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Association Between Ultraprocessed Food Consumption and Risk of Mortality Among Middle-aged Adults in France

Laure Schnabel, MD, MSc; Emmanuelle Kesse-Guyot, PhD; Benjamin Allès, PhD; Mathilde Touvier, PhD; Bernard Srour, PharmD; Serge Hercberg, MD, PhD; Camille Buscail, MD, PhD; Chantal Julia, MD, PhD

IMPORTANCE Growing evidence indicates that higher intake of ultraprocessed foods is associated with higher incidence of noncommunicable diseases. However, to date, the association between ultraprocessed foods consumption and mortality risk has never been investigated.

OBJECTIVE To assess the association between ultraprocessed foods consumption and all-cause mortality risk.

DESIGN, SETTING, AND PARTICIPANTS This observational prospective cohort study selected adults, 45 years or older, from the French NutriNet-Santé Study, an ongoing cohort study that launched on May 11, 2009, and performed a follow-up through December 15, 2017 (a median of 7.1 years). Participants were selected if they completed at least 1 set of 3 web-based 24-hour dietary records during their first 2 years of follow-up. Self-reported data were collected at baseline, including sociodemographic, lifestyle, physical activity, weight and height, and anthropometrics.

EXPOSURES The ultraprocessed foods group (from the NOVA food classification system), characterized as ready-to-eat or -heat formulations made mostly from ingredients usually combined with additives. Proportion (in weight) of ultraprocessed foods in the diet was computed for each participant.

MAIN OUTCOMES AND MEASURES The association between proportion of ultraprocessed foods and overall mortality was the main outcome. Mean dietary intakes from all of the 24-hour dietary records available during the first 2 years of follow-up were calculated and considered as the baseline usual food-and-drink intakes. Mortality was assessed using CépiDC, the French national registry of specific mortality causes. Hazard ratios (HRs) and 95% CIs were determined for all-cause mortality, using multivariable Cox proportional hazards regression models, with age as the underlying time metric.

RESULTS A total of 44 551 participants were included, of whom 32 549 (73.1%) were women, with a mean (SD) age at baseline of 56.7 (7.5) years. Ultraprocessed foods accounted for a mean (SD) proportion of 14.4% (7.6%) of the weight of total food consumed, corresponding to a mean (SD) proportion of 29.1% (10.9%) of total energy intake. Ultraprocessed foods consumption was associated with younger age (45-64 years, mean [SE] proportion of food in weight, 14.50% [0.04%]; $P < .001$), lower income (<€1200/mo, 15.58% [0.11%]; $P < .001$), lower educational level (no diploma or primary school, 15.50% [0.16%]; $P < .001$), living alone (15.02% [0.07%]; $P < .001$), higher body mass index (calculated as weight in kilograms divided by height in meters squared; ≥30, 15.98% [0.11%]; $P < .001$), and lower physical activity level (15.56% [0.08%]; $P < .001$). A total of 602 deaths (1.4%) occurred during follow-up. After adjustment for a range of confounding factors, an increase in the proportion of ultraprocessed foods consumed was associated with a higher risk of all-cause mortality (HR per 10% increment, 1.14; 95% CI, 1.04-1.27; $P = .008$).

CONCLUSIONS AND RELEVANCE An increase in ultraprocessed foods consumption appears to be associated with an overall higher mortality risk among this adult population; further prospective studies are needed to confirm these findings and to disentangle the various mechanisms by which ultraprocessed foods may affect health.

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Supplemental content

Author Affiliations: Université Paris 13, Equipe de Recherche en Epidémiologie Nutritionnelle, Centre de Recherche Epidémiologie et Statistique, Sorbonne Paris Cité, Bobigny, France (Schnabel, Kesse-Guyot, Allès, Touvier, Srour, Hercberg, Buscail, Julia); Département de Santé Publique, Hôpital Avicenne (AP-HP), Bobigny, France (Schnabel, Hercberg, Buscail, Julia).

Corresponding Author: Laure Schnabel, MD, MSc, Université Paris 13, Equipe de Recherche en Epidémiologie Nutritionnelle, Centre de Recherche Epidémiologie et Statistique Sorbonne Paris Cité, Inserm U1153, Inra U1125, Cnam, COMUE Sorbonne Paris Cité, UFR SMBH Paris 13, 74 rue Marcel Cachin, Bobigny F-93017, France (l.schnabel@eren.smbh.univ-paris13.fr).

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Ultraprocessed foods are food products that contain multiple ingredients and are manufactured through a multitude of industrial processes.[1] These food products are usually ready to heat and eat, affordable, and hyperpalatable. Examples include mass-produced and packaged snacks, sugary drinks, breads, confectioneries, ready-made meals, and processed meats.

Consumption of ultraprocessed foods has increased during the past several decades[2-5] and is associated with an overall unbalanced nutritional profile.[6] Prospective cohort studies assessed that ultraprocessed foods intake was associated with a higher risk of dyslipidemia,[7] obesity,[8] hypertension,[9] and cancer.[10] Nutritional characteristics of ultraprocessed foods could partly explain the development of noncommunicable chronic diseases among those who consume them. Ultraprocessed foods are generally energy dense, rich in refined carbohydrates, saturated fats, and salt, and contain low dietary fiber. These features have been associated with several noncommunicable diseases that are the leading causes of mortality.[11,12] Beyond their nutritional aspects, ultraprocessed foods have specific characteristics, owing to the industrial processes they undergo. Thus, concern is rising about the potential harmful health consequences of neoformed contaminants[13] or food additives.[14,15]

Cardiovascular disease (CVD), respiratory disease, cancer, and diabetes account for more than 80% of all premature deaths from noncommunicable disease worldwide.[16] Associations between ultraprocessed foods intake and noncommunicable diseases have been documented,[7-10] but no study has directly investigated the association between ultraprocessed foods consumption and mortality. Our aim was to assess the association between ultraprocessed foods consumption and overall mortality risk in a large cohort study of French adults 45 years or older.

Key Points

Question Is high consumption of ultraprocessed food associated with an increase in overall mortality risk?

Findings In this cohort study of 44 551 French adults 45 years or older, a 10% increase in the proportion of ultraprocessed food consumption was statistically significantly associated with a 14% higher risk of all-cause mortality.

Meaning An increase in ultraprocessed food consumption may be associated with an overall higher mortality risk; further prospective research is needed to confirm these findings.

Methods

The NutriNet-Santé Study was approved by the institutional review board of the French Institute for Health and Medical Research and the Commission Nationale de l'Informatique et des Libertés. All participants provided electronic informed consent. Institutional review board approval and informed consent for the NutriNet-Santé Study apply to the current study.

Population and Data Collection

The current study selected participants from the NutriNet-Santé Study, an ongoing prospective observational cohort study that launched on May 11, 2009, and performed a follow-up through December 15, 2017. The NutriNet-Santé Study includes a large voluntary population of adults in France, and its details are described elsewhere.[17]

At the time of inclusion in the NutriNet-Santé Study, participants completed 5 questionnaires pertaining to their own sociodemographic data, anthropometrics, physical activity, and health status.[18-21] Participants were invited to provide a set of 3 nonconsecutive, web-based 24-hour dietary records (records were randomly assigned over a 2-week period) every 6 months and to complete all 5 questionnaires every year.

The 24-hour dietary records were a detailed collection of food and beverages consumed at each of the 3 main meals daily and at any other eating occasions. Participants estimated the quantities they consumed using validated photographs of portion sizes.[22,23] The NutriNet-Santé Study food composition table contains more than 3000 references reflecting the foods consumed by the French population. Detailed information on macronutrient and micronutrient composition of each food is available in a public database.[24] These self-administered 24-hour dietary records were previously validated through comparisons with interviews by dietitians[25] and biomarkers of nutritional status.[26,27]

Eligible participants in this current study had completed at least 1 food set during the first 2 years of follow-up. We identified dietary underreporting using the Black method and excluded underreporters of energy intake.[28] We calculated the mean dietary intakes from all of the 24-hour dietary records available during the first 2 years of follow-up and considered these as the baseline usual dietary intakes.

Each of the 3000 foods in the NutriNet-Santé Study composition table was classified according to the NOVA food classification system, which categorizes food products into 4 groups according to the nature, extent, and purpose of processing.[1] This current study focused on 1 group classified as ultraprocessed foods, which are manufactured industrially from multiple ingredients that usually include additives used for technological and/or cosmetic purposes. Ultraprocessed foods are mostly consumed in the form of snacks, desserts, or ready-to-eat or -heat meals. A comprehensive description of the NOVA food classification system is in eAppendix in the Supplement.

Self-reported data were collected at baseline, including sociodemographic, lifestyle, physical activity level measured with the International Physical Activity Questionnaire,[21] and weight and height, which were used to compute body mass index (BMI). Self-reported anthropometrics have previously been validated when compared with measured data.[19]

Case Ascertainment

Vital status of all participants and causes of death were systematically verified with CépiDC, the French national registry of specific causes of mortality. Causes of death from chronic diseases were identified using the *International Classification of Diseases, Tenth Revision*.[29]

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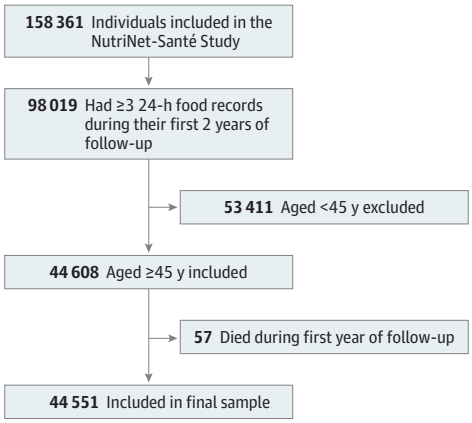
Figure. Study Flowchart



Statistical Analysis

Of the 158 361 participants in the NutriNet-Santé Study, 98 019 provided at least three 24-hour dietary records within the first 2 years of follow-up. We excluded participants younger than 45 years because nutrition-associated causes of deaths were less likely in younger participants. To perform a prospective analysis, we excluded participants who died within the first year of follow-up. Thus, 44 551 people were included for analysis (**Figure**). We used multiple imputations (the fully conditional specification method) to replace missing values.

The proportion in weight of ultraprocessed foods in the diet (% grams per day) was computed for each participant. The energy proportion of ultraprocessed foods in the diet (% kilocalorie per day) was compared with the ultraprocessed foods proportion in a previous study,[6] and proportion in weight was the preferred measure to better consider ultraprocessed foods that did not contribute to energy intake and had features directly related to food processing. For comparison with international data, we also calculated the energy proportion of ultraprocessed foods in the diet.

Adherence to French nutritional recommendations was assessed using the modified Programme National Nutrition Santé Guideline Score (PNNS-GS; no minimum score; maximum: 13.5, with the highest score indicating better compliance with the national nutritional recommendations); this validated score has been described previously.[30] In this current study, using the modified PNNS-GS, we excluded physical activity and considered food-related components only.[31]

Unadjusted means of the proportion of ultraprocessed foods in the diet were calculated and presented for descriptive statistics of the population, using appropriate unpaired, 2-tailed *t* tests or analysis of variance for assessing the between-group differences. Macronutrient and micronutrient intake were log-transformed to approximate normality (log-nutrient). Multivariable regression analysis was performed to assess the association between log-nutrient intake and weight proportion, adjusted for sex, age, and total energy intake. We estimated the proportion of change in nutrient intake for a 10% increase in ultraprocessed foods proportion, using the following transformation of the β coefficient: $100 \times (e^{(\beta)} - 1)$. These analyses were replicated using the energy proportion of ultraprocessed foods in the diet. Analyses were replicated using proportions in weight expressed as quartiles.

We used Cox proportional hazards regression models to estimate the association between ultraprocessed foods proportion (coded as a continuous variable and as quartiles) and overall mortality. Participants contributed person-time until the date of death, the date of last news, or December 15, 2017, whichever occurred first. We estimated hazard ratios (HRs) and 95% CIs for a 10% increase in ultraprocessed foods proportion.

We ran 3 models that were incrementally adjusted to account for known or potential risk factors and confounding factors. Models were computed both on complete cases and imputed data (10 samples). The 3 models were as follows: model 1, minimally adjusted for sex (with age as timescale); model 2, model 1 plus monthly income per household unit (<€1200, €1200-€1799, €1800-€2299, or ≥€2300), educational level (no diploma or primary school, secondary school, graduate studies ≤3 years, or graduate studies >3 years), marital status (married or cohabiting, or single, divorced, widowed), residence (rural, urban unit <20 000 inhabitants, urban unit 20 000-200 000 inhabitants, or urban unit >200 000 inhabitants), BMI (continuous; calculated as weight in kilograms divided by height in meters squared), physical activity level (low, moderate, or high), smoking status (never smoked, former smoker, or current smoker), alcohol intake (continuous; grams per day), energy intake (without alcohol, continuous; kilocalorie per day), first-degree family history of cancer (yes or no), first-degree family history of CVDs (yes or no), number of 24-hour dietary records (continuous), and season of dietary records; and model 3, model 2 plus modified PNNS-GS (continuous). Separating models 2 and 3 enabled us to consider the association between ultraprocessed foods and mortality risk independently from the overall nutritional quality of diet. *P* values for trend were computed using quartiles as ordinal variables. We confirmed that the proportional hazards assumption was satisfied through the examination of the Schoenfeld residual plots.

Two-factor interactions were tested on model 3 between ultraprocessed foods consumption and physical activity, smoking status, and BMI. Because no substantial interaction was detected, all analyses were performed in the overall sample.

We conducted 5 sensitivity analyses by (1) excluding cases of deaths occurring during the first 2 years of follow-up; (2) testing further adjustments on model 3 for prevalent CVDs (myocardial infarction, acute coronary syndrome, stroke, and angioplasty), risk factors for CVDs (type 2 diabetes; hypertension, and dyslipidemia), and prevalent cancer; (3) testing further adjustment on model 3 for a Western dietary pattern derived from principal components analysis; (4) testing the association between ultraprocessed foods and mortality with the absolute amount of ultraprocessed foods consumed (in weight) as the main exposure; and (5) excluding prevalent CVDs and cancers at baseline.

All tests were 2-sided, and a 2-sided $P < .05$ was considered statistically significant. Data management and statistical analysis were performed using SAS software, version 9.4 (SAS Institute Inc).

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Results

A total of 44 551 participants were included, of whom 32 549 (73.1%) were women, with a mean (SD) age at baseline of 56.7 (7.5) years. The mean (SD) number of dietary records during the first 2 years of follow-up was 6.6 (3.1).

Consumption of ultraprocessed foods represented a mean (SD) of 14.4% (7.6%) of the total weight of food and drink intake, corresponding to a mean (SD) of 29.1% (10.9%) of total energy intake. Higher consumption of ultraprocessed foods was associated with younger age (45-64 years, mean [SE] proportion of food in weight, 14.50% [0.04%]; $P < .001$), lower income (<€1200/mo, 15.58% [0.11%]; $P < .001$), lower educational level (no diploma or primary school, 15.50% [0.16%]; $P < .001$), living alone (15.02% [0.07%]; $P < .001$), higher BMI (≥30, 15.98% [0.11%]; $P < .001$), and lower physical activity level (15.56% [0.08%]; $P < .001$) (**Table 1**). Similar results were obtained with ultraprocessed foods proportion coded as quartiles and with energy proportion (eTables 1-3 in the Supplement).

Higher ultraprocessed foods consumption was associated with a lower adherence rate to nutritional recommendations, with a lower modified PNNS-GS (−5.7% for a 10% increase in ultraprocessed foods proportion; $P < .001$). A 10% increment in ultraprocessed foods proportion was associated with higher intake of saturated fats (change in nutrient intake, 3.05% [0.002%]; $P < .001$), and sugars (3.59% [0.002%]; $P < .001$). Conversely, a 10% increment in ultraprocessed foods proportion was associated with lower intake of fiber (−4.88% [0.002%]; $P < .001$; **Table 2**). Similar results were obtained analyzing ultraprocessed foods proportion coded as quartiles and energy proportion (eTables 4-6 in the Supplement).

During follow-up, 602 deaths (1.4%) occurred, including 219 deaths caused by cancer and 34 by CVDs. The median (interquartile range) follow-up time was 7.1 (5.7-7.9) years (mean [SD] follow-up, 6.6 [1.8] years). Associations between ultraprocessed foods consumption and mortality are shown in **Table 3**. After adjusting for a range of covariates (model 3), we found that an increase in ultraprocessed foods consumption was positively associated with all-cause mortality; the HR per 10% increment of ultraprocessed foods consumed was 1.14 (95% CI, 1.04-1.27; $P = .008$). Similar results were observed with ultraprocessed foods proportion coded as quartiles and complete case analyses (eTables 7 and 8 in the Supplement). Associations between energy-weighted proportion of ultraprocessed foods and mortality are tabulated in eTable 9 in the Supplement.

These results were not substantially modified for the sensitivity analyses, carried out with further adjustment in model 3 for prevalent CVDs and cancer, with adjustment for a Western dietary pattern, and with the absolute amount (in weight) of ultraprocessed foods consumed as the exposure. When excluding death cases during the first 2 years of follow-up and when excluding prevalent CVDs and cancer cases, the associations were no longer statistically significant, probably owing to a loss of statistical power (data tabulated in eTables 10 and 11 in the Supplement).

Table 1. Proportion of Ultraprocessed Food in the Diet of Study Participants

Variable	Proportion (in Weight) of Ultraprocessed Food in the Diet	
	Mean (SE), %	*P* Value[a]
Age, y		
45-64	14.50 (0.04)	<.001
≥65	14.08 (0.09)	
Sex		
No.	44 551	
Male	14.89 (0.07)	<.001
Female	14.27 (0.04)	
Income per household unit, €/mo		
No. (%)	39 744 (89.2)	
<1200	15.58 (0.11)	
1200-1799	14.86 (0.08)	<.001
1800-2299	14.63 (0.09)	
≥2300	13.86 (0.06)	
Marital status		
No. (%)	44 521 (99.9)	
Single/divorced/widowed	15.02 (0.07)	<.001
Married/cohabiting	14.24 (0.04)	
Educational level		
No. (%)	44 158 (99.1)	
No diploma or primary school	15.50 (0.16)	
Secondary school	14.95 (0.06)	<.001
Graduate studies, y		
≤3	14.12 (0.07)	
>3	13.81 (0.07)	
Residence		
No. (%)	43 898 (98.5)	
Rural	14.72 (0.08)	
Urban unit		<.001
<20 000 inhabitants	14.47 (0.09)	
20 000-200 000 inhabitants	14.48 (0.08)	
>200 000 inhabitants	14.19 (0.06)	
Smoking status		
No. (%)	44 529 (99.9)	
Never	14.51 (0.05)	<.001
Former	14.23 (0.05)	
Current	14.96 (0.11)	
BMI		
No. (%)	44 415 (99.7)	
<18.5	13.80 (0.21)	
18.5-24.99	14.05 (0.05)	<.001
25-29.99	14.76 (0.07)	
≥30	15.98 (0.11)	
IPAQ activity level		
No. (%)	39 168 (87.9)	
Low	15.56 (0.08)	<.001
Moderate	14.41 (0.06)	
High	13.85 (0.06)	

(continued)

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Table 1. Proportion of Ultraprocessed Food in the Diet of Study Participants (continued)

Variable	Proportion (in Weight) of Ultraprocessed Food in the Diet	
	Mean (SE), %	P Value[a]
First-degree family history of cancer		
No. (%)	44 387 (99.6)	
No	14.47 (0.05)	.40
Yes	14.40 (0.05)	
First-degree family history of CVDs		
No. (%)	44 387 (99.6)	
No	14.46 (0.05)	.30
Yes	14.38 (0.06)	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CVDs, cardiovascular diseases; IPAQ, International Physical Activity Questionnaire.

[a] *P* values were obtained with unpaired, 2-tailed *t* tests or analysis of variance when appropriate.

Discussion

Findings from this prospective study of a large French cohort suggest for the first time, to our knowledge, that an increased proportion of ultraprocessed foods in the diet is associated with a higher risk of overall mortality. Other prospective studies previously observed that ultraprocessed foods intake was associated with higher incidence of dyslipidemia[7] and higher risk of obesity,[8] hypertension,[9] and cancer.[10]

In our sample, ultraprocessed foods accounted for 14.4% of the total weight of food and drink consumed and 29.1% of total energy intake. This proportion of energy intake derived from ultraprocessed foods was lower than in other industrialized countries,[32-34] and it may be a consequence of participants' dietary habits that involve high consumption of unprocessed foods.[6,35] In line with previous findings, the proportion of ultraprocessed foods in the diet varied according to a person's socioeconomic profile and lifestyle.[32,36,37] These results underline the social inequalities associated with food choices. Ultraprocessed foods are attractive products for consumers as they are widely available in supermarkets,[3,4] affordable, highly marketed, ready to eat, and made with a long shelf life.[1]

Several hypotheses could explain the associations between increasing ultraprocessed foods consumption and higher mortality risk. First, some of these foods have a high salt content, and high sodium intake has been associated with cardiovascular deaths[38] and increased stomach cancer risk.[12] Likewise, ultraprocessed foods tend to contribute to excessive intake of added sugar,[33] whereas added sugar consumption has been associated with an increased risk for CVD mortality.[39] Sugary beverages and processed meats may likely be factors in the observed correlation between ultraprocessed foods and mortality, as they have been consistently associated with mortality in prospective studies.[40-43] Conversely, ultraprocessed foods have generally little fiber content, and higher ultraprocessed foods consumption was associated with lower fiber intake, whereas dietary fiber was previously linked with a substantially decreased mortality risk.[44,45] Studies have documented that high ultraprocessed foods consumption was associated with unhealthy dietary patterns involving high intake of calories, fats, sugars, and salt.[32,33,46-49] Those dietary factors could be associated with the development of noncom-

Table 2. Association Between Ultraprocessed Food Consumption and Nutrient Intake of 44 551 Study Participants

Nutrient	Proportion (in Weight) of Ultraprocessed Food in the Diet	
	Change in Nutrient Intake, % (SE)[a]	P Value[b]
Modified PNNS-GS	−5.74 (0.001)	<.001
EI, kcal/d	1.15 (0.001)	<.001
Carbohydrates, % EI	1.61 (0.001)	<.001
Protein, % EI	−1.98 (0.001)	<.001
Lipids, % EI	0.80 (0.001)	<.001
Alcohol, % EI	−13.15 (0.009)	<.001
Alcohol, g/d	−13.21 (0.009)	<.001
Carbohydrates, g/d		
Complex[c]	−0.12 (0.002)	.50
Simple	3.59 (0.002)	<.001
Fibers, g/d	−4.88 (0.002)	<.001
SFA, g/d	3.05 (0.002)	<.001
MUFA, g/d	−0.95 (0.001)	<.001
Fatty acids, g/d		
ω-3	−5.81 (0.003)	<.001
ω-6	1.66 (0.002)	<.001
Cholesterol, g/d	−0.57 (0.002)	.01
Protein, g/d		
Animal	−2.65 (0.002)	<.001
Plant	−2.27 (0.001)	<.001
Sodium, mg/d	2.03 (0.001)	<.001
Potassium, mg/d	−3.67 (0.001)	<.001
Calcium, mg/d	−1.94 (0.002)	<.001
Iron, mg/d	−3.14 (0.002)	<.001
β-Carotene, μg/d	−7.28 (0.004)	<.001
Vitamin		
B_6, mg/d	−2.00 (0.001)	<.001
B_9, μg/d	−3.46 (0.002)	<.001
B_{12}, μg/d	−4.16 (0.004)	<.001
C, mg/d	−10.74 (0.003)	<.001
D, μg/d	−2.94 (0.004)	<.001
E, mg/d	−1.02 (0.002)	<.001

Abbreviations: EI, energy intake; MUFA, monounsaturated fatty acids; PNNS-GS, modified Programme National Nutrition Santé Guideline Score (no minimum score; maximum: 13.5, with the highest score indicating better compliance with the national nutritional recommendations); SFA, saturated fatty acids.

[a] Estimated using the following transformation of the β coefficient: $100 \times (e^{(\beta)}-1)$.

[b] *P* values are obtained with multivariable linear regression adjusted for sex, age, and EI.

[c] Complex carbohydrates refer to carbohydrates that are converted into glucose during digestion (starches such as amylose and amylopectin), as opposed to simple carbohydrates (such as glucose, lactose, and fructose).

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Table 3. Association Between the Proportion of Ultraprocessed Food in the Diet and Overall Mortality Risk in Study Participants

	Proportion of Ultraprocessed Food in the Diet (in Weight)		
Imputed Data	No. of Cases/Noncases	HR (95% CI)[d]	Continuous *P* Value[e]
Model 1[a]	602/43 949	1.20 (1.08-1.32)	<.001
Model 2[b]	602/43 949	1.15 (1.04-1.27)	.005
Model 3[c]	602/43 949	1.14 (1.04-1.27)	.008

Abbreviations: BMI, body mass index; HR, hazard ratio; PNNS-GS, Programme National Nutrition Santé Guideline Score.

[a] Model 1: Adjusted for sex and age.

[b] Model 2: Adjusted for model 1 plus income level, education level, marital status, residence, BMI, physical activity level, smoking status, energy intake, alcohol intake, season of food records, first-degree family history of cancer or cardiovascular diseases, and number of food records.

[c] Model 3: Adjusted for model 2 plus modified PNNS-GS.

[d] HR for an increase of 10% of ultraprocessed foods proportion.

[e] *P* values were obtained with Cox proportional hazards regression model using ultraprocessed foods proportion as a continuous variable.

municable diseases, which further lead to higher mortality risk.[50,51] Studies have estimated that reducing saturated and trans fats, salt, and added sugar from the diet could present major advantages, such as preventing cardiovascular deaths.[52,53]

Associations between ultraprocessed foods consumption and mortality risk were somewhat weakened after adjustment for the modified PNNS-GS, suggesting that the overall nutritional quality of the diet may have a confounding role in the observed association. Even so, the results remained statistically significant after this adjustment; thus, we raise other hypotheses to explain these findings.

First, studies have documented the carcinogenicity of exposure to neoformed contaminants found in foods that have undergone high-temperature processing.[54] The European Food Safety Authority stated in 2015 that acrylamide was suspected to be carcinogenic and genotoxic,[13] and the International Agency for Research on Cancer classified acrylamide as "probably carcinogenic to humans" (group 2A).[13(p11)] Some studies reported a modest association between dietary acrylamide and renal or endometrial cancer risk.[54] Further research is necessary to confirm these speculative hypotheses. Similarly, meat processing can produce carcinogens. The International Agency for Research on Cancer reported in 2015 that processed meat consumption was carcinogenic to humans (group 1), citing sufficient evidence for colorectal cancer.[55] Moreover, the agency found a positive association between processed meat consumption and stomach cancer.[55]

In addition, ultraprocessed foods are characterized by the frequent use of additives in their formulations, and some studies have raised concerns about the health consequences of food additives. For instance, titanium dioxide is widely used by the food industry. However, findings from experimental studies suggest that daily intake of titanium dioxide may be associated with an increased risk of chronic intestinal inflammation and carcinogenesis.[14,56,57] Likewise, experimental studies have suggested that consumption of emulsifiers could alter the composition of the gut microbiota, therefore promoting low-grade inflammation in the intestine and enhancing cancer induction[58] and metabolic syndrome.[15] In addition, some findings suggest that artificial intense sweeteners could alter microbiota and be linked with the onset of type 2 diabetes and metabolic diseases, which are major causes of premature mortality.[59]

Food packaging is also suspected to have endocrine-disrupting properties.[60,61] During storage and transportation of food products, chemicals from food-contact articles can migrate into food, some of which might negatively affect health, such as bisphenol A.[62] Epidemiologic data have suggested that endocrine disruptors are associated with an increased risk of endocrine cancers and metabolic diseases, such as diabetes and obesity.[61]

Concerns about the increased consumption of ultraprocessed foods have led to the September 2018 presentation of a parliamentary report to the French National Assembly. The report emphasized policy actions aimed at improving the nutritional quality of the food supply. In addition, several proposals pertaining to ultraprocessed foods were made, such as product reformulation (eg, limitation in bread salt content, restricted use of additives), reduction of neoformed contaminants and packaging residues found in industrially manufactured food products, and marketing restrictions on ultraprocessed foods.[63] In accordance with a precautionary principle, the objective of reducing ultraprocessed foods consumption by 20% between 2018 and 2021 was introduced for the French 2018-2022 public health nutritional policy.[64]

Strengths and Limitations

Strengths of this study include its prospective design, the use of validated and repeated 24-hour dietary records accounting for intraindividual variability,[25-27] and adjustment for the overall nutritional quality of the diet. Moreover, a large range of confounding factors were considered.

However, the study also has some limitations. First, the sample was taken from the NutriNet-Santé Study, which comprises a voluntary cohort of adults with long-term involvement in this nutrition study; that is, the participants are more health conscious than the general population.[65] We selected participants who provided at least three 24-hour dietary records, which enabled us to increase the quality of dietary data collected, but we may have overrepresented compliant and healthy individuals. Thus, both the mortality rates and ultraprocessed foods intake amounts are probably lower than those in the general population, and consequently we may have underestimated the association observed. Overall caution is warranted when generalizing these results. Second, the risk of reverse causation is a general concern in observational mortality studies because individuals may change their diet after they develop a chronic disease. Exclusion of deaths during the first year has helped to

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minimize this bias. Reverse causation might be biased toward the null hypothesis (rather than inflate estimates), given that individuals with noncommunicable diseases may have modified their diet to follow nutritional recommendations (less consumption of ultraprocessed foods is likely).

Third, access to the type of food processing was not systematic for all of the food items. Each food product was categorized into the most likely NOVA group, but we cannot rule out some misclassification of food items at the individual level. This nondifferential classification bias may have led to an underestimation of the association observed between ultraprocessed foods consumption and mortality. The low number of death cases may have restricted our ability to detect some of the suspected associations. The statistical power was limited by the low number of CVD (n = 34) and cancer (n = 219) deaths, which did not allow us to perform the analysis for cause-specific mortality. The follow-up was rather short (median 7.1 years), although diet-related noncommunicable diseases develop over decades. Lastly, despite accounting for a wide range of confounding factors, we cannot exclude the hypothesis of residual confounding because of the observational design of this study, with its modest HRs and statistical significance. Thus, no causality can be established for the observed associations.

To tackle the issue of residual confounding, we performed models of incremental adjustment to observe the association independently from the nutritional characteristics of ultraprocessed foods and to limit the risk of overadjusted models. To test the robustness of the results in view of the risk for confounding factors resulting from the association between ultraprocessed foods and less healthy diets, we performed sensitivity analyses with adjustment for a Western dietary pattern. These results were consistent with the main analysis findings.

Conclusions

To our knowledge, this prospective study was the first to investigate the association between ultraprocessed foods consumption and mortality risk in a large population-based French cohort. Results suggested a positive association between increased ultraprocessed foods consumption and all-cause mortality risk. Further studies are needed to confirm those results in different populations and to disentangle the various mechanisms by which ultraprocessed foods may affect health, including both their nutritional features and their food processing–related characteristics. Ultraprocessed foods consumption has largely increased during the past several decades and may drive a growing burden of noncommunicable disease deaths.

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Concept and design: Schnabel, Kesse-Guyot, Allès, Touvier, Buscail, Julia.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Schnabel, Kesse-Guyot.
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Statistical analysis: Schnabel, Kesse-Guyot, Srour, Julia.
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REFERENCES

1. Monteiro CA, Cannon G, Moubarac JC, Levy RB, Louzada MLC, Jaime PC. The UN Decade of Nutrition, the NOVA food classification and the trouble with ultra-processing. *Public Health Nutr*. 2018;21(1):5-17. doi:10.1017/S1368980017000234

2. Moodie R, Stuckler D, Monteiro C, et al; Lancet NCD Action Group. Profits and pandemics: prevention of harmful effects of tobacco, alcohol, and ultra-processed food and drink industries. *Lancet*. 2013;381(9867):670-679. doi:10.1016/S0140-6736(12)62089-3

3. Stuckler D, McKee M, Ebrahim S, Basu S. Manufacturing epidemics: the role of global producers in increased consumption of unhealthy commodities including processed foods, alcohol, and tobacco. *PLoS Med*. 2012;9(6):e1001235. doi:10.1371/journal.pmed.1001235

4. Monteiro CA, Moubarac J-C, Cannon G, Ng SW, Popkin B. Ultra-processed products are becoming dominant in the global food system. *Obes Rev*. 2013;14(suppl 2):21-28. doi:10.1111/obr.12107

5. Moubarac J-C, Batal M, Martins APB, et al. Processed and ultra-processed food products: consumption trends in Canada from 1938 to 2011. *Can J Diet Pract Res*. 2014;75(1):15-21. doi:10.3148/75.1.2014.15

6. Julia C, Martinez L, Allès B, et al. Contribution of ultraprocessed foods in the diet of adults from the French NutriNet-Santé study. *Public Health Nutr*. 2018;21(1):27-37.

7. Rauber F, Campagnolo PD, Hoffman DJ, Vitolo MR. Consumption of ultra-processed food products and its effects on children's lipid profiles: a longitudinal study. *Nutr Metab Cardiovasc Dis*. 2015;25(1):116-122. doi:10.1016/j.numecd.2014.08.001

8. Mendonça RD, 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(5):1433-1440. doi:10.3945/ajcn.116.135004

9. Mendonça RD, Lopes ACS, Pimenta AM, Gea A, Martinez-Gonzalez MA, Bes-Rastrollo M. Ultra-processed food consumption and the incidence of hypertension in a Mediterranean cohort: the Seguimiento Universidad de Navarra Project. *Am J Hypertens*. 2017;30(4):358-366.

10. 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.

11. Joint WHO-FAO Expert Consultation. *Diet, Nutrition, and the Prevention of Chronic Diseases. Report of a WHO-FAO Expert Consultation*. Geneva, Switzerland: World Health Organization; 2003.

12. World Cancer Research Fund, American Institute for Cancer Research. Diet, Nutrition, Physical Activity and Cancer: A Global Perspective. The Third Expert Report. dietandcancerreport.org. Accessed April 6, 2018.

13. EFSA Panel on Contaminants in the Food Chain. Scientific Opinion on acrylamide in Food. *EFSA J*. 2015;13(6):4104. doi:10.2903/j.efsa.2015.4104

14. Bettini S, Boutet-Robinet E, Cartier C, et al. Food-grade TiO_2 impairs intestinal and systemic immune homeostasis, initiates preneoplastic lesions and promotes aberrant crypt development

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in the rat colon. *Sci Rep*. 2017;7:40373. doi:10.1038/srep40373

15. Chassaing B, Koren O, Goodrich JK, et al. Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome. *Nature*. 2015;519(7541):92-96. doi:10.1038/nature14232

16. World Health Organization. Noncommunicable diseases. http://www.who.int/mediacentre/factsheets/fs355/en/. Accessed April 20, 2018.

17. Hercberg S, Castetbon K, Czernichow S, et al. The Nutrinet-Santé Study: a web-based prospective study on the relationship between nutrition and health and determinants of dietary patterns and nutritional status. *BMC Public Health*. 2010;10(1):242. doi:10.1186/1471-2458-10-242

18. Vergnaud A-C, Touvier M, Méjean C, et al. Agreement between web-based and paper versions of a socio-demographic questionnaire in the NutriNet-Santé study. *Int J Public Health*. 2011;56(4):407-417. doi:10.1007/s00038-011-0257-5

19. Lassale C, Péneau S, Touvier M, et al. Validity of web-based self-reported weight and height: results of the Nutrinet-Santé study. *J Med Internet Res*. 2013;15(8):e152. doi:10.2196/jmir.2575

20. Touvier M, Méjean C, Kesse-Guyot E, et al. Comparison between web-based and paper versions of a self-administered anthropometric questionnaire. *Eur J Epidemiol*. 2010;25(5):287-296. doi:10.1007/s10654-010-9433-9

21. Craig CL, Marshall AL, Sjöström M, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc*. 2003;35(8):1381-1395. doi:10.1249/01.MSS.0000078924.61453.FB

22. Le Moullec N, Deheeger M, Preziosi P, et al. Validation du manuel-photos utilisé pour l'enquête alimentaire de l'étude SU. VI. MAX. *Cah Nutr Diét*. 1996;31(3):158-164.

23. Hercberg S, Deheeger M. *Portions Alimentaires: Manuel Photos pour l'Estimation des Quantités*. Paris, France: SU-VI-MAX; 1994.

24. Etude Nutrinet-Santé. *Table de Composition des Aliments de l'étude NutriNet-Santé*. Paris, France: Economica Anthropos; 2013.

25. Touvier M, Kesse-Guyot E, Méjean C, et al. Comparison between an interactive web-based self-administered 24 h dietary record and an interview by a dietitian for large-scale epidemiological studies. *Br J Nutr*. 2011;105(7):1055-1064. doi:10.1017/S0007114510004617

26. Lassale C, Castetbon K, Laporte F, et al. Correlations between fruit, vegetables, fish, vitamins, and fatty acids estimated by web-based nonconsecutive dietary records and respective biomarkers of nutritional status. *J Acad Nutr Diet*. 2016;116(3):427-438.e5. doi:10.1016/j.jand.2015.09.017

27. Lassale C, Castetbon K, Laporte F, et al. Validation of a Web-based, self-administered, non-consecutive-day dietary record tool against urinary biomarkers. *Br J Nutr*. 2015;113(6):953-962. doi:10.1017/S0007114515000057

28. Black AE. Critical evaluation of energy intake using the Goldberg cut-off for energy intake: basal metabolic rate. A practical guide to its calculation, use and limitations. *Int J Obes Relat Metab Disord*. 2000;24(9):1119-1130. doi:10.1038/sj.ijo.0801376

29. World Health Organization. *International Statistical Classification of Diseases, Tenth Revision (ICD-10)*. Geneva, Switzerland: World Health Organization; 1992.

30. Estaquio C, Kesse-Guyot E, Deschamps V, et al. Adherence to the French Programme National Nutrition Santé Guideline Score is associated with better nutrient intake and nutritional status. *J Am Diet Assoc*. 2009;109(6):1031-1041. doi:10.1016/j.jada.2009.03.012

31. Assmann KE, Lassale C, Galan P, Hercberg S, Kesse-Guyot E. Dietary quality and 6-year anthropometric changes in a sample of French middle-aged overweight and obese adults. *PLoS One*. 2014;9(2):e87083. doi:10.1371/journal.pone.0087083

32. 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(1):160. doi:10.1186/s12966-015-0317-y

33. Martínez Steele E, Baraldi LG, Louzada ML, Moubarac JC, Mozaffarian D, Monteiro CA. Ultra-processed foods and added sugars in the US diet: evidence from a nationally representative cross-sectional study. *BMJ Open*. 2016;6(3):e009892. doi:10.1136/bmjopen-2015-009892

34. Moubarac J-C, Martins APB, Claro RM, Levy RB, Cannon G, Monteiro CA; Evidence from Canada. Consumption of ultra-processed foods and likely impact on human health. *Public Health Nutr*. 2013;16(12):2240-2248. doi:10.1017/S1368980012005009

35. de Saint Pol T, Ricroch L. *Le Temps de L'alimentation en France*. Paris, France: Insee Premiere; 2012:1417.

36. Djupegot IL, Nenseth CB, Bere E, et al. The association between time scarcity, sociodemographic correlates and consumption of ultra-processed foods among parents in Norway: a cross-sectional study. *BMC Public Health*. 2017;17(1):447. doi:10.1186/s12889-017-4408-3

37. Simões BDS, Barreto SM, Molina MDCB, et al. Consumption of ultra-processed foods and socioeconomic position: a cross-sectional analysis of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). *Cad Saude Publica*. 2018;34(3):e00019717.

38. Mozaffarian D, Fahimi S, Singh GM, et al; Global Burden of Diseases Nutrition and Chronic Diseases Expert Group. Global sodium consumption and death from cardiovascular causes. *N Engl J Med*. 2014;371(7):624-634. doi:10.1056/NEJMoa1304127

39. Yang Q, Zhang Z, Gregg EW, Flanders WD, Merritt R, Hu FB. Added sugar intake and cardiovascular diseases mortality among US adults. *JAMA Intern Med*. 2014;174(4):516-524. doi:10.1001/jamainternmed.2013.13563

40. Abete I, Romaguera D, Vieira AR, Lopez de Munain A, Norat T. Association between total, processed, red and white meat consumption and all-cause, CVD and IHD mortality: a meta-analysis of cohort studies. *Br J Nutr*. 2014;112(5):762-775. doi:10.1017/S000711451400124X

41. Larsson SC, Orsini N. Red meat and processed meat consumption and all-cause mortality: a meta-analysis. *Am J Epidemiol*. 2014;179(3):282-289. doi:10.1093/aje/kwt261

42. Schwingshackl L, Schwedhelm C, Hoffmann G, et al. Food groups and risk of all-cause mortality: a systematic review and meta-analysis of prospective studies. *Am J Clin Nutr*. 2017;105(6):1462-1473. doi:10.3945/ajcn.117.153148

43. Wang X, Lin X, Ouyang YY, et al. Red and processed meat consumption and mortality: dose-response meta-analysis of prospective cohort studies. *Public Health Nutr*. 2016;19(5):893-905. doi:10.1017/S1368980015002062

44. Yang Y, Zhao L-G, Wu Q-J, Ma X, Xiang Y-B. Association between dietary fiber and lower risk of all-cause mortality: a meta-analysis of cohort studies. *Am J Epidemiol*. 2015;181(2):83-91. doi:10.1093/aje/kwu257

45. Veronese N, Solmi M, Caruso MG, et al. Dietary fiber and health outcomes: an umbrella review of systematic reviews and meta-analyses. *Am J Clin Nutr*. 2018;107(3):436-444. doi:10.1093/ajcn/nqx082

46. Luiten CM, Steenhuis IH, Eyles H, Ni Mhurchu C, Waterlander WE. Ultra-processed foods have the worst nutrient profile, yet they are the most available packaged products in a sample of New Zealand supermarkets. *Public Health Nutr*. 2016;19(3):530-538. doi:10.1017/S1368980015002177

47. Cediel G, Reyes M, da Costa Louzada ML, et al. Ultra-processed foods and added sugars in the Chilean diet (2010). *Public Health Nutr*. 2018;21(1):125-133. doi:10.1017/S1368980017001161

48. Moubarac J-C, Batal M, Louzada ML, Martinez Steele E, Monteiro CA. Consumption of ultra-processed foods predicts diet quality in Canada. *Appetite*. 2017;108:512-520. doi:10.1016/j.appet.2016.11.006

49. Poti JM, Mendez MA, Ng SW, Popkin BM. 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(6):1251-1262.

50. Micha R, Peñalvo JL, Cudhea F, Imamura F, Rehm CD, Mozaffarian D. Association between dietary factors and mortality from heart disease, stroke, and type 2 diabetes in the United States. *JAMA*. 2017;317(9):912-924. doi:10.1001/jama.2017.0947

51. Murray CJ, Atkinson C, Bhalla K, et al; U.S. Burden of Disease Collaborators. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. *JAMA*. 2013;310(6):591-608. doi:10.1001/jama.2013.13805

52. Moreira PV, Baraldi LG, Moubarac J-C, et al. Comparing different policy scenarios to reduce the consumption of ultra-processed foods in UK: impact on cardiovascular disease mortality using a modelling approach. *PLoS One*. 2015;10(2):e0118353. doi:10.1371/journal.pone.0118353

53. Moreira PV, Hyseni L, Moubarac J-C, et al. Effects of reducing processed culinary ingredients and ultra-processed foods in the Brazilian diet: a cardiovascular modelling study. *Public Health Nutr*. 2018;21(1):181-188. doi:10.1017/S1368980017002063

54. Virk-Baker MK, Nagy TR, Barnes S, Groopman J. Dietary acrylamide and human cancer: a systematic review of literature. *Nutr Cancer*. 2014;66(5):774-790. doi:10.1080/01635581.2014.916323

55. Bouvard V, Loomis D, Guyton KZ, et al; International Agency for Research on Cancer

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Monograph Working Group. Carcinogenicity of consumption of red and processed meat. *Lancet Oncol*. 2015;16(16):1599-1600. doi:10.1016/S1470-2045(15)00444-1

56. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Carbon black, titanium dioxide, and talc. *IARC Monogr Eval Carcinog Risks Hum*. 2010;93:1-413.

57. Chang X, Zhang Y, Tang M, Wang B. Health effects of exposure to nano-TiO2: a meta-analysis of experimental studies. *Nanoscale Res Lett*. 2013;8(1):51. doi:10.1186/1556-276X-8-51

58. Viennois E, Merlin D, Gewirtz AT, Chassaing B. Dietary Emulsifier-Induced Low-Grade Inflammation Promotes Colon Carcinogenesis. *Cancer Res*. 2017;77(1):27-40.

59. Suez J, Korem T, Zeevi D, et al. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. *Nature*. 2014;514(7521):181-186. doi:10.1038/nature13793

60. Muncke J. Endocrine disrupting chemicals and other substances of concern in food contact materials: an updated review of exposure, effect and risk assessment. *J Steroid Biochem Mol Biol*. 2011;127(1-2):118-127. doi:10.1016/j.jsbmb.2010.10.004

61. Kabir ER, Rahman MS, Rahman I. A review on endocrine disruptors and their possible impacts on human health. *Environ Toxicol Pharmacol*. 2015;40(1):241-258. doi:10.1016/j.etap.2015.06.009

62. Alonso-Magdalena P, Vieira E, Soriano S, et al. Bisphenol A exposure during pregnancy disrupts glucose homeostasis in mothers and adult male offspring. *Environ Health Perspect*. 2010;118(9):1243-1250. doi:10.1289/ehp.1001993

63. L'alimentation Industrielle. Qualité Nutritionnelle, Rôle Dans l'émergence de Pathologies Chroniques, Impact Social et Environnemental de Sa Provenance. Assemblée Nationale. http://www.assemblee-nationale.fr/15/rap-enq/r1266-tI.asp. Accessed October 1, 2018.

64. Haut Conseil de la Santé Publique. Avis relatif aux objectifs quantifiés pour la politique nutritionnelle de santé publique (PNNS) 2018-2022. https://www.hcsp.fr/Explore.cgi/avisrapportsdomaine?clefr=648. Accessed April 6, 2018.

65. Andreeva VA, Deschamps V, Salanave B, et al. Comparison of dietary intakes between a large online cohort study (Etude NutriNet-Santé) and a nationally representative cross-sectional study (Etude Nationale Nutrition Santé) in France: addressing the issue of generalizability in e-epidemiology. *Am J Epidemiol*. 2016;184(9):660-669. doi:10.1093/aje/kww016

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