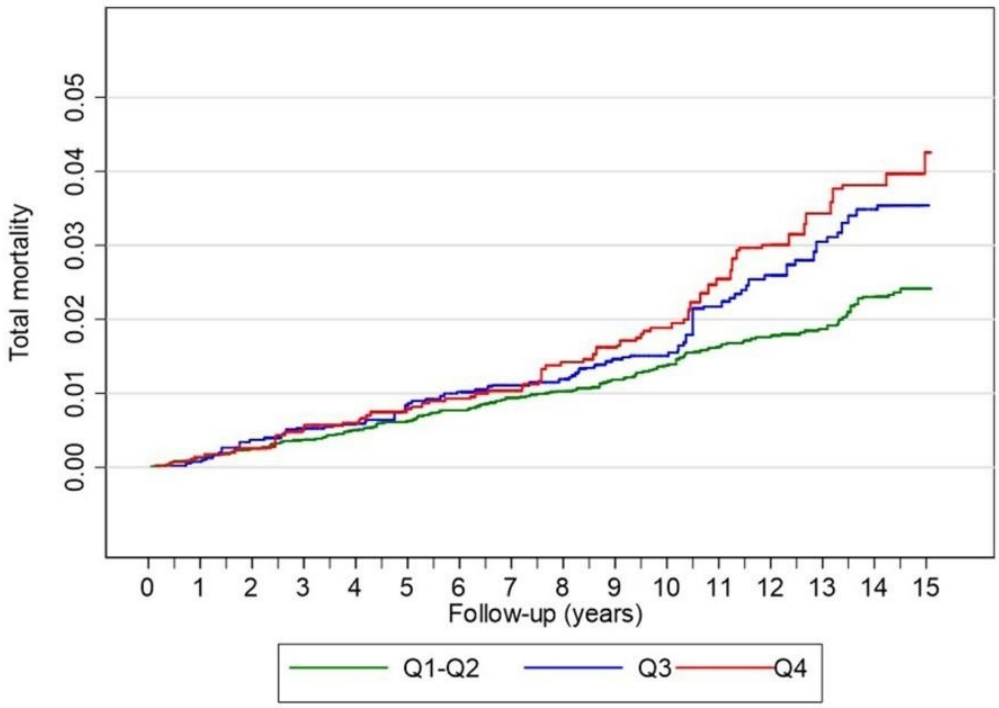

Kaplan-Meier failure estimate of ultra-processed foods consumption categories adjusted through IPW1.

[1]: IPW: Inverse probability weighting

[2] Adjusted for age, sex, marital-status, physical activity (quartiles), smoking status (never smoked, active smoker, former smoker), snacking (dichotomous), following a special diet at baseline (dichotomous), body mass index (linear and quadratic terms), total energy intake (continuous), alcohol consumption (continuous), family history of CVD (dichotomous), diabetes at baseline (dichotomous), hypertension at baseline (dichotomous), self-reported hypercholesterolemia at baseline (dichotomous), CVD at baseline (dichotomous), cancer at baseline (dichotomous), depression at baseline (dichotomous) and education level (continuous) stratified by recruitment period, deciles of age, sedentary index[3], and television viewing (>=3h/d).

[3] Sum of television viewing (h/d), computer use (h/d) and driving (h/d).

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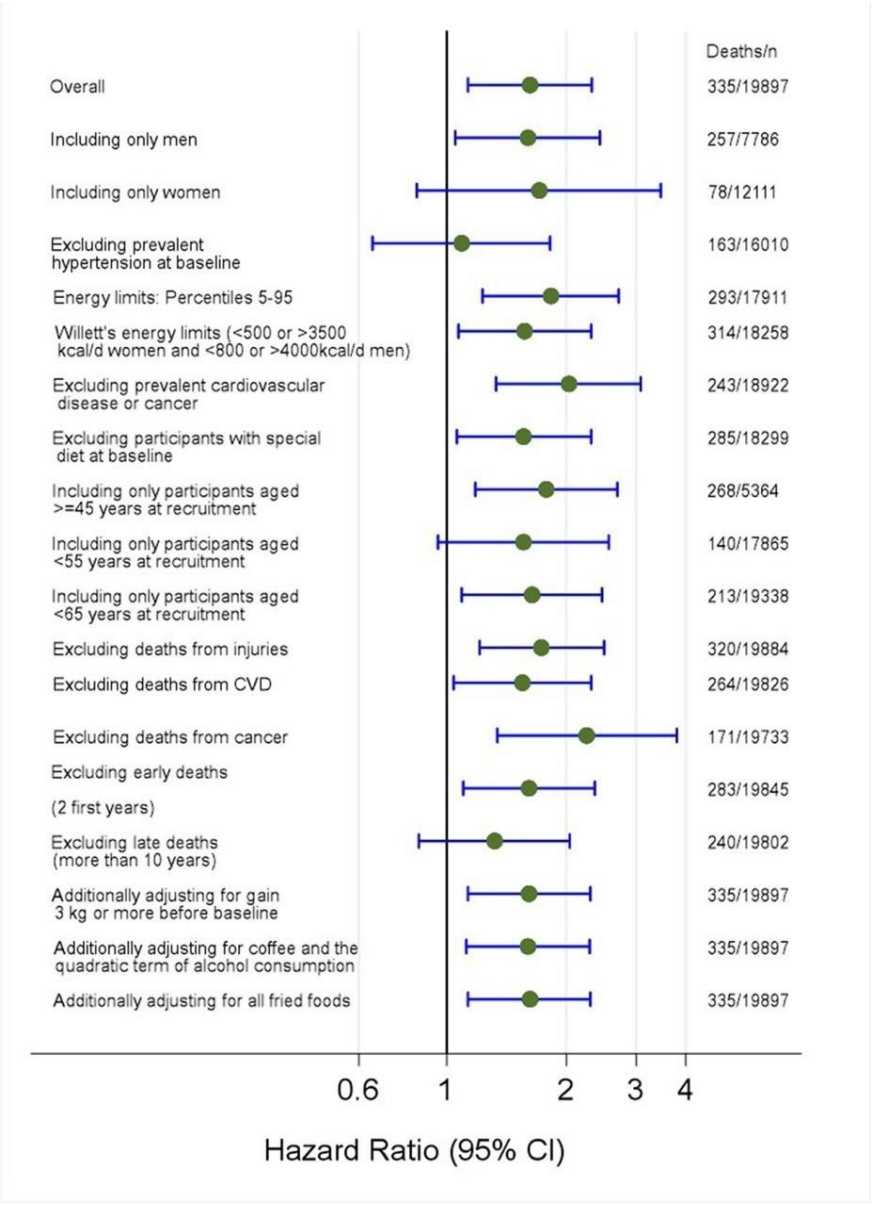

Sensitivity analyses exploring the association between ultra-processed foods consumption and all-cause mortality (highest quartile vs lowest quartile).

HR: hazard ratio. FFQ: Food frequency questionnaire. CVD: Cardiovascular disease

[1] Adjusted for age (underlying time variable), sex, marital-status, physical activity (quartiles), smoking status (never smoked, active smoker, former smoker), snacking (dichotomous), following a special diet at baseline (dichotomous), body mass index (linear and quadratic terms), total energy intake (continuous), alcohol consumption (continuous), family history of CVD (dichotomous), diabetes at baseline (dichotomous), hypertension at baseline (dichotomous), self-reported hypercholesterolemia at baseline (dichotomous), CVD at baseline (dichotomous), cancer at baseline (dichotomous), depression at baseline (dichotomous) and

education level (continuous) stratified by recruitment period, deciles of age, sedentary index[2], and television viewing (>=3h/d).

[2] Sum of television viewing (h/d), computer use (h/d) and driving (h/d).

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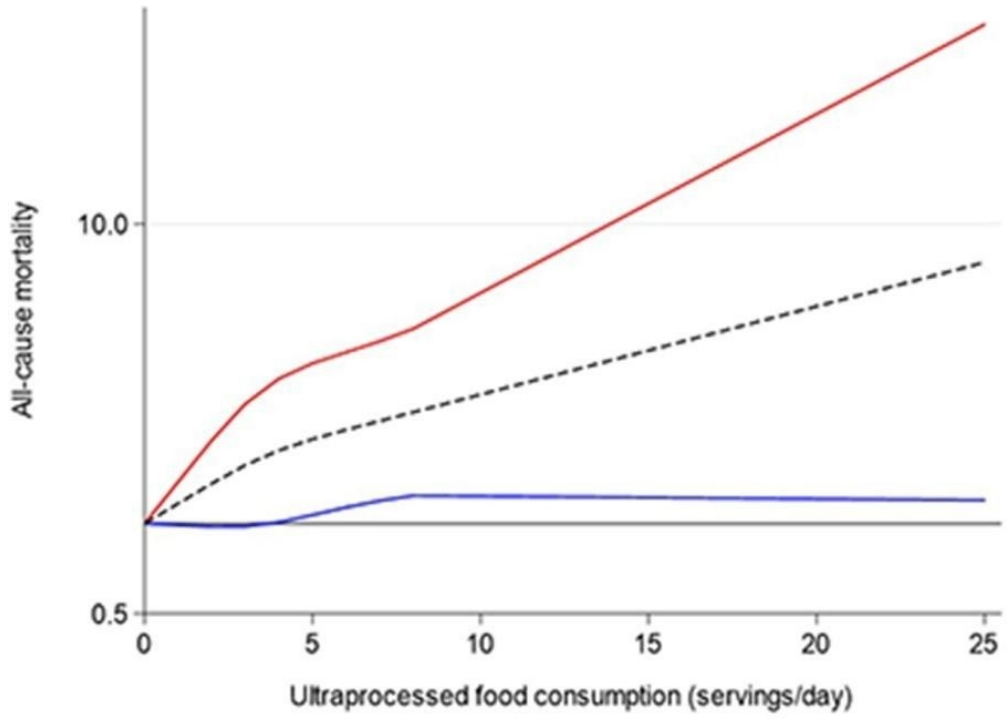

Restricted cubic splines analysis of the association between ultra-processed foods consumption and all-cause mortality.

[1] Adjusted for age (underlying time variable), sex, marital-status, physical activity (quartiles), smoking status (never smoked, active smoker, former smoker), snacking (dichotomous), following a special diet at baseline (dichotomous), body mass index (linear and quadratic terms), total energy intake (continuous), alcohol consumption (continuous), family history of CVD (dichotomous), diabetes at baseline (dichotomous), hypertension at baseline (dichotomous), self-reported hypercholesterolemia at baseline (dichotomous), CVD at baseline (dichotomous), cancer at baseline (dichotomous), depression at baseline (dichotomous) and education level (continuous) stratified by recruitment period, deciles of age, sedentary index[2], and television viewing (>=3h/d).

[2] Sum of television viewing (h/d), computer use (h/d) and driving (h/d).

239x170mm (96 x 96 DPI)

Supplemental Table 1. Classification of foods according to the processing level (NOV*A*).

Food group	Food-frequency questionnaire
Unprocessed or minimally processed foods	Fruits, vegetables, legumes, milk (whole, semi-skimmed and non-fat), eggs, meats, poultry, fish and seafood, fermented milk as yogurt, grains (white rice, pasta), artisanal pastries, natural juice, coffee, water
Processed culinary ingredients	Salt, sugar, honey, vegetable oils (olive, sunflower, corn), chili, butter, and lard
Processed foods	Condensed milk, cream milk, cheeses, cured traditional ham, bacon, canned and bottled fruits, breads (white and whole), beer, and wine
Ultra-processed foods	*Petit suisse*, custard, flan, pudding, ice-cream, ham, processed meat (*chorizo*, *salami*, *mortadella*, sausage, hamburger, *morcilla*), pate, *foie-gras*, spicy sausage/meatballs, potato chips, breakfast cereals, pizza including pre-prepared pies, margarine, cookies, chocolate cookies, muffins, donuts, croissant or other business-type pastries, cakes, *churros*, chocolates and candies, nougat, marzipan, carbonated drinks, artificially sugared beverages, fruit drinks, milkshake, instant soups and creams, croquettes, mayonnaise, and alcoholic drinks produced by fermentation followed by distillation such as whisky, gin, and rum

Supplemental Table 2. Sensitivity analyses exploring the association between ultra-processed foods consumption and all-cause mortality highest quartile vs lowest quartile.

Variable	n	Deaths	HR (95% CI)[1]
Overall	19897	335	1.62 (1.13-2.32)
Including only men	7786	257	1.60 (1.05-2.43)
Including only women	12111	78	1.71 (0.84-3.46)
Excluding prevalent hypertension at baseline	16010	163	1.09 (0.65-1.82)
Energy limits: Percentiles 5-95	17911	293	1.83 (1.23-2.71)
Willett's energy limits (<500 or >3500 kcal/d women and <800 or >4000 kcal/d men)	18258	314	1.57 (1.07-2.31)
Excluding prevalent cardiovascular disease or cancer	18922	243	2.03 (1.33-3.08)
Excluding participants with special diet at baseline	18299	285	1.56 (1.06-2.31)
Including only participants age at recruitment >45 years	5792	273	1.78 (1.18-2.69)
Including only participants age at recruitment <55 years	17865	140	1.56 (0.95-2.56)
Including only participants age at recruitment <65 years	19338	213	1.64 (1.09-2.46)
Excluding deaths from injuries	19884	320	1.73 (1.21-2.49)
Excluding early deaths (2 first years)	19845	283	1.61 (1.10-2.36)
Excluding late deaths (more than 10 years)	19802	240	1.32 (0.85-2.04)
Additionally adjusting for gain 3 kg or more at baseline	19897	335	1.61 (1.13-2.30)
Additionally adjusting for coffee consumption and the quadratic term of alcohol consumption	19897	335	1.60 (1.12-2.29)
Additionally adjusting for all fried foods	19897	335	1.62 (1.13-2.30)

HR: hazard ratio. FFQ: Food frequency questionnaire. CVD: Cardiovascular disease

[1]Adjusted for sex, marital-status, physical activity (quartiles), smoking status (never smoked, active smoker, former smoker), snacking (dichotomous), following a special diet at baseline (dichotomous), body mass index (linear and quadratic terms), total energy intake (continuous), alcohol consumption (continuous), family history of CVD (dichotomous), diabetes at baseline (dichotomous), hypertension at baseline (dichotomous), self- reported hypercholesterolemia at baseline (dichotomous), CVD at baseline (dichotomous), cancer at baseline (dichotomous), depression at baseline (dichotomous) and education level (continuous) stratified by recruitment period, deciles of age, sedentary index[2], and television viewing (>=3h/d). [2]Sum of television viewing (h/d), computer use (h/d) and driving (h/d).