Ultra-processed food intake and risk of cardiovascular disease: prospective cohort study (NutriNet-Santé)

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ABSTRACT

OBJECTIVE
To assess the prospective associations between consumption of ultra-processed foods and risk of cardiovascular diseases.

DESIGN
Population based cohort study.

SETTING
NutriNet-Santé cohort, France 2009-18.

PARTICIPANTS
105 159 participants aged at least 18 years. Dietary intakes were collected using repeated 24 hour dietary records (5.7 for each participant on average), designed to register participants' usual consumption of 3300 food items. These foods were categorised using the NOVA classification according to degree of processing.

MAIN OUTCOME MEASURES
Associations between intake of ultra-processed food and overall risk of cardiovascular, coronary heart, and cerebrovascular diseases assessed by multivariable Cox proportional hazard models adjusted for known risk factors.

RESULTS
During a median follow-up of 5.2 years, intake of ultra-processed food was associated with a higher risk of overall cardiovascular disease (1409 cases; hazard ratio for an absolute increment of 10 in the percentage of ultra-processed foods in the diet 1.12 (95% confidence interval 1.05 to 1.20); P<0.001, 518 208 person years, incidence rates in high consumers of ultra-processed foods (fourth quarter) 277 per 100 000 person years, and in low consumers (first quarter) 242 per 100 000 person years), coronary heart disease risk (665 cases; hazard ratio 1.13 (1.02 to 1.24); P=0.02, 520 319 person years, incidence rates 124 and 109 per 100 000 person years, in the high and low consumers, respectively), and cerebrovascular disease risk (829 cases; hazard ratio 1.11 (1.01 to 1.21); P=0.02, 520 023 person years, incidence rates 163 and 144 per 100 000 person years, in high and low consumers, respectively). These results remained statistically significant after adjustment for several markers of the nutritional quality of the diet (saturated fatty acids, sodium and sugar intakes, dietary fibre, or a healthy dietary pattern derived by principal component analysis) and after a large range of sensitivity analyses.

CONCLUSIONS
In this large observational prospective study, higher consumption of ultra-processed foods was associated with higher risks of cardiovascular, coronary heart, and cerebrovascular diseases. These results need to be confirmed in other populations and settings, and causality remains to be established. Various factors in processing, such as nutritional composition of the final product, additives, contact materials, and neoformed contaminants might play a role in these associations, and further studies are needed to understand better the relative contributions. Meanwhile, public health authorities in several countries have recently started to promote unprocessed or minimally processed foods and to recommend limiting the consumption of ultra-processed foods.

STUDY REGISTRATION
ClinicalTrials.gov NCT03335644.

WHAT IS ALREADY KNOWN ON THIS TOPIC

The consumption of ultra-processed foods has increased during the past decades in many countries

Epidemiological studies have found associations between intake of ultra-processed food and a higher incidence of dyslipidaemia in children and higher risks of overweight, obesity, and hypertension, as well as higher risks of overall and breast cancers in the French NutriNet-Santé prospective cohort.

Some mechanistic studies suggest cardiometabolic effects for several components commonly found in ultra-processed foods; however, epidemiological evidence is lacking

WHAT THIS STUDY ADDS

In this large prospective cohort (n=105 159), an absolute increment of 10 in the percentage of ultra-processed foods in the diet was associated with a >10% increase in the rates of overall cardiovascular, coronary heart, and cerebrovascular diseases

Further studies are needed to investigate the relative impact of nutritional composition, food additives, contact materials, and neoformed contaminants in this relation

Considering other studies that have shown associations between consumption of ultra-processed foods and other non-communicable diseases, the proportion of ultra-processed food in the diet should be limited and the consumption of unprocessed or minimally processed foods should be promoted instead

Introduction

Cardiovascular disease (CVD) is the main cause of death worldwide, representing one third of all deaths globally.[1] Among modifiable risk and preventive factors in the development and prevention of CVD, the role of diet is crucial.[2] Dietary factors make the largest contribution to CVD mortality at the population level across Europe: 56% of CVD deaths in men and 48% in women were attributable to dietary factors in 2015.[3] In addition to tobacco avoidance, reaching a

balanced diversified diet (regular consumption of fruit, vegetables, fish, and whole grain foods, along with a restriction of sodium, saturated fats, and refined carbohydrates), avoiding excessive alcohol intake, and engaging in regular physical activity are recognised as key factors in the primary and secondary preventions of CVD, according to the World Health Organization and European and American guidelines.[1 4 5]

During the past decades the consumption of ultra-processed foods worldwide has increased substantially.[6-11] According to nationwide food surveys assessing intakes, household expenses, or supermarket sales in European countries, the US, Canada, New Zealand, and Latin American countries, ultra-processed products represent between 25% and 60% of total daily energy intake.[12-23] These trends are triggering the recent interest in researchers to investigate the links between ultra-processed foods and health outcomes. Ultra-processed foods are formulations of many ingredients, several of exclusive industrial use, that result from a sequence of physical and chemical processes applied to foods and their constituents. These foods are thought to be microbiologically safe, convenient, and highly palatable.[24] They often have a higher content of total fat, saturated fat, added sugar, energy density, and salt, along with a lower fibre and vitamin density,[12-20 25] many of these nutritional features being directly related to cardiometabolic health.[2] It is also suggested that these foods might affect satiety control and glycaemic responses.[26] Moreover, food processing might affect nutrient availability in the small intestine by altering the properties of the plant and animal cells in food.[27] Beyond nutritional composition, several compounds of ultra-processed foods that are neoformed during processing could also play a role in cardiovascular health. According to a recent study, acrylamide, a contaminant present in heat treated processed food products (industrially or not) as a result of the Maillard reaction, might be associated with an increased risk of CVD.[28] In addition, acrolein, a compound formed during the heating of fat and that can be found in caramel candies, might be associated with an increased risk of CVD.[29] Furthermore, the packaging of ultra-processed foods might contain materials in contact with food, such as bisphenol A, which could, according to a meta-analysis of observational studies, increase the risk of cardiometabolic disorders,[30] even though prospective cohort studies are still limited. Finally, ultra-processed foods generally contain additives. Although most of them are probably safe, adverse cardiometabolic effects have been suggested for some, such as glutamates,[31] emulsifiers,[32] sulfites,[33] and carrageenan[34] in studies performed on animal models.

NOVA, a classification of foods and drinks based on levels of processing developed by researchers from the University of São Paulo,[24] has enabled research to be carried out on the relation between food processing and health. Some cross sectional and ecological studies have linked the intake of ultra-processed foods of the NOVA classification to overweight, obesity, metabolic syndrome, and functional gastrointestinal disorders.[10 11 35-39] Consumption of ultra-processed food has also been associated with a higher risk of dyslipidaemia in a prospective study conducted on Brazilian children,[40] and higher incidences of overweight, obesity,[41] and hypertension [42] in a cohort of Spanish university students, as well as a higher risk of overall cancer and breast cancer in the French NutriNet-Santé cohort.[43]

We assessed the association between the consumption of ultra-processed foods and the risk of CVD, using up-to-date information on dietary intake.

Methods

Study population

The NutriNet-Santé study is an ongoing web based cohort launched in 2009 in France with the objective of studying the associations between nutrition and health as well as the determinants of dietary behaviours and nutritional status. Details about this cohort have been described previously.[44] Briefly, participants aged 18 years or older with access to the internet have been continuously recruited among the general population since May 2009 using multimedia campaigns. Questionnaires are completed online using a dedicated website (www.etude-nutrinet-sante.fr). Participants are followed using an online platform linked to their email address. Electronic informed consent is obtained from each participant.

Data collection

At baseline, participants completed a set of five questionnaires related to sociodemographic and lifestyle characteristics[45] (for example, sex, date of birth, occupation, educational level, smoking status, number of children), anthropometry[46 47] (height, weight), dietary intakes, physical activity (validated seven day International Physical Activity Questionnaire),[48] and health status (for example, personal and family history of diseases, drug treatment).

Participants were also invited to complete a series of three non-consecutive validated web based 24 hour dietary records at baseline and every six months (to vary the season of completion), randomly assigned over a two week period (two weekdays and one weekend day).[49-51] To be included in the nutrition component of the NutriNet-Santé cohort, it was mandatory to have two dietary records during the overall baseline period. In this prospective analysis, we averaged the mean dietary intakes from the 24 hour dietary records available during the first two years of each participant's follow-up (≤15 records) and considered these as baseline usual dietary intakes. The web based self administered 24 hour dietary records have been tested and validated against both an interview by a trained dietitian[49] and blood and urinary biomarkers.[50 51] Participants used the dedicated web interface to record all foods and beverages consumed during a 24 hour period for each of the three main meals (breakfast, lunch, and dinner) and any other eating occasion. We used previously validated photographs or usual containers

to estimate portion sizes.[52] Dietary underreporting was identified with the method proposed by Black, using the basal metabolic rate and Goldberg cut-off, in order to screen participants with abnormally low energy intakes, and energy under-reporters (20.0% of the cohort) were excluded[53] (see supplementary appendix 1 for details about energy underreporting in the cohort). We calculated mean daily intakes of alcohol, micronutrients, macronutrients, and energy using the NutriNet-Santé food composition database, which contains more than 3300 different items.[54] Amounts consumed from composite dishes were estimated using French recipes validated by nutrition professionals. Sodium intake was assessed through a specific module included in the 24 hour records, taking into account native sodium in foods, salt added during cooking, and salt added on the plate. This method has been validated against sodium urinary excretion biomarkers.[51]

To avoid any modification of dietary behaviours, no individual data were transmitted to the participants, or advice given. We only provided general information on scientific results from the study.

Extent and purpose of food processing

Three trained dieticians categorised the food and beverage items of the NutriNet-Santé composition table into one of the four food groups in NOVA, based on the extent and purpose of industrial food processing.[24 55 56] A committee of specialists in nutritional epidemiology—three dietitians and five researchers—then reviewed the classification. When uncertainty existed about a food or beverage item, researchers reached a consensus based on the percentage of homemade and artisanal foods versus industrial brands of processed and ultra-processed foods reported by the participants. This study primarily focused on the NOVA group of ultra-processed foods. This group includes mass produced packaged breads and buns, sweet or savoury packaged snacks, industrialised confectionery and desserts, sodas and sweetened beverages, meatballs, poultry and fish nuggets, and other reconstituted meat products transformed with the addition of preservatives other than salt (eg, nitrites), instant noodles and soups, frozen or shelf stable ready meals, and other food products made mostly or entirely from sugar, oils, and fats, and other substances not commonly used in culinary preparations, such as hydrogenated oils, modified starches, and protein isolates. Industrial processes notably include hydrogenation, hydrolysis, extrusion, moulding, reshaping, and pre-processing by frying. Flavouring agents, colours, emulsifiers, humectants, non-sugar sweeteners, and other cosmetic additives are often added to these products to imitate sensorial properties of unprocessed or minimally processed foods and their culinary preparations, or to disguise undesirable qualities of the final product. In the ultra-processed group we also included food and beverages that did not fit in the three NOVA groups for unprocessed or minimally processed foods: (fresh, dried, grounded, chilled, frozen, pasteurised, or fermented staple foods such as fruit, vegetables, pulses, rice, pasta, eggs, meat, fish, or milk), processed culinary ingredients (salt, vegetable oils, butter, sugar, and other substances extracted from foods and used in kitchens to transform unprocessed or minimally processed foods into culinary preparations), and processed foods (canned vegetables with added salt, sugar-coated dried fruit, meat products only preserved by salting, cheeses and freshly made unpackaged breads, and other products manufactured with the addition of salt, sugar, or other substances of the "processed culinary ingredients" group). As previously described,[57] we used standardised recipes to identify and disaggregate homemade and artisanal food preparations, and we applied the NOVA classification to the ingredients. Supplementary appendix 2 presents the details about the NOVA classification along with some examples.

Case ascertainment

Participants were asked to report major health events through the yearly health questionnaire, a check-up questionnaire every three months, or at any time through a specific interface on the study website. We then invited participants to provide their medical records (eg, diagnoses, hospital admissions, radiological reports, electrocardiograms) and, if necessary, the study doctors contacted the participants' doctors or medical facilities (clinic, hospital, or laboratory) to collect additional information. A committee of study doctors then reviewed the medical data to validate any major health events. Participants' families or doctors were contacted when there had been no response to the study website for more than one year. This process constituted the main source of case ascertainment in the cohort. Our research team was authorised by the Council of State (No 2013-175) to link data from our general population based cohorts to medico-administrative databases of national health insurance (SNIIRAM). Thus, for participants who provided their social security number (n=50 240), we linked their data to medico-administrative databases of SNIIRAM, limiting potential bias from those who had not reported their CVD to the study investigators. A low proportion of participants (1.7%) emigrated and were not covered by SNIIRAM. Lastly, to identify deaths and potentially missed CVD cases for deceased participants we linked data to CépiDC, the French national cause specific mortality registry, which includes dates and causes of death. This registry is accessible to all French citizens, without specific authorisation or identification number. We classified CVD cases using ICD-CM codes (international classification of diseases-clinical modification, 10th revision). The present study focused on first incident cases of stroke (I64), transient ischaemic attack (G45.8 and G45.9), myocardial infarction (I21), acute coronary syndrome (I20.0 and I21.4), and angioplasty (Z95.8) occurring between inclusion and January 2018.

Statistical analysis

Up to 11 January 2018, 105 159 participants without CVD at baseline and who provided at least two valid 24 hour dietary records during their first two years of follow-up were included (fig 1). For each participant, we calculated the proportion (%) of ultra-processed foods in the total weight of food and beverages consumed (g/day). We determined this by creating a weight ratio rather than energy ratio to account for processed food that does not provide energy (eg, artificially sweetened beverages) and non-nutritional factors related to food processing (eg, neoformed contaminants, additives, and alterations to the structure of raw foods). A sensitivity analysis was also performed by weighting the ultra-processed variable by the energy (%Kcal/day) instead of weight. For all covariates except physical activity, 5% or less of values were missing and were imputed to the modal value (for categorical variables) or median (for continuous variables). For physical activity, the proportion of missing values was higher (14%) because we needed answers to all the questions in the International Physical Activity Questionnaire to calculate the score. To avoid massive imputation for a non-negligible number of participants or exclusion of those with missing data and risk of selection bias, we included a missing class into the models for this variable (main analysis). However, we also tested complete case analysis and multiple imputation in sensitivity analyses: multiple imputation for missing data was performed using the MICE method[58] by fully conditional specification (20 imputed datasets) for the outcome[59] and for several covariates: level of education (5.0% missing data), physical activity level (13.9% missing data), and body mass index (0.6% missing data). Results were combined across imputations based on Rubin's combination rules[60 61] using the SAS PROC MIANALYZE procedure.[62]

To examine differences in baseline characteristics of participants between quarters of the percentage of ultra-processed food in the diet with sex specific cut-offs (computed with PROC RANK BY SEX procedure in SAS), we used analysis of variance (ANOVA) or χ^2 tests when appropriate. We chose sex specific cut-offs because women generally having a healthier diet and consume lower food amounts than men, and this allowed us to ensure equivalent sex ratios between quarters. To provide some information on the nutritional quality of ultra-processed foods, we calculated the proportion across the different categories of the Nutri-score. This score is calculated based on a modified version of the Food Standard Agency Nutrient Profiling system, and it has been endorsed by the French, Spanish, and Belgian ministries of health as the official nutrient profiling system in these countries (see supplementary appendix 3 for details about its calculation).

We used Cox proportional hazards models with age as the primary timescale to evaluate the association between the proportion of ultra-processed foods in the diet (coded as a continuous variable or as quarters with sex specific cut-offs) and incidence of overall CVD, cerebrovascular diseases (stroke and transient ischaemic attack), and coronary heart diseases (myocardial infarction, acute coronary syndrome, and angioplasty). In these models, we censored CVDs other than the one studied at the date of diagnosis (ie, they were considered as non-cases for the disease of interest and contributed person years until the date of diagnosis of CVD). We generated log-log (survival) versus log-time plots to confirm risk proportionality assumptions (see supplementary appendix 4). Hazard ratios and 95% confidence intervals were computed. In continuous models, hazard ratios corresponded to the ratio of instantaneous risks for an absolute increment of 10 in the percentage of ultra-processed foods in the diet (ie, a 0.1 absolute increase in the proportion of ultra-processed foods in the diet). In models based on quarters of the percentage of ultra-processed food in the diet, we obtained P values for linear trends by coding quarters of ultra-processed food as an ordinal variable (1, 2, 3, or 4). We verified the assumption of linearity between consumption of ultra-processed food and risk of CVD using restricted cubic spline functions with the SAS macro written by Desquilbet and Mariotti.[63] Participants contributed person time until the date of CVD diagnosis, date of last completed questionnaire, date of death, or 11 January 2018, whichever occurred first.

Models were adjusted for age (timescale) and sex (model 0), in addition to body mass index (BMI, continuous), physical activity (high, moderate, low, calculated according to International Physical Activity Questionnaire recommendations[48]), smoking status (never, former, and current smokers), number of 24 hour dietary records (continuous), alcohol intake (g/day, continuous), energy intake (kcal/day, continuous), family history of CVD (yes or no), and educational level (less than high school degree, <2 years after high school degree, ≥2 years after high school degree) (model 1). To test for the potential influence of the nutritional quality of the diet in the association between intake of ultra-processed food and risk of CVD, we additionally adjusted this model for saturated fatty acids and sodium and sugar intakes (model 2), or for a healthy dietary pattern derived from principal component analysis (model 3) (see

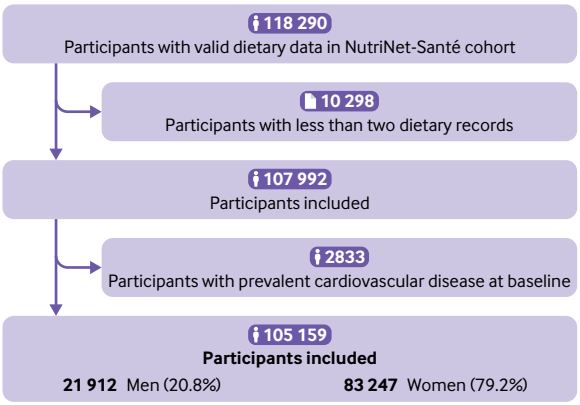

Fig 1 | Flowchart for study sample, NutriNet-Santé cohort, France, 2009-18

supplementary appendix 5 for details), or for intakes of sugary products, red and processed meat, salty snacks, beverages, and fats and sauces (model 4). We also tested a model without adjustment for BMI (model 5) to account for the potential mediating role of BMI in the association. In model 6, we performed further adjustments (based on model 1) for baseline prevalent type 2 diabetes, dyslipidaemia, hypertension, and hypertriglyceridemia (yes or no) as well as treatments for these conditions (yes or no).

We also investigated the association between consumption of ultra-processed food and overall risk of CVD separately in stratums of the population: men and women, younger adults (<45 years) and older adults (≥45 years), participants with a high lipid intake (more than the median) and those with a lower lipid intake, participants with a BMI less than 25 and those with a BMI of 25 or more, participants following a healthy dietary pattern and those following a less healthy one (discriminated by the median of the healthy dietary pattern obtained by the principal component analysis), and participants who tended to be sedentary (the low class of International Physical Activity Questionnaire) and those who tended to be more physically active.

Sensitivity analyses were performed based on model 1 by excluding CVD cases diagnosed during the first two, three, four, and five years of each participant's follow-up to avoid reverse causality bias, by no adjustment for BMI and energy intake, and by testing further adjustments for a Western dietary pattern (continuous), number of smoked cigarettes in pack years (continuous), overall consumption of fruit and vegetables (continuous), dietary fibre intake (continuous), region of residence (Ile-de-France (Paris area) and east, centre east, west, north, southwest, Mediterranean region, or French overseas territories and departments), and season of inclusion in the cohort (spring, summer, autumn, or winter). Models were also tested after restriction of the population study to the participants with six or fewer, or more than six, 24 hour dietary records during the first two years of follow-up. We tested the associations between the quantity (g/day) (rather than the proportion) of intake of ultra-processed food and risk of CVD; as well as the associations between the quantity (g/day) of each ultra-processed food group and risk of CVD; we similarly tested the associations between the quantity (g/day) of non-ultra-processed foods in each group and risk of CVD to check that the associations were not driven by the consumption of specific food groups by themselves. A supplementary analysis was also performed by focusing on participants for whom the proportion of ultra-processed foods in the diet varied varied by less than |0.1| (that is, the absolute (non-negative) value of the difference) between the beginning and end of their follow-up. In the main model we included transient ischaemic attack (corresponding to a brief episode of neurological dysfunction, which has the same underlying mechanism as ischaemic stroke), but we performed a sensitivity analysis by excluding this CVD event. In this study we included angina pectoris events as acute coronary syndrome (ICD code I20), but not stable anginas (considered as soft events occurring only during effort or intense physical activity, which usually do not require hospital admission and might have other causes than coronary obstruction, such as anaemia, abnormal heart rhythms, and heart failure). However, we also tested sensitivity analyses including stable angina events.

Finally, we performed secondary analyses to test the associations between the proportions of unprocessed or minimally processed foods in the diet (continuous) with risk of CVD, using multivariate Cox models adjusted for model 1 covariates.

All tests were two sided, and we considered $P<0.05$ to be statistically significant. SAS version 9.4 (SAS Institute) was used for the analyses.

Patient and public involvement

The research question developed in this article corresponds to a strong concern of the participants involved in the NutriNet-Santé cohort, and of the public in general. The results of the present study will be disseminated to the NutriNet-Santé participants through the cohort website, public seminars, and a press release.

Results

A total of 105 159 participants (21 912 (20.8%) men and 83 247 (79.2%) women) were included in the present study. The mean baseline age of participants was 42.7 (SD 14.5) years (range 18.0-72.8 years). The mean number of dietary records for each participant over their first two years of follow-up was 5.7 (SD 3.0); the minimum was 2, but this applied to only 7.6% (7992 among 105 159 participants) of the participants. Table 1 shows the main baseline characteristics of participants according to quarters of the proportion of ultra-processed foods in the diet. Compared with the first quarter (low consumption), participants among the highest quarters of ultra-processed food intake tended to be younger, be current smokers, be less highly educated, have less family history of CVD, and have lower physical activity levels. Furthermore, they had higher BMI, higher intakes of energy, lipids, carbohydrates, and sodium, lower intakes of alcohol, fruit, vegetables, and dietary fibre, and a lower prevalence of metabolic diseases. The mean contribution of ultra-processed foods to the overall diet (in weight) was 17.6% in men and 17.3% in women. Supplementary appendix 6 presents the distribution of the proportion of ultra-processed food in the diet in the study population. Main food groups contributing to ultra-processed food intake were sugary products (28%, for example, confectionaries, ice cream, pastries, sweetened dairy desserts) followed by ultra-processed fruit and vegetables (18%, for example, instant powder dehydrated vegetable soups and broths, vegetable nuggets, fruit based sweetened desserts), beverages (16%, for example, sodas, sugary and artificially sweetened non-carbonated beverages), starchy foods and breakfast cereals (12%, for example, pre-packaged bread, industrial dough, ready-to-eat

industrial pasta or potato based dishes, breakfast cereals), and processed meat and fish (11%, for example, nuggets, fish fingers, sausages, processed ham) (fig 2). Ultra-processed foods and beverages were usually products with a lower nutritional quality: ultra-processed foods in the NutriNet-Santé food composition database represented more than 85% of the products in the "E" category of the Nutri-score five colour labelling system (the category of lowest nutritional quality) versus less than 24% in the "A" category (the category of highest nutritional quality) (see supplementary appendix 3).

Main associations between ultra-processed food intake and CVD risk

During follow-up (518 208 person years, median follow-up time 5.2 years, interquartile range 2.6-7.3 years), 1409 first incident CVD events occurred, including 106 myocardial infarctions, 485 angioplasties, 74 acute coronary syndromes, 155 strokes, and 674 transient ischaemic events. Table 2 shows the associations between the proportion of ultra-processed foods in the diet and overall cardiovascular, coronary heart, and cerebrovascular diseases. Absolute incidence rates for CVD in the whole population were 253 per 100 000 person years: age and sex corrected absolute rates were 242 per 100 000 person years in the first quarter (low consumers) of the proportion of ultra-processed food intake in the diet, 254 in the second quarter, 252 in the third quarter, and 277 in the fourth quarter (high consumers); with respective rates for coronary heart disease of 109, 116, 125, and 124 per 100 000 person years, and for cerebrovascular diseases of 144, 148, 143, and 163 per 100 000 person years.

In model 1 (adjusted for age (timescale), sex, BMI, physical activity level, smoking status, number of 24 hour dietary records, alcohol intake, energy intake, family history of CVD, and educational level), during a median follow-up of 5.2 years, intake of ultra-processed food was associated with increased risks of

Table 1 | Baseline characteristics of study population according to quarters of ultra-processed food consumption with sex specific cut-offs (n=105 159), NutriNet-Santé cohort, France, 2009-18.* Values are numbers (percentages) unless stated otherwise

		Quarters of ultra-processed food consumption†				
Characteristics	All participants	First (n=26 396) (low intake)	Second (n=26 418)	Third (n=26 326)	Fourth (n=26 019) (high intake)	P value‡
Mean (SD) age (years)	42.7 (14.5)	47.6 (13.6)	44.8 (14.1)	41.8 (14.4)	36.4 (13.5)	<0.001
Sex:						
Women	83 247 (79.2)	20 890 (79.1)	20 905 (79.1)	20 845 (79.2)	20 607 (79.2)	
Men	21 912 (20.8)	5506 (20.9)	5513 (20.9)	5481 (20.8)	5412 (20.8)	
Mean (SD) body mass index	23.6 (4.4)	23.6 (4.2)	23.6 (4.2)	23.6 (4.4)	23.8 (4.8)	<0.001
Family history of CVD§	28 000 (26.6)	8431 (31.9)	7548 (28.6)	6655 (25.3)	5366 (20.6)	<0.001
Educational level:						<0.001
‹High school degree	18 152 (17.3)	4797 (18.2)	4596 (17.4)	4380 (16.6)	4379 (16.8)	
‹2 years after high school	17 971 (17.1)	3896 (14.8)	4006 (15.2)	4527 (17.2)	5542 (21.3)	
≥2 years after high school	69 036 (65.6)	17 703 (67.1)	17 816 (67.4)	17 419 (66.2)	16 098 (61.9)	
Smoking status:						<0.001
Current	17 946 (17.1)	4039 (15.3)	4077 (15.4)	4346 (16.5)	5484 (21.1)	
Former	34 421 (32.7)	10 022 (38.0)	9131 (34.6)	8321 (31.6)	6947 (26.7)	
Never	52 792 (50.2)	12 335 (46.7)	13 210 (50.0)	13 659 (51.9)	13 588 (52.2)	
Physical activity level¶:						<0.001
High	29 443 (28.0)	8776 (33.2)	7555 (28.6)	7146 (27.1)	5966 (22.9)	
Moderate	38 926 (37.0)	9695 (36.7)	10 167 (38.5)	9817 (37.3)	9247 (35.5)	
Low	22 150 (21.1)	4468 (16.9)	5302 (20.1)	5804 (22.0)	6576 (25.3)	
Mean (SD) intakes:						
Energy (kJ/day)	7949.9 (1959.2)	7679.5 (1871.0)	7970.0 (1877.2)	8076.6 (1953.7)	8075.3 (2100.4)	<0.001
Alcohol (g/day)	7.8 (11.8)	9.0 (13.1)	8.5 (11.9)	7.5 (11.1)	5.9 (10.7)	<0.001
Total lipid (g/day)	81.6 (25.3)	77.2 (24.1)	81.4 (24.0)	83.3 (25.0)	84.4 (27.3)	<0.001
Carbohydrate (g/day)	198.1 (57.5)	188.6 (57.4)	197.4 (54.6)	201.9 (56.3)	204.7 (60.2)	<0.001
Sodium (mg/day)	2717.2 (885.6)	2601.1 (867.6)	2749.9 (862.6)	2782.7 (876.9)	2735.3 (923.7)	<0.001
Fruit and vegetables (g/day)	407.1 (221.6)	505.2 (249.9)	434.1 (201.1)	385.2 (192.3)	302.3 (186.5)	<0.001
Total dietary fibre (g/day)	19.5 (7.2)	21.0 (7.7)	20.1 (6.9)	19.3 (6.8)	17.4 (6.9)	<0.001
Ultra-processed food (%)	17.4 (9.9)	7.5 (2.3)	13.0 (1.4)	18.3 (1.8)	30.8 (9.1)	-
Prevalent morbidity:						
Type 2 diabetes	1384 (1.3)	462 (1.7)	366 (1.4)	320 (1.2)	236 (0.9)	<0.001
Hypertension	8279 (7.9)	2613 (9.9)	2277 (8.6)	1993 (7.6)	1396 (5.4)	<0.001
Dyslipidemia	8038 (7.6)	2391 (9.1)	2193 (8.3)	1984 (7.5)	1470 (5.6)	<0.001
Hypertriglyceridemia	1441 (1.4)	384 (1.4)	380 (1.4)	355 (1.3)	322 (1.2)	0.1

IPAQ=International Physical Activity Questionnaire.
*For all covariates except physical activity, a low proportion of values were missing (0-5%); the latter were replaced by the modal value among the population study: ≥2 years of higher education for educational level and 22.9 for body mass index.
†Quarters of proportion of ultra-processed food intake in total quantity of food consumed. Sex specific cut-offs for quarters of ultra-processed proportions were 0.108, 0.156, and 0.220 in men and 0.106, 0.154, and 0.218 in women.
‡Analysis of variance or x^2 test where appropriate.
§Among first degree relatives.
¶Available for 90 519 participants. They were categorised into the high, moderate, and low categories according to IPAQ guidelines.[48]

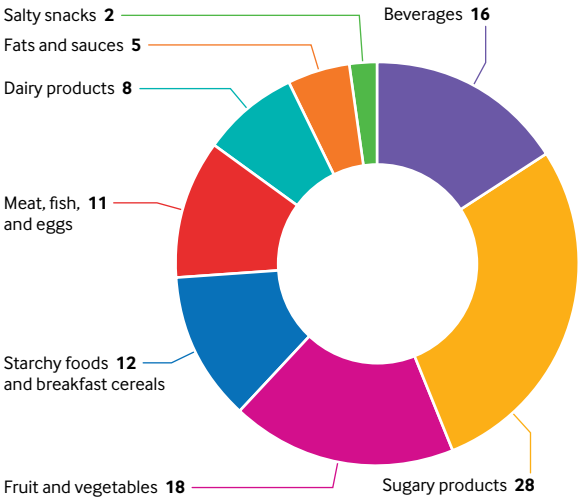

Fig 2 | Relative contribution (%) of each food group to consumption of ultra-processed food in diet

overall CVD (hazard ratio for an absolute increment of 10 in the percentage of ultra-processed foods in the diet 1.12 (95% confidence interval 1.05 to 1.20); P<0.001, 518 208 person years). Intake of ultra-processed food was also associated with increased risks of coronary heart diseases (hazard ratio 1.13 (1.02 to 1.24); P=0.02, 520 319 person years) and cerebrovascular diseases (1.11 (1.01 to 1.21); P=0.02, 520 023 person years). The linearity assumptions between intake of ultra-processed food and risks of overall cardiovascular, coronary heart, and cerebrovascular diseases were confirmed by the restricted cubic spline (respective P values for non-linear associations 0.4, 0.7, and 0.3) (fig 3). Supplementary appendix 4 presents the log-log (survival) versus log-time plots, showing the verification of the proportional hazards assumption. Statistically significant associations were observed for angioplasty (485 cases and 104 674 non-cases, hazard ratio 1.16 (95% confidence interval 1.03 to 1.30); P=0.01) and transient ischaemic attack (674 cases and 104 485 non-cases, 1.13 (1.03 to 1.24); P=0.01). Results were similar for overall CVD when cases of transient ischaemic attack were not considered as CVD (754 cases and 104 405 non-cases, 1.12 (1.02 to 1.23); P=0.02), or when cases of stable angina were considered as CVD (1601 cases and 103 120 non-cases 1.12 (1.06 to 1.19); P<0.001).

Sensitivity analyses

Stratified analyses

The association with risk of overall CVD was statistically significant in all stratums of the population investigated, according to sex, age, lipid intakes, healthy dietary pattern, BMI, and physical activity level (see supplementary appendix 7).

Associations by ultra-processed food groups

Ultra-processed beverages were associated with increased risks of overall CVD (hazard ratio for an increase of 100 g/day=1.06 (95% confidence interval 1.02 to 1.10); P<0.001), ultra-processed fats and sauces (1.73 (1.01 to 2.94); P=0.04) and meats (1.28 (1.00 to 1.64); P=0.05) were associated with an increased risk of coronary heart diseases, and ultra-processed beverages (1.06 (1.01 to 1.12); P=0.01), sugary products (1.12 (1.01 to 1.27); P=0.05), and salty snacks (2.03 (1.04 to 3.94); P=0.04) were associated with an increased risk of cerebrovascular diseases (see supplementary appendix 8a). In contrast, no strong evidence was found for an association between these food groups in their non-ultra-processed form and CVD risk (except for salty snacks, but with broad confidence intervals owing to relatively limited consumption in our study population) (see supplementary appendix 8b).

Further adjustments and sensitivity analyses

Further adjustment for several indicators of the nutritional quality of the diet (saturated fatty acids, sodium and sugar intakes, model 2; healthy dietary pattern, model 3; intakes of sugary products, red and processed meat, salty snacks, beverages, and fats and sauces, model 4, table 2) did not modify these findings. Further adjustment for baseline type 2 diabetes, dyslipidaemia, hypertension, and hypertriglyceridaemia, as well as treatments for these conditions, did not modify the findings (model 6, table 2). The incidence rate for participants with six or fewer records was 209 cases per 100 000 person years (mean age 40.6 years), compared with 344 per 100 000 person years in those with more than six records (mean age 46.6 years); however, similar results were observed in both groups of participants: respectively, hazard ratio for an absolute increment of 10 in the percentage of ultra-processed foods in the diet 1.13 (95% confidence interval 1.03 to 1.24); P<0.001, and hazard ratio 1.11 (95% confidence interval 1.01 to 1.23); P=0.03.

In further sensitivity analyses (see supplementary appendix 9), adjustments for additional nutritional factors (dietary fibre, intake of fruit and vegetables, healthy dietary pattern) as well as other potential confounders (ie, number of smoked cigarettes in pack years, season of inclusion in the cohort, region of residence) did not change the results. Not adjusting for BMI and energy did not affect the associations. We tested other methods to deal with missing data: using multiple imputation with the MICE method, in multivariable analyses adjusted for model 1 covariates the associations remained stable (hazard ratio for overall CVDs 1.16 (95% confidence interval 1.08 to 1.24); P<0.001, for coronary heart diseases 1.15 (1.04 to 1.27); P<0.001, and for cerebrovascular diseases 1.15 (1.05 to 1.26); P<0.001). Complete case analyses also showed similar results (see supplementary appendix 9). Results were also similar when analyses included only cases and censored participants with linked medico-administrative data (1.13 (1.06 to 1.1); P<0.001 for CVD risk). The associations were similar when we used the amount of ultra-processed food intake (g/day), rather than the proportion (hazard ratio for a 100 g/day increase of ultra-processed food in the diet 1.04 (95% confidence interval 1.02 to 1.07);

P=0.001 for CVD risk). However, the associations remained significant after the exclusion of CVD cases with a diagnosis during the first two years of follow-up: hazard ratio 1.14 (95% confidence interval 1.05 to 1.23); P<0.001, 1087 cases and 103 750 non-cases (see supplementary appendix 9), as well as during the first three years (1.44 (1.05 to 1.25); P<0.001, 879 cases and 103 750 non cases), four years (1.44 (1.03 to 1.25); P=0.01, 663 cases and 103 750 non-cases), and five years (1.13 (1.00 to 1.28); P=0.04, 441 cases and 103 750 non-cases). The results also remained stable when the ultra-processed variable was weighted by the energy (% Kcal/day instead of % g/day): hazard ratio for an absolute increment of 10 in the percentage of ultra-processed foods in the diet weighted by energy 1.06 (95% confidence interval 1.01 to 1.12); P=0.01, for overall CVD risk, in multivariable analyses adjusted for model 1 covariates.

Sensitivity analysis focusing on the 85 232 participants for whom the proportion of ultra-processed foods in the diet varied by less than |0.1| between the beginning and end of their follow-up, provided similar results (1029 CVD cases and 84 203 non-cases, hazard ratio for an absolute increment of 10 in the percentage of ultra-processed foods in the diet 1.09 (1.00 to 1.19); P<0.001).

Secondary analyses

As a secondary analysis, we also tested the associations between the proportions of the unprocessed or minimally processed group of the NOVA classification in the diet and risk of CVD. Consistently with our findings, the consumption of unprocessed or minimally processed foods was associated with lower risks of overall cardiovascular, coronary, and cerebrovascular diseases (hazard ratio for an absolute increment of 10 in the percentage of unprocessed or minimally processed foods in the diet 0.91 (0.86 to 0.97); P<0.001 for overall CVD, hazard ratio 0.91 (95% confidence interval 0.84 to 0.99); P=0.04 for coronary heart diseases and 0.91 (0.84 to 0.98); P=0.02 for cerebrovascular diseases), in multivariable analyses adjusted for model 1 covariates.

Discussion

In this large prospective cohort, an absolute increment of 10 in the percentage of ultra-processed foods in

Table 2 | Associations between intake of ultra-processed food and overall cardiovascular, coronary heart, and cerebrovascular diseases from multivariable* Cox proportional hazard models, in NutriNet-Santé cohort, France, 2009-18 (n=105 159). Values are hazard ratios (95% confidence intervals) unless stated otherwise

Models by disease type	Quarters of ultra-processed food consumption†						
	First (low intake)	Second	Third	Four (high intake)	P trend	Continuous‡	P value
All cardiovascular diseases							
No of cases/non-cases	446/25 950	410/26 008	330/25 996	223/25 796		1409/103 750	
Model 0	1	1.06 (0.93 to 1.22)	1.08 (0.93 to 1.24)	1.25 (1.06 to 1.47)	0.01	1.13 (1.06 to 1.21)	<0.001
Model 1	1	1.04 (0.91 to 1.19)	1.07 (0.93 to 1.23)	1.23 (1.04 to 1.45)	0.02	1.12 (1.05 to 1.20)	<0.001
Model 2	1	.05 (0.92 to 1.20)	1.08 (0.93 to 1.25)	1.25 (1.05 to 1.47)	0.02	1.13 (1.05 to 1.20)	<0.001
Model 3	1	1.03 (0.90 to 1.18)	1.05 (0.91 to 1.22)	1.20 (1.01 to 1.42)	0.05	1.11 (1.03 to 1.19)	0.003
Model 4	1	1.03 (0.90 to 1.18)	1.06 (0.90 to 1.23)	1.21 (1.02 to 1.45)	0.05	1.12 (1.04 to 1.20)	0.002
Model 5	1	1.05 (0.92 to 1.20)	1.08 (0.93 to 1.24)	1.26 (1.07 to 1.48)	0.01	1.13 (1.06 to 1.21)	<0.001
Model 6	1	1.04 (0.91 to 1.19)	1.06 (0.92 to 1.23)	1.23 (1.04 to 1.45)	0.03	1.12 (1.05 to 1.20)	0.001
Coronary heart diseases§							
No of cases/non-cases	208/26 188	194/26 224	166/26 160	97/25 922		665/104 494	
Model 0	1	1.08 (0.89 to 1.31)	1.19 (0.97 to 1.46)	1.23 (0.96 to 1.57)	0.04	1.15 (1.04 to 1.26)	0.006
Model 1	1	1.07 (0.87 to 1.30)	1.19 (0.97 to 1.46)	1 20 (0.93 to 1.53)	0.07	1.13 (1.02 to 1.24)	0.02
Model 2	1	1.07 (0.87 to 1.30)	1.20 (0.97 to 1.47)	1.22 (0.95 to 1.56)	0.05	1.14 (1.03 to 1.26)	0.01
Model 3	1	1.05 (0.86 to 1.28)	1.17 (0.95 to 1.44)	1.16 (0.90 to 1.49)	0.1	1.11 (1.00 to 1.23)	0.04
Model 4	1	1.05 (0.86 to 1.28)	1.17 (0.95 to 1.46)	1.18 (0.91 to 1.53)	0.1	1.12 (1.01 to 1.24)	0.03
Model 5	1	1.07 (0.88 to 1.31)	1.20 (0.97 to 1.47)	1.22 (0.96 to 1.57)	0.05	1.14 (1.03 to 1.26)	0.009
Model 6	1	1.06 (0.87 to 1.29)	1.18 (0.96 to 1.45)	1.18 (0.93 to 1.52)	0.08	1.12 (1.02 to 1.24)	0.02
Cerebrovascular diseases¶							
No of cases/non-cases	267/26 129	238/26 180	188/26 138	136/25 883		829/104 330	
Model 0	1	1.03 (0.87 to 1.23)	1.01 (0.84 to 1.22)	1.24 (1.00 to 1.53)	0.1	1.11 (1.02 to 1.21)	0.02
Model 1	1	1.01 (0.85 to 1.21)	0.99 (0.82 to 1.20)	1.24 (1.00 to 1.53)	0.1	1.11 (1.01 to 1.21)	0.02
Model 2	1	1.02 (0.86 to 1.22)	1.01 (0.84 to 1.22)	1.25 (1.01 to 1.55)	0.1	1.12 (1.02 to 1.22)	0.02
Model 3	1	1.00 (0.84 to 1.20)	0.99 (0.81 to 1.19)	1.21 (0.98 to 1.51)	0.2	1.10 (1.00 to 1.20)	0.04
Model 4	1	1.01 (0.84 to 1.21)	1.00 (0.82 to 1.21)	1.23 (0.98 to 1.54)	0.2	1.11 (1.01 to 1.22)	0.03
Model 5	1	1.02 (0.85 to 1.21)	1.00 (0.83 to 1.21)	1.26 (1.01 to 1.55)	0.1	1.11 (1.02 to 1.22)	0.01
Model 6	1	1.01 (0.85 to 1.21)	0.99 (0.82 to 1.20)	1.23 (1.00 to 1.53)	0.1	1.11 (1.01 to 1.21)	0.02

Mean follow-up times for overall cardiovascular, coronary heart, and cerebrovascular diseases were all equal to 5.2 years. Person years were, respectively, 518 208, 520 319, and 520 023.
*Model 0 is an age (timescale) and sex-adjusted Cox proportional hazard model.
Model 1 is a multivariable Cox proportional hazard model adjusted for age (timescale), sex, energy intake, number of 24 hour dietary records, smoking status, educational level, physical activity, body mass index, alcohol intake, and family history of cardiovascular disease. Model 2=model 1+saturated fatty acid intake, sodium intake, sugar intake. Model 3=model 1+healthy dietary pattern (derived by factor analysis). Model 4=model 1+intakes of sugary products, red and processed meat, salty snacks, beverages, and fats and sauces. Model 5=model 1 without adjustment for body mass index. Model 6=model 1+baseline prevalent type 2 diabetes, dyslipidemia, hypertension, and hypertriglyceridemia (yes or no) as well as treatments for these conditions (yes or no).
†Sex specific cut-offs for quarters of ultra-processed proportions were 0.108, 0.156, and 0.220 in men and 0.106, 0.154, and 0.218 in women.
‡Hazard ratio for an absolute increment of 10 in percentage of ultra-processed foods in diet.
§Includes myocardial infarctions, angioplasties, and acute coronary syndromes.
¶Includes strokes and transient ischaemic attacks.

the diet was associated with a 12%, 13%, and 11% statistically significant increase in the rates of overall cardiovascular, coronary heart, and cerebrovascular disease, respectively. Although consumption of ultra-processed food has been associated with increased risks of cancer in the NutriNet-Santé cohort,[43] and with cardiometabolic disorders, such as obesity,[41] hypertension,[42] and dyslipidaemia,[40] no prospective epidemiological study had evaluated the association between the proportion of processed food in the diet and risk of CVD.

Interpretation and comparison with other studies

Several hypotheses could explain our findings. Firstly, ultra-processed foods generally have a poorer nutritional quality than unprocessed or processed foods, as they tend to be richer in sodium, energy, fat, and sugar, and poorer in fibres[12-19 25]; they are also associated with a higher glycaemic response.[26] Several of these nutritional compounds are known risk factors for cardiometabolic health, with a high level of evidence for high sodium, saturated fat, and added sugars, and low dietary fibre, and a "general concordance" for high glycaemic index or load.[2] In addition, several food groups that are mainly ultra-processed and are largely consumed in Western type diets have been associated with increased risks of cardiometabolic outcomes with a "high concordance"—that is, sugar sweetened beverages and processed meats.[2] Sugar sweetened beverages might delay the trigger of the internal satiety signal, leading to excessive caloric ingestion.[64] Among other determinants, excessive intakes of energy, fat, and sugar contribute to weight gain and the risk of overweight or obesity, the latter being recognised as a major risk factor for CVDs.[65] However, several ultra-processed foods and beverages (confectionery snacks, sugar sweetened beverages, cakes, sports drinks, breakfast cereals) might contain relatively high levels of glucose-derived advanced glycation end products,[66] which over time could lead to or accelerate vascular disease.[67] In addition, high consumers of ultra-processed food in our study sample had lower intakes of fruit and vegetables; high intakes of which, along with adherence to a healthy dietary pattern, are known to be beneficial to cardiometabolic health (a high level of evidence).[2] More generally, part of the association between intake of ultra-processed food and risk of CVD may partly come from the simultaneous lower consumption of non-ultra-processed foods. It is difficult to distinguish between both effects because, by construction, people who had an overall higher share of ultra-processed foods in their diet also had a lower overall proportion of non-ultra-processed foods (Pearson correlation coefficient between the proportions of minimally processed and ultra-processed foods in the diet −0.8). This did not, however, explain the whole association. Indeed, several ultra-processed food groups were associated with an increased risk of CVD, but not the non-ultra-processed form of these food groups. Besides, the associations observed in this study between intake of ultra-processed food and risk of CVD were statistically significant even after adjustment for BMI, and they remained significant after further adjustment for healthy and Western dietary patterns, energy, fat, sugar, salt, and fibre content of the diet, as well as consumption of sugary products, salty snacks, fats and sauces, red and processed meat, beverages, fruit, and vegetables. This suggests that the nutritional composition of ultra-processed foods was not the only factor driving the associations observed and that other bioactive compounds specifically contained in ultra-processed food could be contributing to the observed relations.

A second interpretation concerns the wide range of additives in ultra-processed foods. Although maximum authorised levels normally protect consumers against adverse effects of individual substances in certain

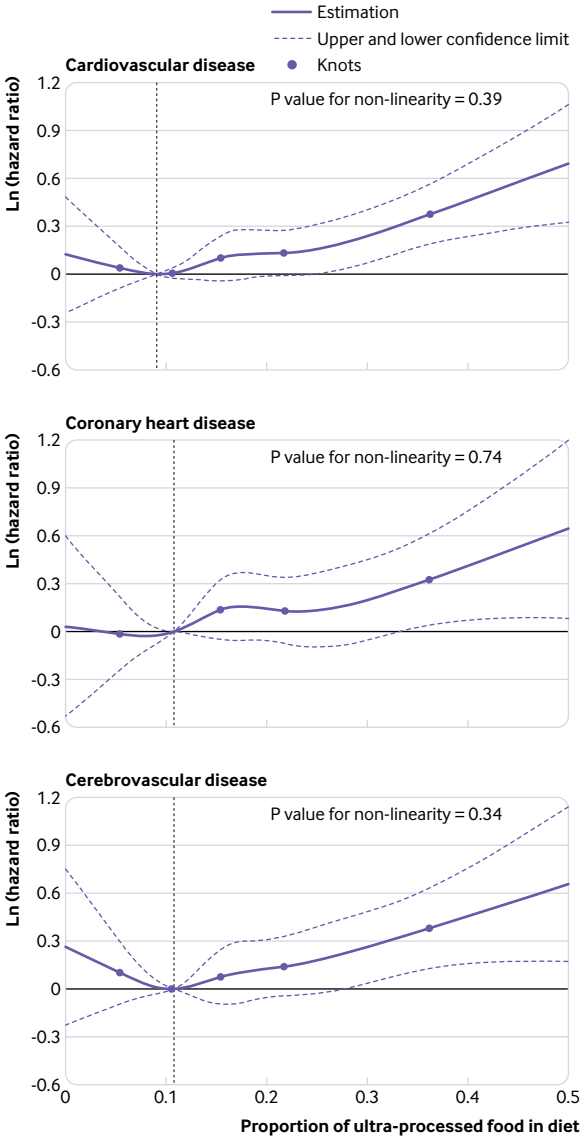

Fig 3 | Spline plot for linearity assumption of association between proportion of ultra-processed food in diet and risks of overall cardiovascular, coronary heart, and cerebrovascular diseases. Restricted cubic spline SAS macro developed by Desquilbet and Mariotti[63]

food products,[68] the health impact of the cumulative intake across all ingested foods and potential cocktail or interaction effects remain largely unknown. For some of the roughly 350 different authorised additives in Europe, several adverse effects for cardiovascular health have been suggested in experimental studies on animal or cellular models. For example, high oral doses of sulphites, which can be found in some ready-to-consume sauces containing vinegar, caused damage to rat hearts[33]; doses of monosodium glutamate (high levels present especially in sauces and ready-to-eat soups and noodles) at doses of 4 mg/g body weight or more in mice increased the oxidative stress through lipid peroxidation and thereby might initiate atherosclerosis and other coronary heart diseases.[31] Moreover, monosodium glutamate has suspected obesogenic properties, with epidemiological evidence positively correlating its consumption to increased body mass index and higher prevalence of metabolic syndrome.[69] In addition, emulsifiers, often found in ultra-processed foods, and particularly carboxymethylcellulose and polysorbate-80, have shown potential roles in inducing low grade inflammation and obesity or metabolic syndrome in mice.[32] Carrageenan, used as a food additive for its thickening properties, might lead to glucose intolerance, insulin resistance, and inhibition of insulin signalling, as shown in a study on cell and animal models.[34] Non-caloric artificial sweeteners could play a role in these associations: long term consumption of acesulfame K might accelerate atherosclerosis in cellular models,[70] whereas in a randomised control trial, sucralose was found to increase glucose and insulin levels in obese women, alter metabolic response to a glucose load, and slow down insulin clearance from plasma.[71]

Food processing, and particularly heat treatments, also produce neoformed contaminants, such as acrylamide in fried potatoes, biscuits, bread, or coffee, and acrolein in grilled sausages and caramel candies. Acrylamide was associated with higher odds of CVDs in the NHANES (National Health and Nutrition Examination Survey) study,[28] whereas in the Louisville Healthy Heart Study exposure to acrolein was associated with platelet activation and suppression of circulating angiogenic cell levels, as well as increased risks of CVD.[29]

Finally, ultra-processed foods might be contaminated by contact materials (those suspected of migrating from packaging), among which is bisphenol A in some plastic packaging, judged as "a substance of very high concern" by the European Chemicals Agency,[72] and which in a recent meta-analysis was found to be associated with an increased risk of cardiometabolic outcomes (in particular hypertension and coronary artery disease).[30]

In this observational study, to avoid modification of dietary behaviours, the participants received no individual data or advice (only general information on scientific results from the study). Moreover, the topic of ultra-processed food is relatively new to French people, thus substantial media driven dietary modifications on this specific aspect are of low probability in the timeframe considered in this study. Besides, models that focused on participants whose proportion of ultra-processed foods in the diet varied by less than |0.1| provided similar results between the beginning and end of their follow-up.

Strengths and limitations of this study

Strengths of this study relate to its prospective design, along with a detailed and up-to-date assessment of dietary intake. Repeated 24 hour dietary records (including 3300 different food items) are more accurate than food frequency questionnaires with aggregated food groups, or than household purchasing data.[73] However, the study has several limitations. Firstly, residual confounding from unmeasured behavioural factors or imprecision in the measure of included covariates cannot be excluded owing to the observational design of this study. For example, in model 6, we considered treatments for each metabolic disorder as binary variables, since the duration of treatment and compliance were not measured. To limit residual confounding, we accounted for many potential confounders, and several sensitivity analyses (testing further adjustments or stratifications) showed the high stability of the results. Causality of the associations cannot be established from this single study. Although randomised controlled trials are considered ideal for eliminating confounding bias, they would not be ethically feasible for studying exposures with a suspected deleterious effect. Besides, they do not capture consumption as it is in daily life. Our large observational cohort was therefore particularly adapted to provide such insights. Secondly, some misclassification in the NOVA category of ultra-processed food cannot be ruled out, although the committee that performed or reviewed the classifications tried to avoid any unidirectional and systematic bias. Any remaining misclassification could have led to a non-differential measurement error (identically in future cases and non-cases), most probably leading to an underestimation of the observed associations, although an overestimation cannot be excluded. Moreover, ultra-processed foods represent a broad and diverse spectrum of food products. In this study, some associations were observed for several different ultra-processed food groups (beverages, fats and sauces, meat, fish and eggs, sugary products, and salty snacks). Most importantly, the effects of ultra-processed foods on human health might go through complex mechanisms involving synergic effects of many compounds and characteristics of ultra-processed foods. Chronic exposure to multiple factors, including cocktails of commonly used food additives (eg, glutamate salts in sauces, artificial sweeteners in beverages, preservatives in ready-to-eat meals), neoformed compounds, and contact materials could play a role in the studied association. These mechanisms can hardly be distinguished based on food groups as they should be considered globally. Creating an indicator for the proportion of ultra-processed foods

in the diet allows those with a high or low exposure to these multiple interactions to be distinguished. The fact that the associations were stronger when the overall ultra-processed food proportion in the diet was considered rather than the associations in specific food groups, argue in favour of these potential cocktail effects. Thirdly, a multi-source strategy for case ascertainment (combining validation of health events self reported by participants, thorough investigation by study doctors of participants, their families, and their doctors, medico-administrative databases from the health insurance for all participants who provided their identification number, and the exhaustive national death and causes of death registry), allowed us to maximise cases detection, but complete ascertainment cannot be guaranteed. Furthermore, statistical power was somehow limited for specific types of CVD, which could have affected our ability to detect hypothesised associations. Fourthly, the length of follow-up was relatively limited, as the cohort was launched in 2009. Thus, it allowed us to study mostly mid-term associations between consumption of ultra-processed food and risk of CVD, while having recent data on dietary behaviours, covering the consumption of "contemporary" ultra-processed foods on the market. Still, a classic assumption in nutritional epidemiology is that the measured exposure at baseline (especially since we averaged a two year period of exposure) actually reflects more generally the usual eating habits of people not only at the moment of the study but also several years before and several years after their inclusion in the cohort. Thus, we assume that our study provided insights into the associations between long term consumption of ultra-processed foods and risk of CVD. To investigate longer term associations, it will be important in the future to reassess the associations between intake of ultra-processed food and risk of CVD in the cohort.

Fifthly, we used a weight ratio (in % g/day) to calculate the proportion of ultra-processed foods in the diet rather than an energy ratio to account for ultra-processed food that does not provide energy (eg, artificially sweetened beverages) and non-nutritional factors related to food processing (eg, neoformed contaminants, food additives, and alterations to the structure of raw foods). However, because the densities of different types of ultra-processed foods differ (eg, salty snacks vs. beverages), no ideal weighting method exists. Nonetheless, sensitivity analyses were carried out using an energy ratio, and results were unchanged. Sixthly, the effect sizes observed in this study are consistent with those usually observed in large nutritional epidemiological cohorts.[74 75] Even though the hazard ratios might seem relatively limited for nutritional exposures, the potential public health impact of these associations could be important because the consumption of the studied factors (ultra-processed foods) is common and widespread in the general population. Lastly, as is usually the case in volunteer based cohorts, participants in the NutriNet-Santé cohort were younger, more often women, and had higher socio-professional and educational levels than the general French population.[76] They were also less likely to smoke,[77] to be overweight or obese (28.2% of men and 29.4% of women in NutriNet-Santé *v* 54% and 44% in French population),[78] and to have type 2 diabetes (baseline prevalence in cohort 1.6% *v* 6% in French population[79]). Participants in the NutriNet-Santé cohort also had healthier dietary intakes than the French population: higher intakes of fruit, vegetables, and fish, and lower intakes of red meat and added fats.[77] This could have resulted in a lower incidence of CVDs compared with national estimates (age and sex standardised incidence rate per 100 000 population yearly: 495 cases in our cohort (253 before standardisation) *v* 500 in France,[80] although these figures are not strictly comparable because, unlike in our cohort, no national data are available in France for patients with CVD who were not admitted to hospital) and an underrepresentation of consumers of high ultra-processed food, leading to a lower contrast between extreme categories.[80] These points most probably resulted in an underestimation of the strength of the associations. However, the possibility that selection bias might have led to an overestimation of some associations cannot be ruled out. To date, no nationally representative data are available on the proportion of ultra-processed food in the diet in the French population, thus comparison with our population study is not straightforward. The nationally representative INCA3 study conducted by the French Food safety Agency in 2016[81] was not based on the NOVA classification. However, the authors provided a list of all food groups that they considered as "transformed" (sweet pastries, biscuits, dairy desserts, ice cream, fruit purée and fruit in syrup, fruit and vegetable juices, soups and broths, sandwiches, pizzas, and salted pastries, as well as mixed dishes composed of egg, meat, fish, vegetable, or starchy foods). More than half of the "transformed" foods consumed outside catering establishments by adults aged between 18 and 79 years were manufactured (about one third were homemade, with the remainder handcrafted, such as by a caterer).

Conclusions and policy implications

In this large prospective cohort we identified an increase in the risk of CVDs associated with the proportion of ultra-processed food in the diet. These findings need to be confirmed by other large scale population based studies in different populations and settings. Besides, the concept of food processing is complex, as the possible processes and the authorised additives are multiple. Further studies are needed to investigate the relative impact of nutritional composition, food additives, contact materials, and neoformed contaminants in this association. Our research team is currently launching a large scale programme on chronic exposure to food additives (single substances and multi-exposure "cocktails") and health.[82] The NutriNet-Santé cohort is in an excellent position to conduct such an investigation

as the participants record all commercial names and brands of industrial products consumed in dietary records, which is crucial for an accurate evaluation of exposure at the individual level, as a result of the high variability in additive composition between brands for a similar type of product. Further investigations are also planned in the future, related to contact materials (eg, containers used for microwave heating of ready-made meals) and some neoformed compounds. If causality is established, increasing trends of ultra-processed food intake in developed countries could contribute to the increase in burden from CVD. Even if it remains unclear what specific processes, compounds, or ultra-processed food subtypes play a more important role, evidence is accumulating for an association between increased overall proportion of ultra-processed food in the diet and increased risks of several chronic diseases.[37 40-43] It is therefore important to inform consumers about these associations and to implement actions targeting product reformulation (eg, improving nutritional quality and reducing the use of unnecessary additives), taxation, and communication to limit the proportion of ultra-processed foods in the diet and promote the consumption of unprocessed or minimally processed foods instead.[7 24] For precautionary reasons, several countries, such as France and Brazil, have already introduced these recommendations in their official nutritional guidelines.[83 84]

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Supplementary information: appendices 1-9