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Title: Association Between Ultra-Processed Food İntake and All-Cause Mortality: A Systematic Review and Meta-Analysis

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Abstract

Ultra-processed food (UPF) consumption have increased in the world during the last decades since they are hyper-palatable, cheap and ready-to-consume products. However, uncertainty exists on their impact on health. We conducted a systematic review and meta-analysis evaluating the association of UPF consumption with the all-cause mortality risk. Five bibliographic databases were searched for relevant studies. Random effects models were used to calculate pooled relative risks (RR) and 95% confidence intervals (CI). Of 6,951 unique citations, 40 unique prospective cohort studies comprising 5,750,133 individuals were included. Publication date of the included studies ranged from 1984 to2021. Compared to low consumption, highest consumption of UPF (RR=1.29, 95% CI 1.17-1.42), sugar-sweetened beverages (SSB) (RR=1.11, 95% CI, 1.04-1.18), artificially sweetened beverages (ASB) (RR=1.14, 95% CI, 1.05-1.22) and processed meat/red meat (RR=1.15, 95% CI, 1.10-1.21) were significantly associated with increased risk of mortality. On the contrary, breakfast cereals were associated with a lower mortality risk (RR=0.85, 95% CI, 0.79-0.92). Conclusion: This meta-analysis suggests that high consumption of UPF, SSB, ASB, processed meat and processed red meat might increase all-cause mortality, while breakfast cereals might decrease it. Future studies are needed to address lack of standardized methods in UPF categorization.

INTRODUCTION

Researchers at the University of Sao Paulo, Brazil have defined ultra-processed foods (UPF) as 'formulations of ingredients, mostly of exclusive industrial use, typically created by a series of industrial techniques and processes' by NOVA (not an abbreviation) classification (1). Some examples of UPF include soft and energy drinks, packaged snacks, cakes, biscuits,

cookies candies, pastries, packaged breads and buns, margarine, ; sweetened breakfast cereals, fruit yoghurt; ,pre-prepared meat, pasta, poultry nuggets, cheese, pizza, fish nuggets, hot dogs, sausages and other reconstituted meat products (1).

UPF are mostly energy-dense, with high fat, sugar or salt content and generally obesogenic, and because UPF are hyper-palatable, cheap and ready-to-eat and drink products, they have become a dominant food consumption pattern at first in high-income countries, followed by a rapid spread in the middle-income countries (2). Western Europe, North America and Australia have the highest sales of ultra-processed products and baked goods (cakes, pastries, and industrial breads) and are the main market of UPF (3). Despite these high consumption rates, thus far there is limited evidence about the health outcomes associated with UPF.

A study combining data from 80 countries' reported a positive correlation between an increase in volume sales per capita of UPF and mean population BMI in both men and women (3). In addition to obesity/overweight (4, 5), UPF consumption has been associated with increase in the risk of hypertension, dyslipidemia, metabolic syndrome, diabetes mellitus, heart disease, cerebrovascular disease, depression, cancer and all-cause mortality (6-14). Furthermore, UPF have associations with not only on the human health but also the environment (15).

To our knowledge, until now, four systematic reviews and meta-analysis have been published on UPF and their association with overweight, obesity and health status (4, 6, 16, 17). While other studies have addressed the association between some UPF categories and mortality risk (6, 17), to date, there is no comprehensive summary, addressing the association between UPF subgroups and all-cause mortality. Therefore, in this systematic

review and meta-analysis, we aim to investigate the prospective association between all-cause mortality and not only UPF consumption as total, but also different UPF categories. "PICO" statements which were created to address the specific aims of the systematic review are shown in Table 1.

METHODS

We followed the guideline developed by Muka et al., to conduct the systematic review and meta-analysis, and for reporting, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and MOOSE guidelines (18-20). The protocol of the study is registered in PROSPERO (CRD42020151201).

Data source and strategy

We performed systematic literature searches in MEDLINE via Ovid, EMBASE, Web of Science Core Collection, Cochrane Library, and Google Scholar to identify relevant articles. Databases were from inception until 29th January 2021, and the search was limited to human studies. No limitations on publication date or language were applied. The references of eligible articles and studies that have cited the final included articles in the analysis were further searched for additional studies. The complete search strategy can be found in the eAppendix 1.

Study selection and eligibility criteria

Studies were included if they (i) were of prospective design (nested case-control studies, case-cohort studies, prospective cohort studies); (ii) included adult population (18+ years old); (iii) evaluated consumption of ultra-processed foods (every food item in NOVA classification were taken into consideration)(1), and (iv) evaluated the risk of all-cause

mortality. We excluded abstracts, cost effectiveness studies, randomized and non-randomized clinical trials intervention studies, cross-sectional studies, case-control studies, letters to the editor, conference proceedings, systematic reviews or meta-analyses.

Data extraction

Six independent reviewers screened the titles and abstracts according to the selection criteria. We recorded author's name, year of publication, study location, study name, sample size, baseline age, follow-up time, methods used to assess UPF intake, type of exposure, outcome assessment method, number of events, measures of associations and level of adjustment in a data extraction form. The form was developed, piloted, and discussed within the review group before the initiation of the full data extraction. Two reviewers extracted data from the selected studies.

Risk of bias assessment

The Newcastle-Ottawa Scale for cohort studies was used to assess the quality of the included studies. The assessment was done by one author and checked for accuracy by a second author (21). A third author adjudicated in case consensus was not reached. The Newcastle-Ottawa Scale assesses quality in three categories, namely, selection of study groups/participants, comparability of the groups/participants, and the assessment of exposure/outcome of interest. Based on a 9-point scale, the studies were classified as good quality (8-9 points), fair quality (5-7), and poor quality (<5).

Data synthesis and analysis

We computed pooled relative risks (RR) and 95% confidence intervals (CI) for all-cause mortality between overall UPF, processed meat/red meat, sugar-sweetened beverages

(SSB), artificially sweetened beverages (ASB) and breakfast cereal consumers vs. non-consumers, and highest vs. lowest intake. In analysis, we used the most adjusted RRs reported. For articles reporting data from same cohort study, we extracted and used in our analysis the most recently published data. Odds ratios reported by Kahn et al. were converted to RR using the method described by Grant (22).

RRs were pooled using the inverse variance weighted method based on the random-effects models, which takes into account the between study heterogeneity. Fixed-effects models were reported in forest plots as sensitivity analysis. Fixed effects models were also used to pool results from different groups from same study, which were then included in our meta-analyses. Heterogeneity of each meta-analyses was quantified as low ($I^2 \leq 25\%$), moderate ($I^2 > 25\%$ and $<75\%$), or high ($I^2 \geq 75\%$), based on the I^2 statistic. In addition, a Q-statistic ≥ 0.05 was indicated no significant heterogeneity. A priori, we specified population mean age, publication year, median percentage of female population, mean follow-up, location, funding source and risk of bias as characteristics for the assessment of heterogeneity, and were evaluated by using stratified analyses and random-effects meta-regression if ≥8 studies were included in the meta-analysis(23). Funnel plot, and Egger's test was used to assess publication bias in meta-analyses that included five or more studies. All analyses were conducted using STATA 15.1 (Statacorp, Texas, US, 2017). We calculated 2-tailed tests and a p-value <0.05 was considered significant.

RESULTS

Study Identification and Selection

6,951 unique citations were identified, of which 111 were selected for full-text evaluation. Of those, 40 unique prospective cohort studies (47 articles) comprising 5,750,133 individuals

were included in the qualitative synthesis (Figure 1). Five studies provided information on UPF with NOVA classification, seventeen studies on processed meat, five studies on processed red meat, nine on sugar-sweetened beverages, six on artificially sweetened beverages, ten on breakfast cereals, five on sweets/sugar and two on take-away foods. There were no studies reporting on other UPF items in NOVA classification. All studies' results were adjusted for age, sex (when both sexes were included in analysis) and at least one lifestyle factor except one (Fortes, 2000). Detailed characteristics of the included studies can be found in **Web Table 1**. In brief, most of the identified studies (n=18) were conducted in USA, while the rest were conducted in Sweden (n=4), Spain (n=3), Denmark (n=3), UK (n=2), Europe (cohort studies that included participants from multiple European countries) (n=2), Netherlands (n=2), Italy (n=2), Singapore (n=1), Australia (n=1), China (n=1), and France (n=1). The follow up time ranged between 5 and 34 years. All studies were of fair (14.9%) to good quality (85.1%), except one study (Lee, 1998, classified as poor quality) (**Web Table** 2).

Association between UPF consumption and risk of all-cause mortality

Five studies (24-28), comprising 110,721 individuals with occurrence of 5,044 deaths, were included in the meta-analysis of UPF consumption and all-cause mortality. The overall follow-up duration ranged from 7 to 19 years.

Compared to lowest consumption, highest consumption of UPF was significantly associated with increased risk of mortality (RR=1.29, 95% CI 1.17-1.42), with low heterogeneity between studies (I^2=0.0%, P=0.519) (**Table 2**, **Web Figure** 1)

Association between SSB consumption and risk of all-cause mortality

Eleven unique studies from ten articles (29-38) were included in the meta-analysis of SSBs and risk of all-cause mortality. In total, 135,427 deaths were reported among 1,351,875 participants.

The pooled RR for the highest compared with the lowest categories of SSBs was 1.11 (1.04 to 1.18), with high heterogeneity (I^2 = 82.1%, p < 0.001) (**Table 2**, **Web Figure** 2). The stratified analysis showed mean age of population, publication year, follow-up time and percentage of female population to partially explain heterogeneity, while location and funding had no impact (**Table** 3).

All-cause mortality risk among SSB consumers was not significantly higher than non-consumers (RR=1.05, 95% CI 0.98-1.13, I^2=89.6% p<0.001) (**Table** 2, **Web Figure** 3). There was no evidence of publication bias for the association between SSB and all-cause mortality (p = 0.152, **Web Figure** 4).

Association between ASB consumption and risk of all-cause mortality

Data of 895,485 individuals with 111,564 reported deaths from seven unique studies from six articles (30, 32, 33, 37-39) were pooled for the analysis of ASB and risk of all-cause mortality.

The pooled RR for the highest compared with the lowest categories of ASBs was 1.14 (1.05 to 1.22), with high heterogeneity (I^2 = 76.2%, p<0.001) (**Table** 2, **Web Figure** 5). ASB consumers did not have higher all-cause mortality risk than non-consumers (RR=1.11, 95%CI 0.96-1.27, I^2= 87.4%, p<0.001) (**Table** 2, **Web Figure** 6). Drinking more than one serving per month of ASBs was not associated with all-cause mortality risk (RR=0.99, 95%CI 0.97-1.02,

I^2=71.8%, p=0.06) (**Table** 2, **Web Figure** 7). There was no evidence of publication bias for the association between ASB and all-cause mortality (p = 0.174, **Web Figure** 8).

Association between processed meat/ processed red meat consumption and all-cause mortality

Fifteen unique studies (40-53) evaluating the association between processed meat consumption and all-cause mortality and reporting 194,031 deaths among 1,711,016 individuals were pooled in our meta-analysis. The median follow-up duration ranged from 7 to 22 years in these prospective studies.

Pooled RR for highest vs. lowest intake was 1.15 (95% CI 1.10 to 1.21) with high heterogeneity between studies (I^2=78.5%, P<0.001) (**Table** 2, **Web Figure** 9). After excluding the study by Wang et al. which include prostate cancer patients, RR was found 1.16 (95% CI 1.10 to 1.22). Also, there was a higher mortality risk among processed meat consumers compared to non-consumers (RR= 1.05, 95% CI 1.02-1.07, I2=11.2%, p=0.342) (**Table** 2, **Web Figure** 10). When prostate cancer patients excluded from analysis RR was 1.04 (95% CI 1.01 to 1.08). There was no evidence of publication bias (P = 0.176, **Web Figure** 11).

Meta-regression analysis revealed mean age of population, percentage of female population, follow-up time, location, funding and publication year as sources of heterogeneity, but stratification analysis did not show significant differences across the strata of these characteristics (**Table** 3).

Five unique studies from four articles (42, 48, 49, 52), comprising data from 749,397 individuals with death occurring among 165,506 of them, contributed to our meta-analysis

investigating the association of processed red meat consumption and risk of all-cause mortality. Highest consumption of processed red meat vs. lowest was significantly associated with increased risk of mortality (RR=1.19, 95% CI 1.11-1.27), with high heterogeneity between studies (I^2=81.8%, P=0.001) (**Table** 2, **Web Figure** 12).

Association between breakfast/ ready to eat cereal consumption and all-cause mortality

We included in the analysis a total 529,204 individuals with 50,499 reported deaths from six unique studies (54-59). After comparing highest vs. lowest breakfast cereal intake, the results showed there was an inverse association between breakfast cereal consumption and all-cause mortality risk (RR=0.85, 95% CI 0.79-0.92) with high heterogeneity (I^2=77.5%, P=0.000) (**Table** 2, **Web Figure** 13). After excluding the study by Li et al. which focus only myocardial infarction survivors, the RR was 0.85 (95% CI 0.78-0.94 , I^2=80.7%, P<0.001).

Highest consumption of whole grain breakfast cereal vs. lowest was significantly associated with decreased risk of mortality (RR=0.77, 95% CI 0.72-0.81) with no heterogeneity between studies (I^2=0.0%, P=0.381) (**Table** 2, **Web Figure** 14). Highest consumption of refined (non whole grain) breakfast cereals was not associated with all-cause mortality risk compared to lowest (RR=1.09, 95% CI 0.96-1.23, I^2=0.0%, P=0.951) (**Table** 2, **Web Figure** 15).

We were not able to pool five studies; three of them (60-62) had overlapping cohorts and others had continuous results. Chuang et al. reported with 5 g/d increase the all-cause mortality significantly decrease in both women (RR=0,92; 95%CI 0,89-0,95) and men (RR=0,93; 95%CI 0,91-0,95) (63). Streppel et al. showed no significant association per 10 g/d increase in bread & other cereal consumption (64).

Other UPF components and risk of all-cause mortality

Burke et al. showed that greater intake of takeaway foods such as sausages, meat pies, hamburger and fish fingers (>9 serves/month vs. ≤9 serves/month) is associated with all-cause mortality risk in Australian Aborigines (HR 1.78, 95% CI 0.96, 3.29)(65). Barrington et al. reported increased risk of mortality in highest consumption (>2.5 servings/week) vs. lowest consumption (<0.5 servings/week) of fast-food items (RR=1.16, 95%CI 1.04- 1.29)(29).

Lee et al. conducted a prospective study in men to assess the association between candy consumption and all-cause mortality. They found that compared with non-consumers, consumers had lower risk of all-cause mortality (RR=0.73; 95CI% 0.60 to 0.89) (66). Similarly, Liu et al. reported an association between added sugar intake from beverages/foods and mortality (67). Gonzalez et al. showed no significant association of sugar and sweet (chocolate, honey, candies) consumption with mortality risk (RR=1.29; 95%CI 0.88–1.90) (68). Due to heterogenous exposure categorization/definition and population, we were not able to pool the results from these studies.

Discussion

Principal findings

This systematic review and meta-analysis found an increased risk of all-cause mortality with higher consumption of UPF, SSB, ASB and processed meat/red meat. Our research, on the other hand, revealed that eating breakfast cereal might reduce the risk of dying from any cause.

Comparison with other studies

Our results are consistent with previous meta-analyses reporting that UPF (6,16, 17), SSB(69), ASB(69) and processed meat consumption (70) could be linked to increased risk of mortality. Compared to the most recent meta-analyses, our meta-analysis includes more studies (2 studies for SSB, 1 study for ASB and 4 studies on processed meat). Additionally, we enhance previous literature by showing an association between already being a consumer of UPF, SSB, ASB, processed meat and processed red meat with an elevated mortality risk. Yet, it is not clear whether any level of consumption of SSB, ASB and processed food is associated with increased risk of mortality. For instance, while ASB consumers had higher risk of mortality compared to non-consumers, drinking more than one ASB serving per month was not associated with mortality risk. Future studies among consumers, need to explore whether linear associations / dose-response relationship exists.

To our knowledge, this is the first meta-analysis on the association between breakfast cereal/ ready-to-eat cereal consumption and all-cause mortality. We found that breakfast cereals might have the potential to reduce the risk of all-cause mortality, regardless of processing conditions. These conclusions are supported by a previous meta-analysis, reporting that high cereal fibre intake decrease the all-cause mortality risk (8). Nevertheless, our study showed that the association between breakfast cereals intake and risk of mortality could depend on type of cereal fibre; while whole grain cereals were associated with lower risk of mortality, non-whole grain cereals were not.

Potential underlying mechanisms

The health outcomes of some UPFs can be explained by a variety of mechanisms. UPF can increase the risk of major chronic non-communicable diseases: cardiovascular diseases, type 2 diabetes, obesity and cancers, which can further increase the risk of mortality (8). During

food processing natural ingredients are subjected to the mechanical, thermal, fermentative, enzymatic, packaging and conservation, and decontamination treatments, which affect nutrient bioavailability, digestion and glycemic satiety, antioxidant or alkalinizing potential and gut microbiota(71). The more foods are being processed – the more initial complex foods are fractioned or refined, the bigger the impact on its matrix and composition - the higher their glycemic index and lower satiety potential (72). Recent studies have shown a causal association between UPF consumption and excess caloric intake, body weight and fat gain (5), which were shown to lead to metabolic syndrome (10). Weight gain and obesity are recognized as major risk factors for numeral malignancies, including prostate, liver, ovary, kidney, and pancreas cancers (73).

Moreover, the risk could lie with not only high-energy intake, but in nutritional quality of the food as well. Composition of micro- and macronutrients, added sugars, sodium, trans and saturated fat together with lower fibre content could impact mortality risk (74). Fibre has a significant impact on the gut microbiota and may reduce inflammatory indicators such as C-reactive protein and TNF-alpha receptor 2 (8), which might explain the inverse association between fibre and mortality. The potential benefits of a higher fiber content in morning cereals could also be the underlying reason for a lower risk of death.

Furthermore, other artificial compounds are either added as preservatives or formed during UPF production. More than 250 different additives are authorized for addition to food products in Europe and the US (75, 76). For instance, titanium dioxide (TiO2), which a common food additive used as an antimicrobial or whitening agent or, was shown to cause intestinal inflammation and to promote the development of pre-neoplastic lesions in colon (77). High temperature treatment during food processing such as frying, roasting and baking

leads to formation of acrylamide, acrolein and 5-hydroxymethylfurfural (78). These compounds react with amino acids to form various derivatives, which after digestion and absorption could act as mutagenic compounds, leading to point mutations and potential activation of oncogenes or tumor suppressor genes (79). High acrylamide intake was associated with increased risk of ovarian and endometrial cancers through oxidative imbalance leading to neoplastic transformation (80). Bisphenol A, suspected of migrating from plastic packaging into the food, was shown to exhibit endocrine disruptor properties and causing cancer (81, 82).

High salt and phosphate content of UPF mostly processed meats, have been reported to promote intestine inflammation, leading to higher intestinal permeability and dysbiosis (83). In particular, high sodium salt intake is associated with blood pressure in humans – a major risk factor for cardiovascular system (84, 85). Kim et al. have shown that the risk of stroke was dependent on the type of consumed meat, namely consumption of total, red and processed meat was associated with higher risks of stoke, while white meat consumption led to lower risks (86). Nitrites in curing salt can produce peroxynitrites, which enhance the development of atherosclerosis, diabetes (87) and gastric cancer (88).

Strength and limitations of the study

To the best of our knowledge, this is the first comprehensive systematic review on the association of UPF & its food components with all-cause mortality. Searching literature and covering not only UPF but all the other foods included to that category by NOVA is the main strength of the study. In addition, it is noteworthy that we performed multiple sensitivity analysis and confirmed the robustness of our findings. Also we included more unique studies

than previous systematic reviews and meta-analysis hence we had a larger population in our analysis. However, limitations in the current study merit careful consideration.

We would like to note out that there are just a few observational studies in the literature about UPF and their relationship with overall mortality, hence some of our analyses have a small number of studies. Current literature provides prospective studies that report the health outcomes of processed meats, which involve both processed and ultra-processed meats as defined by NOVA. For this reason, we could not make this distinction in the analysis of processed meat and mortality; hence the results on processed meat should be interpreted with caution. Due to limited studies and different categories with different levels of consumption provided by the included studies, we were not able to perform meta-analysis for some of our exposures comparing consumers vs. not consumers. The majority of studies in our meta-analyses adjusted for a range of relevant confounders, although one study was entirely unadjusted(51). Also, most of studies did not adjust for lifestyle factors and socioeconomic status, such as overall quality of diet, physical activity, income and education. Therefore, our results comparing highest vs. lowest intake could be a proxy for lifestyle and socioeconomic status. Nevertheless, restriction of some of our analysis to studies that considered all these factors did not materially change the results. In addition, the level of consumption across different populations we studied could be different, and thus comparing lowest vs. highest intake could result in biased estimates. Yet, the results comparing consumers vs. non-consumers were generally in line with the findings comparing highest vs. lowest intake. Similarly, stratifying by location did not change the main results. It is noteworthy that this comparison was between US and European countries including mainly countries of high and upper-middle income, hence the generalizability of the findings is limited. Also, worth mentioning, that we could not address the association between all kind

of cereals and all-cause mortality, since the initial search term included only “ready to eat cereal”, excluding specific publications regarding whole grain, oat cereals, which points a direction for the future research. Lastly, we would like to point out that, depending on how it has been cooked, a food item can be classified as UPF or processed food. With that in mind, we have to consider that food frequency questionnaires might not be able to make this distinction, hence in the studies UPF items may be underreported or over-reported. We acknowledge that different dietary assessment methods may cause potential misclassification in identifying UPF, however we were not able to stratify by the dietary assessment method since only one of the total UPF studies was using 24h recall to assess the consumption.

Implications for clinicians and policy makers

UPF consumption has been so far associated with an increased risk of clinical outcomes, including overweight/obesity, high waist circumference, metabolic syndrome, all-cause mortality, CVD, cerebrovascular disease, depression, hypertension, irritable bowel syndrome, overall cancer, postmenopausal breast cancer, gestational obesity, adolescent asthma and wheezing, and frailty (6, 16, 17). Some experimental studies indicated that putting front-of-package nutrient warning labels on sugar-sweetened beverages and ultra-processed foods could be an effective solution to reduce consumption (89). However more research is needed in that area.

Considering UPF are easy accessible, public health policies limiting their use from the population should be explored. More research is needed not only to improve the UPF-NOVA classification, but also policies that could work in decreasing their uptake from the population.

The NOVA classification divides foods into four groups according to the nature, extent and purpose of the industrial processing. Since it has been declared in 2010; the NOVA classification has been recognized by international organizations such as PAHO and FAO (90). However, in some situations processes may increase the bioavailability of nutrients and some foods on the UPF NOVA classification can be prepared at home or in industrial settings. Thus, it is suggested that the terminology may be misleading and cause confusion for public health (91).

Our results highlight that the degree of food processing is not the sole determinant of nutritional quality. Moreover, it is relevant to define nutritional values and assess UPF against these nutritional standards. Regularly-consumed foods also require some processing (i.e. heating, concentration, salinization, fermentation) but are not necessarily harmful(92). In our study we found that breakfast cereal consumption might be associated with lower risk of mortality. In previous studies, breakfast cereals have been shown to provide potential health benefits such as lowering obesity/overweight, type 2 diabetes mellitus, hypertension and cardiovascular diseases (93). According to that it is safe to say not all ultra-processed foods have overall negative health outcomes and that should be considered by researchers, developers of the food classification systems and decision makers.

Finally, UPFs impact not just human health but also the environment. Corn, palm and soy oil contained in many UPFs and produced in industrial amounts leads to the deforestation and monoculture. Restricting biodiversity requires intensive use of pesticides and fertilizers causing degradation of land, soil and freshwater(94). Extensive packaging is a major source of environmental waste production(15, 95). Production of animal-based foods in general leads to higher emissions of greenhouse gases – one of the reasons of climate disruption,

massive deforestation to create farms for the growth of animal feed and for animals themselves, and to higher water usage(95). Moreover, industrial animal production produces stress on animals, requires extensive antibiotic use, known to generate antibiotic-resistant bacteria, threatening human health, and pollutes natural water systems (96, 97). Producing soft drinks lead to strain on local water resources, especially in the countries where they are scarce(98, 99). Therefore, coming up with the new guidelines and recommendations, encouraging general population to minimize UPFs consumption would benefit not only human, but our planet's health as well.

Conclusion

This study indicates that UPF, SSB, ASB, processed meat and processed red meat consumption is associated with an increased risk of all-cause mortality. On the other hand, breakfast cereals/ ready-to-eat cereals have an inverse relationship with mortality. We conclude that the health consequences of UPF must be carefully assessed, since we showed it is a broad term includes various food components that can cause different health outcomes. Further comprehensive prospective studies with standardized reporting are necessary.

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Table 1. PICO: Defining the research question

Population	Adult population, 18 years and older
Intervention	Any intake or high intake of ultra-processed foods
Control	No intake or low intake of ultra-processed food
Outcome	All-cause mortality

Abbreviation: PICO: Population, intervention, control, and outcomes

Table 2. Meta-analysis of studies assessing the association of upf and all-cause mortality

Foods Categories	Eligible studies			Participants		Meta-analysis results			
	Unique studies, no.	Follow-up duration, median	Median quality score	Total	Deaths	RR	95% CI	I^2 (%)	p value for heterogeneity
Ultra-processed foods[a]	5	9.05	8.50	110,721	5,044	1.29	1.17,1.42	0.00	0.519
Sugar-sweetened beverages[a]	12	13.10	8.00	1,351,875	135,427	1.11	1.04,1.18	82.10	0.000[b]
Sugar-sweetened beverages[c]	5	11.60	8.50	365,831	32,646	1.05	0.98,1.13	89.60	0.000[b]
Artifically sweetened beverages[a]	7	14.10	8.00	895,485	111,564	1.14	1.05,1.22	76.20	0.000[b]
Artifically sweetened beverages[c]	5	11.90	8.00	325,379	33,435	1.11	0.96,1.27	87.40	0.000[b]
Artifically sweetened beverages[d]	3	28.00	8.00	570,106	78,129	0.99	0.97,1.02	71.80	0.060
Processed meat[a]	14	16.00	8.00	1,810,416	225,000	1.15	1.10,1.21	78.50	0.000[b]
Processed meat[c]	5	11.80	8.00	629,687	32,616	1.05	1.02,1.07	11.20	0.342
Processed red meat[a]	5	16.00	8.00	749,387	165,506	1.19	1.11,1.27	81.80	0.001[b]
Cereal[a]	7	11.10	8.00	594,153	59,020	0.85	0.79,0.92	77.50	0.000[b]
Whole grain cereal[a]	5	11.10	8.00	221,991	11,820	0.77	0.72,0.81	0.00	0.381
Refined grain cereal[a]	2	8.25	8.50	101,982	3,981	1.09	0.96,1.23	0.00	0.951

Abbreviation: UPF, ultra-processed food.

[a] Highest vs. lowest.

[b] Statistically significant.

[c] Consumers vs. non-consumers.

[d] > 1 drink per day.

Table 3. Subgroup analysis of studies assessing the association of SSB and processed meat consumption and all-cause mortality

Subgroups by study characteristics	Number of studies	RR	95 % CI	I^2 for heterogeneity (%)	I^2 for heterogeneity (meta-regression) (%)	P value for heterogeneity (meta-regression)
Sugar-sweetened beverages						
Mean age					69.50	0.003[a]
Below 57.6	3	1.27	0.96,1.67	87.10		
Above /or 57.6	4	1.08	1.01,1.14	10.70		
Publication year					82.10	0.000[a]
Before 2019	5	1.03	0.96,1.11	70.80		
2019 and after	7	1.18	1.09,1.28	68.00		
Median percentage of female population					82.20	0.000[a]
<55.9	5	1.11	1.01,1.22	73.40		
≥55.9	6	1.14	1.04,1.26	81.10		
Mean follow-up years					73.80	0.013[a]
<13.1	4	1.27	1.09,1.47	73.00		
≥13.1	7	1.07	1.00,1.15	71.30		
Location					82.10	0.263
USA	7	1.10	1.02,1.19	83.40		
Other	5	1.14	0.99,1.31	83.30		
Funding					82.10	0.182

Public	6	1.10	1.00,1.21	87.60		
Mix	6	1.13	1.02,1.24	74.20		
Processed meat						
Mean age					80.10	0.012 [a]
Below/or 56.3	7	1.19	1.05,1.36	88.50		
Above 56.3	6	1.12	1.10,1.14	0.00		
Median percentage of female population					78.50	0.024 [a]
<53.2	7	1.12	1.10,1.14	0.00		
>53.2	7	1.19	1.06,1.33	88.50		
Follow up					65.40	0.003 [a]
Below/or 16	8	1.12	1.10,1.15	0.00		
Above 16	5	1.20	1.03,1.39	83.10		
Location					78.50	0.000 [a]
North America	6	1.16	1.08,1.24	76.50		
Europe	8	1.15	1.05,1.26	72.40		
Funding					78.50	0.000 [a]
Public	7	1.18	1.09,1.28	72.10		
Mix	7	1.13	1.05,1.22	75.10		
Publication year					78.50	0.003 [a]
2019 and after	7	1.15	1.05,1.25	84.40		

Before/or 2018	7	1.16	1.08,1.25	53.70		
Quality score					78.50	0.612
<8	3	1.08	0.98,1.18	0.00		
8 and above	11	1.16	1.10,1.23	83.30		
Adjustment					78.50	0.662
Fully adjusted	12	1.15	1.10, 1.21	81.70		
Only adjusted for age/gender/smoking	2	1.00	0.64,1.56	0.00		

Abbreviation: CI, confidence interval.

[a] Statistically significant

Figure 1. PRISMA flow diagram of search strategy.