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ABSTRACT

OBJECTIVE

To assess the associations between exposure to food additive emulsifiers and risk of cardiovascular disease (CVD).

DESIGN

Prospective cohort study.

SETTING

French NutriNet-Santé study, 2009-21.

PARTICIPANTS

95 442 adults (>18 years) without prevalent CVD who completed at least three 24 hour dietary records during the first two years of follow-up.

MAIN OUTCOME MEASURES

Associations between intake of food additive emulsifiers (continuous (mg/day)) and risk of CVD, coronary heart disease, and cerebrovascular disease characterised using multivariable proportional hazard Cox models to compute hazard ratios for each additional standard deviation (SD) of emulsifier intake, along with 95% confidence intervals.

RESULTS

Mean age was 43.1 (SD 14.5) years, and 79.0% (n=75 390) of participants were women. During follow-up (median 7.4 years), 1995 incident CVD, 1044 coronary heart disease, and 974 cerebrovascular disease events were diagnosed. Higher intake of celluloses (E460-E468) was found to be positively associated with higher risks of CVD (hazard ratio for an increase of 1 standard deviation 1.05, 95% confidence interval 1.02 to 1.09, P=0.003) and coronary heart disease (1.07, 1.02 to 1.12, P=0.004). Specifically, higher cellulose E460 intake was linked to higher risks of CVD (1.05, 1.01 to 1.09, P=0.007) and coronary heart disease (1.07, 1.02 to 1.12, P=0.005), and higher intake of carboxymethylcellulose (E466) was associated with higher risks of CVD (1.03, 1.01 to 1.05, P=0.004) and coronary heart disease (1.04, 1.02 to 1.06, P=0.001). Additionally, higher intakes of monoglycerides and diglycerides of fatty acids (E471 and E472) were associated with higher risks of all outcomes. Among these emulsifiers, lactic ester of monoglycerides and diglycerides of fatty acids (E472b) was associated with higher risks of CVD (1.06, 1.02 to 1.10, P=0.002) and cerebrovascular disease (1.11, 1.06 to 1.16, P<0.001), and citric acid ester of monoglycerides and diglycerides of fatty acids (E472c) was associated with higher risks of CVD (1.04, 1.02 to 1.07, P=0.004) and coronary heart disease (1.06, 1.03 to 1.09, P<0.001). High intake of trisodium phosphate (E339) was associated with an increased risk of coronary heart disease (1.06, 1.00 to 1.12, P=0.03). Sensitivity analyses showed consistent associations.

CONCLUSION

This study found positive associations between risk of CVD and intake of five individual and two groups of food additive emulsifiers widely used in industrial foods.

TRIAL REGISTRATION

ClinicalTrials.gov NCT03335644.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Emulsifiers are food additives widely used in industrially processed foods to improve texture and extend shelf-life

Research on healthy individuals suggests deleterious effects of food additive emulsifiers on the intestinal microbiota and metabolome

Such effects can lead to chronic intestinal inflammation and increasing susceptibility to carcinogenesis, and potentially cardiovascular disease (CVD)

WHAT THIS STUDY ADDS

Higher intakes of two emulsifier groups (total celluloses and total monoglycerides and diglycerides of fatty acids), and in particular four emulsifiers (E460, E466, E472b, E472c) were independently and positively associated with risk of CVD

These results suggest that food additive emulsifiers are associated with increased risk of CVD in humans

Given that these food additives are used ubiquitously in thousands of widely consumed ultra-processed food products, these findings have important public health implications

Introduction

In Europe and North America, 30-60% of dietary energy intake in adults is provided by ultra-processed foods—highly processed products often formulated using cosmetic food additives and ingredients of rare culinary use, which have resulted in considerable research interest in the past few years.[1-3] Recent epidemiological studies have linked high intakes of ultra-processed foods with higher risks of obesity and mortality and non-communicable diseases, such as cancers, cardiovascular diseases (CVD), and type 2 diabetes.[4] One major hypothesis proposed to explain these associations is the potential deleterious

properties of some food additives, which are used ubiquitously in ultra-processed foods.[4 5]

In particular, emulsifiers are among the most commonly used additives in industrial foods owing to their emulsifying and thickening properties that improve texture and lengthen shelf-life.[6] Although no worldwide estimate of emulsifier use in the food industry exists, a recent descriptive study of the NutriNet-Santé prospective cohort study revealed that seven of the 10 most consumed food additives among French adults were classified as emulsifiers (total modified starches, lecithins, xanthan gum, pectins, monoglycerides and diglycerides of fatty acids, carrageenan, and guar gum), and modified starches were consumed by more than 90% of the participants.[7] Additionally, more than 53.8% of food or beverage industrial products contain at least one food emulsifier[5] as estimated from Open Food Facts,[8] a database that contains information and data on food products from around the world.

Despite their evaluation of safety and acceptable daily intakes provided by the European Food Safety Authority, recent experimental studies suggested potential deleterious effects of food additive emulsifiers on the gut microbiota and gut inflammation.[9-15] In particular, a recent randomised controlled trial in healthy individuals found that compared with an equivalent additive-free diet, short term intake of 15 g/day (supraphysiological doses) of carboxymethylcellulose (European code E466) increased postprandial abdominal discomfort and rapidly altered the composition and localisation of intestinal microbiota as well as the production of intestinal metabolites,[16] the last of these having shown associations with CVD.[17]

The large epidemiological NutriNet-Santé cohort study collected detailed information on specific commercial brands of industrial food consumed, and performed an estimation of quantitative exposures to food additives individually (including emulsifiers) among more than 100 000 French adults.[7] This work provides the basis for aetiological studies, which are crucially needed to generate hypotheses on the role of food additives on long term health outcomes. The present study assessed the association between intakes of food additive emulsifiers (total and specific substances) and CVD risk among French adults from the NutriNet-Santé prospective cohort study.

Methods

Study population

This study was based on the prospective NutriNet-Santé e-cohort, launched in May 2009, with an open ongoing enrolment of volunteers and the main objective of investigating the associations between nutrition and health.[18] Participants are recruited from the general population of French adults (>18 years) through multimedia campaigns. To enrol, participants are required to create a personal account on the NutriNet-Santé web-based platform (https://etude-nutrinet-sante.fr/). Upon enrolment, participants are invited to complete five questionnaires about their dietary intakes, health (eg, personal and family history of disease, prescribed drugs), anthropometric data (eg, height, weight),[19 20] physical activity (validated seven day assessment through the International Physical Activity Questionnaire),[21] lifestyle and sociodemographic data (eg, date of birth, sex, education level, professional occupation, smoking status, number of children).[22]

Dietary data collection

Usual dietary intakes were assessed at inclusion and then every six months, using repeated sets of three non-consecutive web-based 24 hour dietary records, randomly assigned over a two week period (two weekdays and one weekend day). The NutriNet-Santé web-based self-administered 24 hour dietary records have shown good performances when tested against an interview with a trained dietitian[23] and against blood and urinary biomarkers (showing appropriate estimates of true intakes of fruit, vegetables, fish, β carotene, vitamin C, omega 3 fatty acids, proteins, and potassium).[24 25] In this analysis, we calculated the usual baseline dietary intakes as the average of all 24 hour dietary records completed during the first two years of each participant's follow-up, with a mandatory requirement of having at least completed three valid days of 24 hour dietary records during this period to be included in the analysis.

At all times throughout their assigned dietary record period, participants had access to a dedicated interface of the study website to report all foods and beverages consumed during a 24 hour period: three main meals (breakfast, lunch, dinner) and any other eating occasion. The dietary assessments included details of commercial names and brands of industrial products, to determine individual additive intake. Participants were asked to estimate portion sizes either by entering the weight or volume of food consumed directly in the platform, or by using validated photographs or usual containers.[26] A French food composition database (>3500 items)[27] was used to estimate mean daily intakes of energy, alcohol, macronutrients, and micronutrients. These estimates included contributions from composite dishes using French recipes validated by food and nutrition professionals. Respondents who under-reported total energy intake were identified and excluded based on the method proposed by Black[28] from the original method developed by Goldberg.[29] Several quality control operations were also performed to account for over-reporting (see supplementary eMethod1).

Emulsifier intakes

We quantified the intakes of food additives on the basis of data provided in the participants' dietary records, in which the commercial brand or name of the industrial products consumed were recorded. The method for quantification of food additive intakes has been described previously.[7] Briefly, for qualitative assessment we matched each food item consumed and reported in a specific dietary record against

three databases to identify the presence of any food additive: OQALI,[30] a national database managed by the Institut National de la Recherche pour l'Agriculture, l'alimentation et l'Environnement and the French food safety authority (Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail) to characterise the quality of the food supply, Open Food Facts, an open collaborative database of food products marketed worldwide,[8] and the Mintel Global New Products Database,[31] an online database of innovative food products worldwide. For quantitative assessment, we estimated the dose of food additive ingested with each food item, following a decision tree with a descending order of detail level, based on ad hoc laboratory assays quantifying additives in specific food items (n=2677 food-additive pairs analysed targeted among the main vectors of these additives in our study population, and performed by Mérieux and Eurofins firms and the French Directorate General for Competition Policy, Consumer Affairs and Fraud Control public laboratories), doses in generic food categories provided by the European Food Safety Authority, or generic doses from the Codex General Standard for Food Additives[32] (see supplementary eMethod2 for details). We applied dynamic matching—that is, products were matched date-to-date, whereby the date of consumption of each food or beverage declared by each participant was used to match the product to the closest composition data, thus accounting for potential reformulations.

Among the available food additives quantified from the participants' dietary records, we identified 61 food additives classified as emulsifiers or emulsifying salts from the 261 additives under the functional class "emulsifier" or "emulsifying salt" of Codex General Standard for Food Additives database,[32] or according to US or UK regulations when not included in Codex (eg, E404, E418, E468)[6] and considered the sum of intakes as intake of total emulsifiers (see table 2). In addition, we summed individual emulsifiers with similar chemical structures into eight groups: total phosphates (E339, E340, E341, E343, E450, E451, E452), total lactylates (E481, E482), total polyglycerol esters of fatty acids (E475, E476), total monoglycerides and diglycerides of fatty acids (E471, E472, E472a-b-c-e), total celluloses (E460, E461, E464, E466, E468), total carrageenans (E407, E407a), total alginates (E400, E401, E402, E404, E405), and total modified starches (generic European Union code for this category E14xx).

CVD ascertainment

Participants were invited to declare any major health event, either through the yearly health status questionnaire (a specific health check-up questionnaire sent out every six months) or spontaneously at any time on a dedicated interface on the study website. We asked participants to send their medical records (eg, complementary examinations for diagnosis, hospital admissions, or anatomopathological reports) to support any declaration of a health event. A physician expert committee validated each major health event after reviewing the participants' medical records and collecting additional information from the participants' doctors or medical facilities. In the absence of any response to the study website for more than one year, the physician expert committee contacted the participants' family or physicians. In

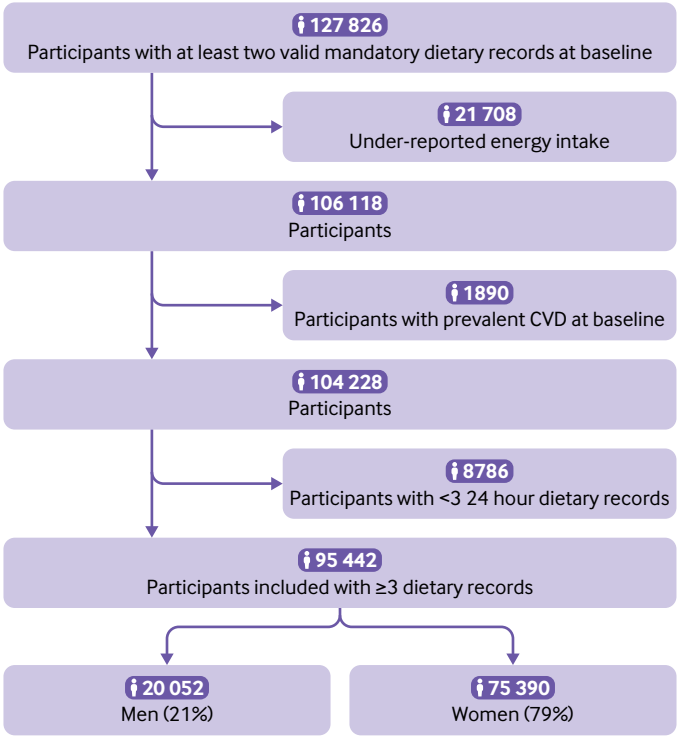

Fig 1 | Flowchart of participants included from NutriNet-Santé cohort, 2009-21 (n=95 442)

Table 1 | Baseline characteristics of study participants from the NutriNet-Santé cohort according to sex specific fourths of intakes of total emulsifiers, 2009-21. Values are mean (standard deviation) unless stated otherwise

Characteristics	Overall (n=95 442)	Sex specific fourths of total emulsifier intakes				P value*
		First fourth (n=23 861)	Second fourth (n=23 860)	Third fourth (n=23 860)	Fourth fourth (n=23 861)	
Age (years)	43.1 (14.5)	45.0 (14.7)	43.9 (14.7)	42.9 (14.5)	40.6 (13.8)	<0.001
Women (No (%))	75 390 (79.0)	18 848 (79.0)	18 847 (79.0)	18 847 (79.0)	18 848 (79.0)	NA
BMI†	23.7 (4.4)	23.6 (4.4)	23.6 (4.3)	23.6 (4.3)	23.9 (4.7)	<0.001
Family history of CVD (No (%))	29 274 (30.7)	7638 (32.0)	7423 (31.1)	7456 (31.2)	6757 (28.3)	<0.001
Education level (No (%))†:						
Less than high school degree	15 639 (16.5)	4441 (18.8)	4038 (17.1)	3757 (15.9)	3403 (14.4)	<0.001
<2 years after high school	14 686 (15.5)	3832 (16.2)	3653 (15.5)	3642 (15.4)	3559 (15.0)	
≥2 years after high school	64 331 (68.0)	15 381 (65.0)	15 949 (67.5)	16 283 (68.8)	16 718 (70.6)	
Smoking status (No (%))†:						
Current smoker	9049 (9.5)	2771 (11.6)	2180 (9.1)	2019 (8.5)	2079 (8.7)	<0.001
Occasional smoker	3797 (4.0)	950 (4.0)	940 (3.9)	931 (3.9)	976 (4.1)	
Former smoker	39 382 (41.3)	10 370 (43.5)	10 053 (42.1)	9763 (40.9)	9196 (38.6)	
Never	43 190 (45.3)	9762 (40.9)	10 681 (44.8)	11 146 (46.7)	11 601 (48.6)	
IPAQ physical activity level (No (%))†:						
Low	27 055 (32.7)	7225 (35.2)	6841 (33.0)	6709 (32.3)	6280 (30.4)	<0.001
Moderate	35 624 (43.1)	8635 (42.1)	8913 (43.0)	9071 (43.6)	9005 (43.7)	
High	19 985 (24.2)	4652 (22.7)	4977 (24.0)	5014 (24.1)	5342 (25.9)	
Dietary intakes:						
Energy without alcohol (kcal/day)	1850 (444.2)	1704 (412.1)	1801 (407.2)	1877 (415.1)	2018 (477.9)	<0.001
Alcohol (g/day)	7.9 (11.7)	8.7 (13.3)	8.2 (11.8)	7.6 (10.9)	7.2 (10.7)	<0.001
Saturated fat (g/day)	33.3 (11.9)	29.0 (10.9)	32.2 (10.8)	34.3 (11.1)	37.8 (12.8)	<0.001
Sodium (mg/day)	2725 (869.0)	2547 (873.4)	2697 (830.0)	2777 (839.7)	2879 (897.3)	<0.001
Fibre (g/day)	19.6 (7.1)	19.5 (8.1)	19.2 (6.7)	19.5 (6.6)	20.1 (6.9)	<0.001
Sugar (g/day)	92.9 (32.4)	81.8 (31.4)	88.7 (29.0)	95.1 (29.6)	106.1 (34.4)	<0.001
Fruit and vegetables (g/day)	412.0 (217.8)	430.7 (245.9)	407.9 (205.9)	406.1 (204.2)	403.2 (211.4)	<0.001
Wholegrain food (g/day)	34.6 (45.4)	39.6 (52.8)	34.6 (43.6)	33.3 (42.5)	31.0 (41.5)	<0.001
Red and processed meat (g/day)	76.7 (51.0)	74.1 (54.7)	76.5 (50.2)	77.0 (48.1)	79.2 (50.5)	<0.001
Ultra-processed food (% daily weight intake)	17.1 (9.5)	13.5 (8.7)	16.2 (8.7)	18.1 (9.0)	20.6 (10.2)	<0.001
Total emulsifiers (mg/day)	4254 (3065)	1232 (592.4)	2874 (435.5)	4555 (587.1)	8357 (2957)	<0.001

BMI=body mass index; CVD=cardiovascular disease; IPA=International Physical Activity Questionnaire; NA=not applicable.
*Kruskal-Wallis rank sum test; Pearson's χ^2 test.
†Number of overall missing values: 793 for BMI, 786 for educational level, 24 for smoking status, and 12 778 for IPAQ.

addition to this process, which constituted the main source of event ascertainment, we linked cohort data from participants to medico-administrative databases from the National Health Insurance (authorisation by the Council of State No 2013-175). Finally, the French national cause specific mortality registry (CépiDC) was used to identify mortality linked to CVD events and to other causes of death that were considered as competing events.

Participants with CVD were identified using ICD-10-CM (international classification of diseases-clinical modification, 10th revision) codes. In this study, we considered as events all primary CVD diagnosed between the inclusion date and 5 October 2021, which included coronary heart diseases such as myocardial infarction (code I21), acute coronary syndrome (I21.4), angioplasty (Z95.8), and angina pectoris (I20.0), along with cerebrovascular diseases such as stroke (I64) and transient ischaemic attack (G45.8 and G45.9).

Statistical analyses

For this study, we included participants from the NutriNet-Santé cohort who completed at least three 24 hour dietary records during their first two years of follow-up and had no diagnosis of any prevalent CVD at baseline. Characteristics of the study sample according to sex specific fourths of intake of total emulsifiers were compared using Kruskal-Wallis rank sum test or Pearson's χ^2 test. In addition, we generated a correlation matrix to visualise the relationships between intakes of individual emulsifiers (see supplementary eFigure1).

We assessed the associations between intakes of emulsifiers (continuous) and risks of CVD, coronary heart disease, and cerebrovascular disease using multivariable proportional hazard Cox models, which computed hazard ratios per additional standard deviation ((SD) to provide a standardised increment given the difference in the distribution and the amounts of the different emulsifiers) of intake and 95% confidence intervals. To ensure acceptable statistical power, we restricted analyses on individual emulsifiers to those consumed by at least 5% of the included participants. The proportional hazard assumption was tested using the Schoenfeld residual method implemented in the *survival* R package (see supplementary eFigure2),[33 34] and the log linearity between emulsifier intakes and hazard ratios was assessed using restricted cubic splines (see supplementary eFigure3).[35] Participants contributed person time to the models until the date of CVD diagnosis, date of death, date of last completed questionnaire, or 5 October 2021, whichever occurred first. Cause specific hazard ratios were computed so that death and CVD events other than the one studied

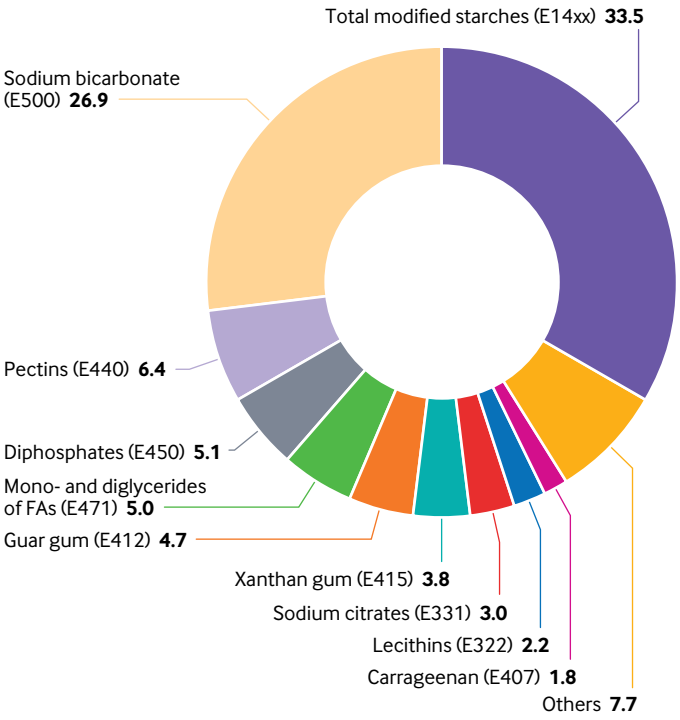

Fig 2 | Contribution of individual emulsifiers to total emulsifier intakes (%) among participants from the NutriNet-Santé cohort, 2009-21 (n=95 442). Other emulsifiers included triphosphates (European code E451), gum arabic (E414), polyphosphates (E452), carob bean gum (E410), cellulose (E460), tricalcium phosphate (E341), monoacetyl and diacetyl tartaric acid esters of monoglycerides and diglycerides of FAs (E472e), hydroxypropyl methylcellulose (E464), polyglycerol esters of FAs (E475), lactic acid esters of monoglycerides and diglycerides of FAs (E472b), polydextrose (E1200), sodium stearoyl-2-lactylate (E481), sodium alginate (E401), ammonium salts of phosphatidic acid (E442), esters of monoglycerides and diglycerides of FAs (E472), polyglycerol esters of interesterified ricinoleic acid (E476), citric acid esters of monoglycerides and diglycerides of FAs (E472c), silicon dioxide (E551), tripotassium phosphate (E340), methylcellulose (E461), carboxymethylcellulose (E466), trisodium phosphate (E339), acetic acid esters of monoglycerides and diglycerides of FAs (E472a), agar (E406), sucrose esters of FAs (E473), propylene glycol esters of FAs (E477), gellan gum (E418), sorbitan tristearate (E492), processed *Euchema* seaweed (E407a), beeswax (E901), potassium alginate (E402), maltitol (E965), triethyl citrate (E1505), xylitol (E967), glycerol esters of rosin (E445), polyoxyethylene sorbitan monooleate (E433), potassium dihydrogen citrate (E332), calcium alginate (E404), calcium stearoyl-2-lactylate (E482), konjac flour (E425), cross linked sodium carboxymethylcellulose (E468), sucrose acetate isobutyrate (E444), sodium tartarate (E335), polyoxyethylene sorbitan monostearate (E435), sorbitan monostearate (E491), alginic acid (E400), propylene glycol (E1520), *Quillaia* extract (E999), sodium aluminium phosphate (E541), magnesium hydrogen phosphate (E343), propylene glycol alginate (E405), and dimethyl polysiloxane (E900). FAs=fatty acids

(for coronary heart disease and cerebrovascular disease specific analyses) occurring during follow-up were handled as competing risks. When values for covariates were missing, we used multiple imputation by additive regression, followed by bootstrapping, and predictive mean matching (n=20 imputed dataset) as implemented in the *Hmisc* R package (see supplementary eMethod3).[36]

The adjustment strategy was defined according to a directed acyclic graph (see supplementary eFigure4). The main model was adjusted for age (timescale); sex; body mass index (BMI, continuous); physical activity (categorical International Physical Activity Questionnaire variable: high, moderate, low); smoking status, (never smoker, former smoker, occasional smoker, regular smoker); number of smoked cigarettes in pack years (continuous); educational level (less than high school degree, <2 years after high school degree, ≥2 years after high school degree); family history of CVD (yes/no); daily alcohol intake (continuous, g/day); consumption of fruit and vegetables (continuous, g/day), red and processed meats (continuous, g/day), and wholegrain foods (continuous, g/day); proportion of ultra-processed food consumed in the diet, in weight (continuous, %), as defined by the NOVA classification[37]; and the number of dietary records (continuous). In addition, even if not considered as direct confounders by the directed acyclic graph, we further adjusted each model for intakes of energy without alcohol (continuous, kcal/day), saturated fatty acids (continuous, g/day), sodium (continuous, mg/day), total fibre (continuous, g/day), and total sugars (continuous, g/day), as markers of overall diet nutritional quality or for having strong links with CVD risk.

We conducted sensitivity analyses for all emulsifiers with at least one statistically significant association with risk of CVD, coronary heart disease, or cerebrovascular disease. The false discovery rate was used to adjust P values obtained from the main model for multiple testing.[38] In sensitivity analyses, model 1 was further adjusted for healthy and western dietary patterns derived by principal component analyses (see supplementary eMethod4). Model 2 was based on the main model and further adjusted for the diagnosis or treatment, or both, of at least one prevalent metabolic disorder (ie, type 2 diabetes, hypertriglyceridaemia, hypertension). Model 3 was based on the main model and further adjusted for the percentage of weight change from baseline. Model 4 was based on the main model and excluded participants with CVD diagnosed during the first two years of follow-up. Model 5 was based on the main model, using the average of all available 24 hour dietary records throughout the follow-up of each participant (≤62 records per participant) instead of averaged values on their first two years of follow-up. Model 6 was based on the main model and further adjusted for the intakes of other emulsifiers than the one studied in the model, and for total artificial sweeteners.[39] Finally, we conducted analyses for all emulsifiers with at least one statistically significant association with the specific outcomes of stroke, myocardial infarction, angioplasty, acute coronary syndrome, transient ischaemic attack, angina pectoris, and severe CVD (ie, total CVD except for transient ischaemic attack and angina pectoris). We found no evidence in the mechanistic literature on specific interactions (for example, with BMI and age), or sexual dimorphism, for the association between intake of emulsifiers and CVD risk.

All statistical tests were two sided, and we considered P<0.05 to be significant. All statistical analyses were conducted in R version 4.1.2,[40] except for the restricted cubic spline method, which was implemented in SAS version 9.4.

Table 2 | Daily emulsifier intakes among study participants from the NutriNet-Santé cohort, 2009-21 (n=95 442)

Emulsifiers	European code	Intake (mg/day)		Consumers (%)
		Mean (SD)	Median (IQR)	
Total emulsifiers		4254.9 (3065.7)	3634.3 (2131.7-5639.0)	99.8
Total alginates:		12.0 (48.5)	0.0 (0.0-0.0)	17.4
Alginic acid	E400	0.0 (0.8)	0.0 (0.0-0.0)	0.1
Sodium alginate	E401	8.4 (33.2)	0.0 (0.0-0.0)	15.0
Potassium alginate	E402	0.3 (4.9)	0.0 (0.0-0.0)	0.9
Calcium alginate	E404	0.0 (3.6)	0.0 (0.0-0.0)	<0.1
Propylene glycol alginate	E405	0.0 (0.0)	0.0 (0.0-0.0)	<0.1
Total carrageenans:		59.8 (73.2)	38.6 (2.5-87.5)	78.8
Carrageenan	E407	57.3 (70.9)	36.9 (1.7-83.3)	77.9
Processed *Euchema* seaweed	E407a	2.5 (13.5)	0.0 (0.0-0.0)	9.1
Total phosphates:		357.2 (487.9)	227.9 (44.6-491.7)	79.8
Trisodium phosphate	E339	9.0 (56.9)	0.0 (0.0-0.0)	6.0
Tripotassium phosphate	E340	8.0 (87.8)	0.0 (0.0-0.0)	5.7
Tricalcium phosphate	E341	27.5 (229.8)	0.0 (0.0-0.0)	18.0
Magnesium hydrogen phosphate	E343	0.0 (0.0)	0.0 (0.0-0.0)	<0.1
Diphosphates	E450	244.5 (338.2)	139.7 (0.0-338.8)	72.6
Sodium tripolyphosphate	E451	44.1 (115.7)	0.0 (0.0-10.3)	25.6
Polyphosphates	E452	24.1 (80.5)	0.0 (0.0-0.0)	22.6
Total celluloses:		18.7 (91.7)	0.0 (0.0-0.0)	20.8
Cellulose	E460	9.8 (68.7)	0.0 (0.0-0.0)	10.3
Methylcellulose	E461	1.9 (16.5)	0.0 (0.0-0.0)	2.4
Hydroxypropyl methylcellulose	E464	3.2 (31.6)	0.0 (0.0-0.0)	4.4
Carboxymethylcellulose	E466	3.8 (30.2)	0.0 (0.0-0.0)	10.8
Cross linked sodium carboxymethylcellulose	E468	0.0 (0.1)	0.0 (0.0-0.0)	0.1
Total monoglycerides and diglycerides of FAs:		204.5 (275.5)	123.7 (22.6-280.7)	83.9
Monoglycerides and diglycerides of FAs	E471	161.2 (200.6)	100.1 (11.0-231.1)	81.6
Esters of monoglycerides and diglycerides of FAs	E472	3.3 (37.7)	0.0 (0.0-0.0)	1.3
Acetic acid esters of monoglycerides and diglycerides of FAs	E472a	6.0 (81.7)	0.0 (0.0-0.0)	3.2
Lactic acid esters of monoglycerides and diglycerides of FAs	E472b	20.8 (99.9)	0.0 (0.0-0.0)	13.4
Citric acid esters of monoglycerides and diglycerides of FAs	E472c	8.2 (54.8)	0.0 (0.0-0.0)	7.4
Monocetyl and diacetyl tartaric acid esters of monoglycerides and diglycerides of FAs	E472e	5.0 (26.8)	0.0 (0.0-0.0)	14.3
Total polyglycerol esters of FAs:		14.2 (61.6)	0.0 (0.0-0.0)	21.7
Polyglycerol esters of FAs	E475	10.5 (59.6)	0.0 (0.0-0.0)	7.0
Polyglycerol esters of interesterified ricinoleic acid	E476	3.7 (15.5)	0.0 (0.0-0.0)	16.0
Total lactylates:		4.2 (21.8)	0.0 (0.0-0.0)	8.6
Sodium stearoyl-2-lactylate	E481	4.1 (21.5)	0.0 (0.0-0.0)	8.5
Calcium stearoyl-2-lactylate	E482	0.1 (3.0)	0.0 (0.0-0.0)	0.2
Total modified starches	E14xx	1301.8 (1119.0)	1056.8 (494.7-1813.8)	93.0
Lecithins	E322	60.3 (75.9)	37.3 (10.9-82.2)	88.4
Sodium citrate	E331	115.5 (266.4)	0.0 (0.0-127.0)	49.4
Potassium dihydrogen citrate	E332	0.0 (0.0)	0.0 (0.0-0.0)	<0.1
Sodium tartarates	E335	0.0 (0.4)	0.0 (0.0-0.0)	<0.1
Agar	E406	3.2 (34.5)	0.0 (0.0-0.0)	2.1
Carob bean gum	E410	31.4 (67.1)	0.0 (0.0-37.9)	45.8
Guar gum	E412	166.5 (223.2)	90.4 (0.0-237.2)	72.9
Gum arabic	E414	51.8 (396.3)	0.0 (0.0-0.0)	10.7
Xanthan gum	E415	134.1 (211.4)	50.2 (9.4-175.9)	82.8
Gellan gum	E418	0.4 (4.5)	0.0 (0.0-0.0)	2.0
Konjac flour	E425	0.0 (0.8)	0.0 (0.0-0.0)	<0.1
Polyoxyethylene sorbitan monooleate	E433	0.3 (4.7)	0.0 (0.0-0.0)	1.1
Polyoxyethylene sorbitan monostearate	E435	0.0 (0.9)	0.0 (0.0-0.0)	<0.1
Pectins	E440	218.4 (302.9)	131.3 (31.4-285.7)	82.8
Ammonium salts of phosphatidic acid	E442	6.1 (41.8)	0.0 (0.0-0.0)	10.6
Sucrose acetate isobutyrate	E444	0.0 (0.8)	0.0 (0.0-0.0)	0.1
Glycerol esters of rosin	E445	0.1 (1.2)	0.0 (0.0-0.0)	1.8
Sucrose esters of FAs	E473	1.2 (12.7)	0.0 (0.0-0.0)	2.6
Propylene glycol esters of FAs	E477	0.4 (7.3)	0.0 (0.0-0.0)	1.9
Sorbitan monostearate	E491	0.2 (5.4)	0.0 (0.0-0.0)	0.2
Sorbitan tristearate	E492	0.6 (11.5)	0.0 (0.0-0.0)	0.5
Sodium bicarbonate	E500	1478.2 (2030.7)	750.0 (0.0-2139.7)	74.2
Sodium aluminium phosphate	E541	0.0 (0.0)	0.0 (0.0-0.0)	<0.1
Silicon dioxide	E551	7.9 (178.4)	0.0 (0.0-0.0)	2.6
Dimethyl polysiloxane	E900	0.0 (0.0)	0.0 (0.0-0.0)	<0.1
Beeswax	E901	0.1 (0.6)	0.0 (0.0-0.0)	6.0
Maltitol	E965	6.3 (90.6)	0.0 (0.0-0.0)	2.1
Xylitol	E967	2.3 (33.9)	0.0 (0.0-0.0)	1.3
Quillaia extract	E999	0.0 (0.1)	0.0 (0.0-0.0)	<0.1
Triethyl citrate	E1505	0.4 (3.6)	0.0 (0.0-0.0)	2.3
Propylene glycol	E1520	0.0 (0.3)	0.0 (0.0-0.0)	<0.1

FAs=fatty acids; IQR=interquartile range; SD=standard deviation.

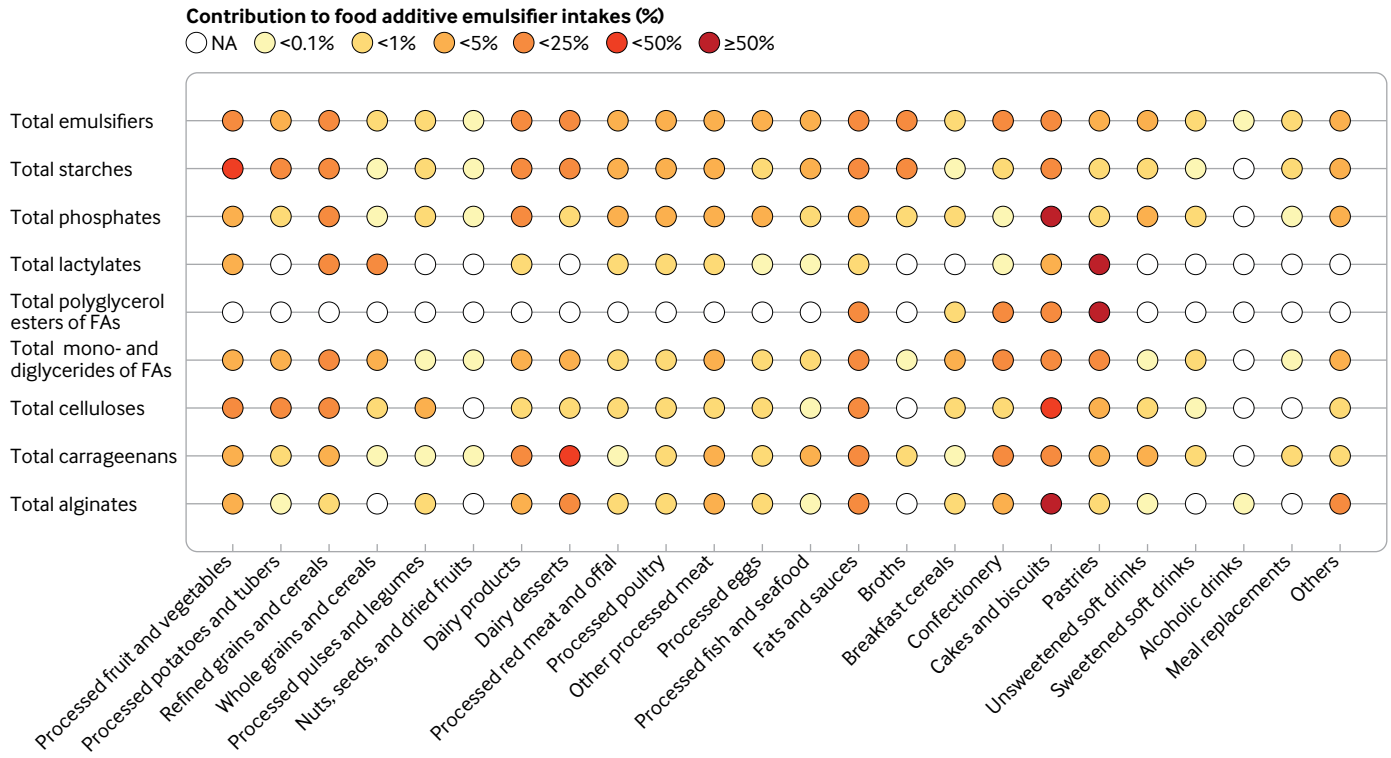

Fig 3 | Dietary sources of total and groups of emulsifier intakes among study participants from the NutriNet-Santé cohort, 2009-21 (n=95 442). Groups of emulsifiers were defined as (European codes) total phosphates (E339, E340, E341, E343, E450, E451, E452), total lactylates (E481, E482), total polyglycerol esters of FAs (E475, E476), total monoglycerides and diglycerides of FAs (E471, E472, E472a, E472b, E472c, E472e), total celluloses (E460, E461, E464, E466, E468), total carrageenans (E407, E407a), total alginates (E400, E401, E402, E404, E405), and total modified starches (E14xx). Also see supplementary eTable1. FAs=fatty acids; NA=not applicable

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. Even though the cohort was launched before patient and public involvement was common, the research our team carries out deals with timely societal public health nutrition topics. Investigators of the NutriNet-Santé cohort regularly deliver presentations to the lay public and patients and participate in media interviews, where they share the latest results, screen the public's current interest in the specialty of nutrition and health, and encourage enrolment in the cohort.

Results

Descriptive characteristics

A total of 95 442 adults (>18 years) were included in the study (fig 1), most of whom were women (n=75 390, 79.0%). Table 1 lists the baseline characteristics of the participants. Mean age was 43.1 (SD 14.5) years, and the average number of dietary records was 6.0 (SD 3.0). Supplementary eFigure5 shows the distribution of the number of dietary records for each participant. At baseline, compared with participants with the lowest intakes, those with the highest intakes of emulsifiers were more likely to be younger, to have a higher BMI, to be never smokers, to have higher education and physical activity levels, and to have higher intakes of energy, saturated fats, sodium, sugars, and fibre, and lower intakes of alcohol. They consumed less fruit, vegetables, and whole grain foods and more red and processed meats and ultra-processed foods (table 1).

The main contributors to total emulsifier intake were modified starches (E14xx, 33.5%), sodium bicarbonate (E500, 26.9%), pectins (E440, 6.4%), diphosphates (E450, 5.1%), and monoglycerides and diglycerides of fatty acids (E471, 5.0%) (fig 2). Overall, correlations between intakes of individual emulsifiers were limited (see supplementary eFigure1). Table 2 shows detailed intakes of individual and groups of emulsifiers. A total of 32 individual emulsifiers were consumed by <5% of the included participants and were therefore not studied individually in relation to CVD risk: E400, E468, E444, E482, E491, E492, E402, E433, E472, E967, E445, E477, E418, E406, E965, E1505, E461, E473, E551, E472a, E464, E404, E405, E343, E332, E335, E425, E435, E541, E900, E999, and E1520 (table 2); however, they contributed to the sum of total emulsifiers. Food additive emulsifiers were mostly found in processed fruit and vegetables (eg, dehydrated soups) (contributing to 18.8% of total emulsifier intakes), cakes and biscuits (14.7%), and dairy products (9.9%) (fig 3, supplementary eTable1). The most important dietary sources of total celluloses were cakes and biscuits (43.4%) and processed potatoes and tubers (20.1%), whereas those of total monoglycerides and diglycerides of fatty acids were fats and sauces (eg, packaged mayonnaise) (22.5%) and cakes and biscuits (22.0%).

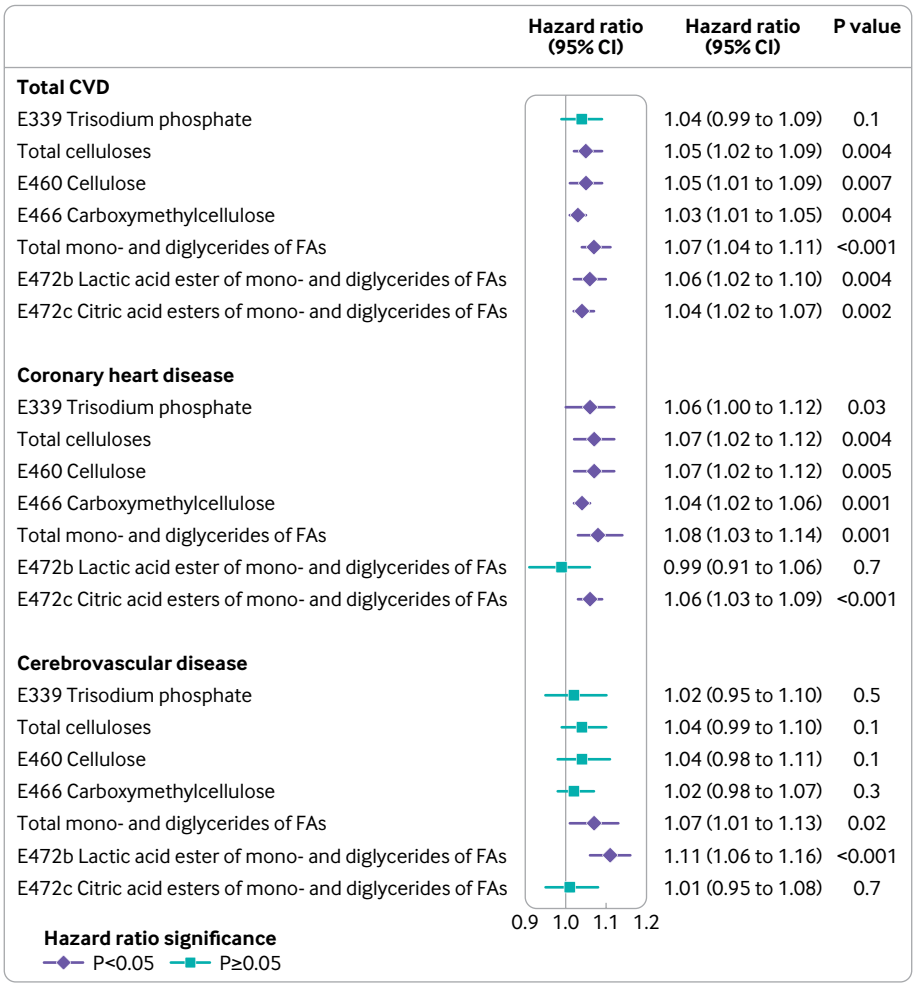

Fig 4 | Associations between selected emulsifier intakes and risk of CVD among participants from the NutriNet-Santé cohort, 2009-21 (n=95 442). Hazard ratio for an increment of 1 standard deviation. Groups of emulsifiers were defined as (European codes) total monoglycerides and diglycerides of FAs (E471, E472, E472a, E472b, E472c, E472e) and total celluloses (E460, E461, E464, E466, E468). Emulsifiers with at least one statistically significant association with CVD risk are represented. Supplementary eTable2 provides the investigated associations between emulsifier intakes and CVD risk with corresponding hazard ratios and 95% confidence intervals. Multivariable Cox proportional hazard models were adjusted for age (timescale); sex; body mass index (continuous); physical activity (categorical International Physical Activity Questionnaire variable: high, moderate, low); smoking status (never smoker, former smoker, occasional smoker, regular smoker); number of smoked cigarettes in pack years (continuous); educational level (less than high school degree, <2 years after high school degree, ≥2 years after high school degree); number of dietary records (continuous); family history of CVD (yes/no); energy intake without alcohol (continuous, kcal/day); daily intakes of alcohol (continuous, g/day), saturated FAs (continuous, g/day), sodium (continuous, mg/day), total fibre (continuous, g/day), sugars (continuous, g/day), fruit and vegetables (continuous, g/day), red and processed meats (continuous, g/day), and whole grains (continuous, g/day); and proportion of ultra-processed food consumed in the diet, in weight (continuous, %). Standard deviations of emulsifier intakes (mg/day) were 3170.8 for total emulsifiers, 52.0 for total alginates, 35.3 for E401, 75.7 for total carrageenans, 73.2 for E407, 14.1 for E407a, 502.6 for total phosphates,58.4 for E339, 96.5 for E340, 227.2 for E341, 349.7 for E450, 122.3 for E451, 86.2 for E452, 93.4 for total celluloses, 69.4 for E460, 32.8 for E464, 32.0 for E466, 287.5 for total monoglycerides and diglycerides of FAs, 208.6 for E471, 103.7 for E472b, 57.6 for E472c, 28.3 for E472e, 63.5 for total polyglycerol esters of FAs, 61.5 for E475, 15.7 for E476, 23.1 for total lactylates, 22.7 for E481, 1147.1 for total modified starches, 78.3 for E322, 280.5 for E331, 69.7 for E410, 233.8 for E412, 428.1 for E414, 221.1 for E415, 310.6 for E440, 42.6 for E442, 2116.7 for E500, and 0.6 for E901. CVD=cardiovascular disease; FAs=fatty acids

Associations between emulsifier intakes and CVD risk

After a mean follow-up of 7.0 (median 7.4, interquartile range 3.5-10.2) years, 1995 incident CVD events were diagnosed between 2009 and 2021 (666 509 person years), including 1044 coronary heart disease and 974 cerebrovascular disease events. Schoenfeld residuals did not show evidence for violation of the proportional hazard assumptions (see supplementary eFigure2), and restricted cubic spline plots (see supplementary eFigure3) globally supported the linearity of the observed associations.

Figure 4 shows the main associations between emulsifier intakes and CVD risk (emulsifiers shown if at least one association was statistically significant with one of the studied outcomes) and supplementary eTable2 provides all associations in detail. Higher intake of total celluloses (E460-E468) was associated with higher risks of CVD (hazard ratio for an increase of 1 standard deviation 1.05, 95% confidence

interval 1.02 to 1.09, P=0.004) and coronary heart disease (1.07, 1.02 to 1.12, P=0.004). Specifically, higher cellulose (E460) intake was associated with higher risk of CVD (1.05, 1.01 to 1.09, P=0.007) and coronary heart disease (1.07, 1.02 to 1.12, P=0.005); and higher intake of carboxymethylcellulose (E466) was associated with higher risks of CVD (1.03, 1.01 to 1.05, P=0.004) and coronary heart disease (1.04, 1.02 to 1.06, P=0.001). Additionally, higher intakes of total monoglycerides and diglycerides of fatty acids (E471 and E472) were associated with higher risks of all three outcomes: CVD (1.07, 1.04 to 1.11, P<0.001), coronary heart disease (1.08, 1.03 to 1.14), P=0.001), and cerebrovascular disease (1.07, 1.01 to 1.13, P=0.02). Within this group of emulsifiers, lactic ester of monoglycerides and diglycerides of fatty acids (E472b) was associated with higher risk of CVD (1.06, 1.02 to 1.10, P=0.004) and cerebrovascular disease (1.11, 1.06 to 1.16, P<0.001). Citric acid ester of monoglycerides and diglycerides of fatty acids (E472c) was associated with higher risk of CVD (1.04, 1.02 to 1.07, P=0.004) and coronary heart disease (1.06, 1.03 to 1.09, P<0.001). Finally, trisodium phosphate (E339) was associated with higher risks of coronary heart disease (1.06, 1.00 to 1.12, P=0.03). No association was observed between the other studied emulsifiers (including carrageenans and lecithins) and any of the cardiovascular outcomes in this study (P>0.5, see supplementary eTable2).

After correction for potential multiple testing, all associations remained significant except for those between cellulose E460 and risk of coronary heart disease and CVD (both adjusted P=0.06), total monoglycerides and diglycerides of fatty acids and risk of cerebrovascular disease (adjusted P=0.1), and trisodium phosphate (E339) and risk of coronary heart disease (adjusted P=0.3). Overall, sensitivity analyses from models 1 to 6 (see supplementary eTable3) were consistent with results from the main models, and all statistically significant associations observed in this study went in the same direction in main and sensitivity analyses, suggesting a low risk of randomly significant associations. All observed associations with CVD risk remained significant when transient ischaemic attack and angina pectoris events were excluded from the CVD definition (severe CVD) (see supplementary eTable4).

Discussion

This prospective cohort study showed positive associations between higher intakes of total cellulose emulsifiers (specifically E460 and E466) and total monoglycerides and diglycerides of fatty acids (specifically E472b and E472c) and CVD risk. Higher intakes of total celluloses (specifically E460 and E466) and total monoglycerides and diglycerides of fatty acids (specifically E472c) as well as trisodium phosphate (E339) were positively associated with risk of coronary heart disease, and those of total monoglycerides and diglycerides of fatty acids (specifically E472b) were positively associated with risk of cerebrovascular disease.

The safety of food additive emulsifiers, as with all other food additives, is regularly assessed by authorities, such as the European Food Safety Authority in Europe, in comprehensive reports based on extensive literature evaluation, defining acceptable daily intakes when necessary. Based on the European Food Safety Authority's latest evaluations, no acceptable daily intakes were deemed necessary to regulate the intakes of sodium citrate (E331),[41] monoglycerides and diglycerides of fatty acids (E471),[42] celluloses (E460, E461, E464, E466, E468),[43] monoglycerides and diglycerides of fatty acids (E471),[42] or lactic acid ester of monoglycerides and diglycerides of fatty acids (E472b).[44] Although the acceptable daily intake for tartaric acid esters of monoglycerides and diglycerides of fatty acids was set at 240 mg/kg of body weight/day in 2020,[44] none of the NutriNet-Santé study participants reached such intakes.[7] Importantly, conclusions from European Food Safety Authority reports can only be drawn from the scientific evidence available at the time of evaluation. Nonetheless, the growing research interest in food additive emulsifiers[14] led to novel and concerning findings from experimental work, which suggest a need for more regular evaluations assessing the safety of long term intakes at lower doses to these food additives, through individual or combined multi-intakes.

Comparison with other studies

This study explored and observed associations between the consumption of food additive emulsifiers and risk of CVD in a large group of adults over a long period. The current understanding about the effects of emulsifiers on health came from in vitro and in vivo experimental studies. For example, studies conducted on porcine small intestinal mucus showed that carboxymethylcellulose (E466) could damage the intestinal barrier, leading to intestinal inflammation.[45] Similarly, high intakes of carboxymethylcellulose have been linked to changes in the composition of gut bacteria and increased risk of colon cancer.[11 46-48] In a recent short term intervention study on humans, a supraphysiological dose of 15 g/day (compared with 3.9 mg/day in our study) of carboxymethylcellulose over 11 days increased markers of gut inflammation and reduced gut microbiota diversity compared with an additive-free diet.[16] Similar pro-inflammatory effects have been observed with monoglycerides and diglycerides of fatty acids (E471) on faecal microbiota in vitro.[49] However, experimental studies have suggested that carrageenan induced colitis could lead to a decrease in the population of *Akkermansia muciniphila*,[50 51] which may have protective effects against atherosclerosis.[52] It is possible that disruptions in gut bacteria and increased gut inflammation could contribute to a systemic low grade inflammation that may affect gut health as well as other organs.[53] In particular, imbalances in gut bacteria have been associated with metabolic and neurological conditions.[54] Furthermore, in our study we observed positive associations between intake of celluloses and

CVD risk. Although this might seem counterintuitive given the protective role of fibre on CVD,[55] the finding could be linked to the disruption of food matrix in industrial products containing added celluloses compared with plants, which might lead to different effects on human health. Owing to the observational nature of our study, we were unable to confirm that emulsifiers are causally related to CVD risk. However, we have as much as possible isolated the role of emulsifiers by adjusting for the proportion of ultra-processed foods in the diet, as well as for several dietary features that might causally impact CVD risk, including intakes of sugar, sodium, saturated fatty acids, energy, fibre, and artificial sweeteners. Future short term human intervention studies, long term epidemiological studies, and preclinical experiments will bring additional arguments to strengthen the plausibility of causal associations.

Strengths and limitations of this study

The strengths of this study included its prospective design and large sample size. The NutriNet-Santé study was able to assess the intakes of food additives qualitatively and quantitatively with accuracy using detailed and repeated 24 hour dietary records, links to multiple food composition databases (OQALI,[30] Open Food Facts,[8] Global New Products Database,[31] European Food Safety Authority, and Codex General Standard for Food Additives[32]), ad hoc laboratory assays, and dynamic matching to account for reformulations of industrial food items over time.[7] Although more limited than in long term historical cohorts such as the Framingham study (20 years), the duration of follow-up (median 7.0 years, maximum 12.4 years) was similar to that of other cohort studies such as the UK Biobank,[56] and to the duration of nutritional intervention studies on cardiovascular diseases prevention such as the Prevención con Dieta Mediterránea trial.[57] In addition, the stability of the associations observed in this study over multiple sensitivity analyses suggest consistency and robustness of the findings.

Nonetheless, this study had some limitations, such as the high proportion of women in the cohort (79.3%), higher educational background, and overall more health conscious behaviours among the NutriNet-Santé study participants compared with the general French population, which may limit the generalisability of the results. This sex imbalance is common in volunteer based studies, especially in those linked to diet and health.[58] The study is likely to have underestimated the strength of the observed associations because women tend to have healthier diets with lower emulsifier intakes (mean intake 4187 mg/day in women *v* 4509 mg/day in men, P<0.001) and a lower absolute risk of CVD. Moreover, ≈17% of the cohort was excluded owing to underreporting of energy intake assessed using a standard method,[28] to eliminate true reporting errors in the absence of any restrictive diet. This proportion was consistent with the one observed in other studies—for example, 25.1% in the American National Health and Nutrition Examination Survey study[59] and 18% in the Norwegian breast cancer screening programme.[60] In the nationally representative Individual and National Studies on Food Consumption 3 study conducted in 2016 by the French Food Safety Agency,[61] 18% of adult participants were found to be under-reporting using the Black method applied in the present study. Moreover, even though dietary records were validated against blood and urinary biomarkers for energy and key nutrients, intake of emulsifiers has not been validated against blood or urine assays owing to lack of specific biomarkers. Besides, intakes might have been underestimated in food items exempt from food labelling (eg, bakery pastries), and non-additive originated emulsifiers occurring naturally in food products, such as lecithins in eggs, were not captured, because to our knowledge food composition databases that estimate their presence in foods are not available. Although these potential measurement errors may have biased the associations towards an unclear direction, this was more likely towards the null (non-differential errors due to the prospective design). In addition, some individual emulsifiers were consumed by an insufficient number of participants to be investigated individually. However, all available intakes of emulsifiers consumed were included in the calculation of exposure to total and groups of emulsifiers. Finally, residual confounding in the observed associations cannot be entirely ruled out, although this concern has been mitigated by using multivariable Cox models accounting for a wide range of potential confounders.

Policy implications and conclusions

Results from this large prospective cohort suggest that additive emulsifiers may be associated with an increased risk of CVD. These findings should be replicated in future epidemiological cohorts and mechanisms should be further elucidated by experimental approaches. Despite the moderate magnitude of the associations, these findings may have important public health implications given that these food additives are used ubiquitously in thousands of widely consumed ultra-processed food products. The results will contribute to the re-evaluation of regulations around food additive usage in the food industry to protect consumers. Meanwhile, several public health authorities recommend limiting the consumption of ultra-processed foods as a way of limiting exposure to non-essential controversial food additives.[62 63]

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Contributors: LS and BS contributed equally and are co-first authors. EC, NDP, YE, FSE, CA, ADS, RL, and MT developed the additives composition database and matched consumption and composition data. CA coordinated dietitian work. FSE coordinated data management work. NDP, YE, EC, and MT supervised the technical work. LS, BS, and MT designed the research. LS and GJ performed the statistical analysis. BS and MT supervised the statistical analysis. LS drafted the first version of the manuscript. BS revised later versions of the manuscript. MT supervised the writing. All authors contributed to the data interpretation, revised each draft of the manuscript for important intellectual content, and approved the final version. BS and MT had primary responsibility for the final content and are the guarantors.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at https://www.icmje.org/disclosure-of-interest/ and declare: the funders are named above; no support from any for profit organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Electronic informed consent is provided by each person included in the NutriNet-Santé cohort. The study is registered at https://clinicaltrials.gov/ct2/show/NCT03335644, conducted according to the Declaration of Helsinki guidelines and approved by the institutional review board of the French Institute for Health and Medical Research (IRB-Inserm) and the Commission Nationale de l'Informatique et des Libertés (CNIL No 908450/909216).

Data sharing: Researchers from public institutions can submit a collaboration request including information on the institution and a brief description of the project to collaboration@etude-nutrinet-sante.fr. All requests will be reviewed by the steering committee of the NutriNet-Santé study. If the collaboration is accepted, a data access agreement will be necessary and appropriate authorisations from the competent administrative authorities might be needed. In accordance with existing regulations, no personal data will be accessible.

BS and MT (the guarantors) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Dissemination to participants and related patient and public communities: The results of the present study will be disseminated to the NutriNet-Santé participants through the cohort website, where lay summaries of all publications are posted (https://etude-nutrinet-sante.fr/link/zone/43-Publications). Additionally, results will be disseminated in public seminars through a press release from the French Medical Institute for Health and Medical Research, in association with the Institut National de la Recherche pour l'agriculture, l'alimentation et l'environnement, Conservatoire National des Arts et Métiers, and Sorbonne Paris Nord communication and direction boards. The press release will be posted on their websites and sent to their journalist contact book in France, Europe, and abroad (translated into English), as well as through Facebook and Twitter.

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1 Calixto Andrade G, Julia C, Deschamps V, et al. Consumption of Ultra-Processed Food and Its Association with Sociodemographic Characteristics and Diet Quality in a Representative Sample of French Adults. *Nutrients* 2021;13:682. doi:10.3390/nu13020682
2 Mertens E, Colizzi C, Peñalvo JL. Ultra-processed food consumption in adults across Europe. *Eur J Nutr* 2022; 61:1521-39. doi:10.1007/s00394-021-02733-7.
3 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:e009892. doi:10.1136/bmjopen-2015-009892
4 Srour B, Kordahi MC, Bonazzi E, Deschasaux-Tanguy M, Touvier M, Chassaing B. Ultra-processed foods and human health: from epidemiological evidence to mechanistic insights. *Lancet Gastroenterol Hepatol* 2022;7:1128-40. doi:10.1016/S2468-1253(22)00169-8
5 Chazelas E, Deschasaux M, Srour B, et al. Food additives: distribution and co-occurrence in 126,000 food products of the French market. *Sci Rep* 2020;10:3980. doi:10.1038/s41598-020-60948-w
6 Cox S, Sandall A, Smith L, Rossi M, Whelan K. Food additive emulsifiers: a review of their role in foods, legislation and classifications, presence in food supply, dietary exposure, and safety assessment. *Nutr Rev* 2021;79:726-41. doi:10.1093/nutrit/nuaa038
7 Chazelas E, Druesne-Pecollo N, Esseddik Y, et al. Exposure to food additive mixtures in 106,000 French adults from the NutriNet-Santé cohort. *Sci Rep* 2021;11:19680. doi:10.1038/s41598-021-98496-6
8 Open Food Facts. [cited 2020 Oct 22]. https://world.openfoodfacts.org/discover
9 Elmén L, Zlamal JE, Scott DA, et al. Dietary Emulsifier Sodium Stearoyl Lactylate Alters Gut Microbiota *in vitro* and Inhibits Bacterial Butyrate Producers. *Front Microbiol* 2020;11:892. https://www.frontiersin.org/article/10.3389/fmicb.2020.00892. doi:10.3389/fmicb.2020.00892
10 Naimi S, Viennois E, Gewirtz AT, Chassaing B. Direct impact of commonly used dietary emulsifiers on human gut microbiota. *Microbiome* 2021;9:66. doi:10.1186/s40168-020-00996-6
11 Viennois E, Bretin A, Dubé PE, et al. Dietary Emulsifiers Directly Impact Adherent-Invasive E. coli Gene Expression to Drive Chronic Intestinal Inflammation. *Cell Rep* 2020;33:108229. doi:10.1016/j.celrep.2020.108229
12 Benard C, Cultrone A, Michel C, et al. Degraded carrageenan causing colitis in rats induces TNF secretion and ICAM-1 upregulation in monocytes through NF-kappaB activation. *PLoS One* 2010;5:e8666. doi:10.1371/journal.pone.0008666
13 Um CY, Hodge RA, Tran HQ, Campbell PT, Gewirtz AT, McCullough ML. Association of Emulsifier and Highly Processed Food Intake with Circulating Markers of Intestinal Permeability and Inflammation in the Cancer Prevention Study-3 Diet Assessment Sub-Study. *Nutr Cancer* 2021;74:1701-11.
14 Bancil AS, Sandall AM, Rossi M, Chassaing B, Lindsay JO, Whelan K. Food Additive Emulsifiers and Their Impact on Gut Microbiome, Permeability, and Inflammation: Mechanistic Insights in Inflammatory Bowel Disease. *J Crohns Colitis* 2021;15:1068-79. doi:10.1093/ecco-jcc/jjaa254

15 Roberts CL, Rushworth SL, Richman E, Rhodes JM. Hypothesis: Increased consumption of emulsifiers as an explanation for the rising incidence of Crohn's disease. *J Crohns Colitis* 2013;7:338-41. doi:10.1016/j.crohns.2013.01.004
16 Chassaing B, Compher C, Bonhomme B, et al. Randomized Controlled-Feeding Study of Dietary Emulsifier Carboxymethylcellulose Reveals Detrimental Impacts on the Gut Microbiota and Metabolome. *Gastroenterology* 2022;162:743-56. doi:10.1053/j.gastro.2021.11.006
17 Witkowski M, Weeks TL, Hazen SL. Gut Microbiota and Cardiovascular Disease. *Circ Res* 2020;127:553-70. doi:10.1161/CIRCRESAHA.120.316242
18 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;10:242. doi:10.1186/1471-2458-10-242
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: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;25:287-96. doi:10.1007/s10654-010-9433-9
21 IPAQ Group. *Guidelines for Data Processing and Analysis of the International Physical Activity Questionnaire*. IPAQ, 2005.
22 Vergnaud AC, 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;56:407-17. doi:10.1007/s00038-011-0257-5
23 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;105:1055-64. doi:10.1017/S0007114510004617
24 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;116:427-438.e5. doi:10.1016/j.jand.2015.09.017
25 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;113:953-62. doi:10.1017/S0007114515000057
26 Le Moullec N, Deheeger M, Preziosi P, Montero P, Valeix P, Rolland-Cachera M. Validation du manuel photo utilisé pour l'enquête alimentaire de l'étude SU.VI.MAX[Validation of the food portion size booklet used in the SU.VI.MAX study]. *Cah Nutr Diét* 1996;31:158-64.
27 Arnault N, Caillot L, Castetbon K, Coronel S, Deschamps V, Fezeu L. Table de composition des aliments, étude NutriNet-Santé. [Food composition table, NutriNet-Santé study] (in French). 2013.
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;24:1119-30. doi:10.1038/sj.ijo.0801376
29 Goldberg GR, Black AE, Jebb SA, et al. Critical evaluation of energy intake data using fundamental principles of energy physiology: 1. Derivation of cut-off limits to identify under-recording. *Eur J Clin Nutr* 1991;45:569-81.
30 Observatoire de l'alimentation (Oqali). OQALI - Home page. [cited 2020 Oct 22]. https://www.oqali.fr/oqali_eng/
31 Global New Products Database (GNPD). Banque de données mondiale de nouveaux produits, suivi des tendances nouveaux produits et innovations. [cited 2020 Oct 22]. https://www.gnpd.com/sinatra/anonymous_frontpage/
32 Food and Agriculture Organization/World Health Organization (FAO/WHO). Codex General Standard for Food Additives (GSFA, Codex STAN 192-1995). Codex Alimentarius Commission; 2019 [cited 2018 Sep 19]. https://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FStandards%252FCODEX%2BSTAN%2B192-1995%252FCXS_192e.pdf
33 Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika* 1982;69:239-4110.1093/biomet/69.1.239.
34 Therneau TM. A Package for Survival Analysis in R. 2020. https://CRAN.R-project.org/package=survival
35 Desquilbet L, Mariotti F. Dose-response analyses using restricted cubic spline functions in public health research. *Stat Med* 2010;29:1037-57. doi:10.1002/sim.3841
36 Harrell F, Dupont C. Harrell Miscellaneous. https://cran.r-project.org/web/packages/Hmisc/Hmisc.pdf
37 Martinez-Steele E, Khandpur N, Batis C, et al. Best practices for applying the Nova food classification system. *Nat Food* 2023;4:445-8. doi:10.1038/s43016-023-00779-w
38 Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *J R Stat Soc B* 1995;57:289-300. doi:10.1111/j.2517-6161.1995.tb02031.x.
39 Debras C, Chazelas E, Sellem L, et al. Artificial sweeteners and risk of cardiovascular diseases: results from the prospective NutriNet-Santé cohort. *BMJ* 2022;378:e071204. doi:10.1136/bmj-2022-071204
40 R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2021. https://www.R-project.org/
41 WHO, FAO. Seventeenth Report of the Joint FAO/WHO Expert Committee on Food Additives. 1974. (FAO Nutrition Meetings Report Series). Report No.: 53.
42 EFSA. Re-evaluation of mono- and di-glycerides of fatty acids (E 471) as food additives. 2017 Nov [cited 2022 Jan 30]. https://www.efsa.europa.eu/en/efsajournal/pub/5045
43 EFSA. Re-evaluation of celluloses E 460(i), E 460(ii), E 461, E 462, E 463, E 464, E 465, E 466, E 468 and E 469 as food additives. 2017 Sep [cited 2022 Jan 30]. https://www.efsa.europa.eu/en/efsajournal/pub/5047
44 EFSA. Re-evaluation of acetic acid, lactic acid, citric acid, tartaric acid, mono- and diacetyltartaric acid, mixed acetic and tartaric acid esters of mono- and diglycerides of fatty acids (E 472a-f) as food additives. 2020 Mar [cited 2022 Jan 30]. https://www.efsa.europa.eu/en/efsajournal/pub/6032
45 Lock JY, Carlson TL, Wang CM, Chen A, Carrier RL. Acute Exposure to Commonly Ingested Emulsifiers Alters Intestinal Mucus Structure and Transport Properties. *Sci Rep* 2018;8:10008. doi:10.1038/s41598-018-27957-2
46 Viennois E, Chassaing B. Consumption of Select Dietary Emulsifiers Exacerbates the Development of Spontaneous Intestinal Adenoma. *Int J Mol Sci* 2021;22:2602. doi:10.3390/ijms22052602
47 Viennois E, Merlin D, Gewirtz AT, Chassaing B. Dietary Emulsifier-Induced Low-Grade Inflammation Promotes Colon Carcinogenesis. *Cancer Res* 2017;77:27-40. doi:10.1158/0008-5472.CAN-16-1359
48 Furuhashi H, Higashiyama M, Okada Y, et al. Dietary emulsifier polysorbate-80-induced small-intestinal vulnerability to indomethacin-induced lesions via dysbiosis. *J Gastroenterol Hepatol* 2020;35:110-7. doi:10.1111/jgh.14808
49 Elmén L, Zlamal JE, Scott DA, et al. Dietary Emulsifier Sodium Stearoyl Lactylate Alters Gut Microbiota *in vitro* and Inhibits Bacterial Butyrate Producers. *Front Microbiol* 2020;11:892. https://www.frontiersin.org/article/10.3389/fmicb.2020.00892. doi:10.3389/fmicb.2020.00892
50 Shang Q, Sun W, Shan X, et al. Carrageenan-induced colitis is associated with decreased population of anti-inflammatory bacterium, Akkermansia muciniphila, in the gut microbiota of C57BL/6J mice. *Toxicol Lett* 2017;279:87-95. doi:10.1016/j.toxlet.2017.07.904
51 Daniel N, Gewirtz AT, Chassaing B. *Akkermansia muciniphila* counteracts the deleterious effects of dietary emulsifiers on microbiota and host metabolism. *Gut* 2023;72:906-17. doi:10.1136/gutjnl-2021-326835
52 Li J, Lin S, Vanhoutte PM, Woo CW, Xu A. Akkermansia Muciniphila Protects Against Atherosclerosis by Preventing Metabolic Endotoxemia-Induced Inflammation in Apoe-/- Mice. *Circulation* 2016;133:2434-46. doi:10.1161/CIRCULATIONAHA.115.019645
53 Hou MF, Ou-Yang F, Li CL, et al. Comprehensive profiles and diagnostic value of menopausal-specific gut microbiota in premenopausal breast cancer. *Exp Mol Med* 2021;53:1636-46. doi:10.1038/s12276-021-00686-9
54 Rutsch A, Kantsjö JB, Ronchi F. The Gut-Brain Axis: How Microbiota and Host Inflammasome Influence Brain Physiology and Pathology. *Front Immunol* 2020;11:604179. doi:10.3389/fimmu.2020.604179
55 Threapleton DE, Greenwood DC, Evans CEL, et al. Dietary fibre intake and risk of cardiovascular disease: systematic review and meta-analysis. *BMJ* 2013;347:f6879. doi:10.1136/bmj.f6879
56 Said MA, Verweij N, van der Harst P. Associations of Combined Genetic and Lifestyle Risks With Incident Cardiovascular Disease and Diabetes in the UK Biobank Study. *JAMA Cardiol* 2018;3:693-702. doi:10.1001/jamacardio.2018.1717
57 Estruch R, Ros E, Salas-Salvadó J, et al, PREDIMED Study Investigators. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. *N Engl J Med* 2018;378:e34. doi:10.1056/NEJMoa1800389

58 Smith LH. Selection Mechanisms and Their Consequences: Understanding and Addressing Selection Bias. *Curr Epidemiol Rep* 2020;7:179-89. doi:10.1007/s40471-020-00241-6.
59 Murakami K, Livingstone MBE. Prevalence and characteristics of misreporting of energy intake in US adults: NHANES 2003-2012. *Br J Nutr* 2015;114:1294-303. doi:10.1017/S0007114515002706
60 Markussen MS, Veierød MB, Ursin G, Andersen LF. The effect of under-reporting of energy intake on dietary patterns and on the associations between dietary patterns and self-reported chronic disease in women aged 50-69 years. *Br J Nutr* 2016;116:547-58. doi:10.1017/S000711451600218X
61 Anses. Etude Individuelle Nationale des Consommations Alimentaires 3 (INCA 3). 2017.
62 Haut Conseil de la Santé Publique (HCSP). Pour une Politique nutritionnelle de santé publique en France. PNNS 2017-2021. Paris: Haut Conseil de la Santé Publique; 2017 Sep [cited 2019 Feb 5]. https://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=632
63 Monteiro CA, Cannon G, Lawrence M, da Costa Louzada ML, Pereira Machado P. Ultra-processed foods,diet quality, and health using the NOVA classification system. Rome, FAO. 2019 [cited 2019 Sep 4]; https://www.fao.org/3/ca5644en/ca5644en.pdf

Supplementary information: eMethod1-4, eTables1-4, eFigures1-5, and references