Food additive emulsifiers and the risk of type 2 diabetes: analysis of data from the NutriNet-Santé prospective cohort study

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Summary

Background Experimental studies have suggested potential detrimental effects of emulsifiers on gut microbiota, inflammation, and metabolic perturbations. We aimed to investigate the associations between exposures to food additive emulsifiers and the risk of type 2 diabetes in a large prospective cohort of French adults.

Methods We analysed data from 104 139 adults enrolled in the French NutriNet-Santé prospective cohort study from May 1, 2009, to April 26, 2023; 82 456 (79·2%) were female and the mean age was 42·7 years (SD 14·5). Dietary intakes were assessed with three 24 h dietary records collected over three non-consecutive days, every 6 months. Exposure to additive emulsifiers was evaluated through multiple food composition databases and ad-hoc laboratory assays. Associations between cumulative time-dependent exposures to food additive emulsifiers and the risk of type 2 diabetes were characterised with multivariable proportional hazards Cox models adjusted for known risk factors. The NutriNet-Santé study is registered at ClinicalTrials.gov (NCT03335644).

Findings Of 104 139 participants, 1056 were diagnosed with type 2 diabetes during follow-up (mean follow-up duration 6·8 years [SD 3·7]). Intakes of the following emulsifiers were associated with an increased risk of type 2 diabetes: total carrageenans (hazard ratio [HR] 1·03 [95% CI 1·01–1·05] per increment of 100 mg per day, p<0·0001), carrageenans gum (E407; HR 1·03 [1·01–1·05] per increment of 100 mg per day, p<0·0001), tripotassium phosphate (E340; HR 1·15 [1·02–1·31] per increment of 500 mg per day, p=0·023), acetyl tartaric acid esters of monoglycerides and diglycerides of fatty acids (E472e; HR 1·04 [1·00–1·08] per increment of 100 mg per day, p=0·042), sodium citrate (E331; HR 1·04 [1·01–1·07] per increment of 500 mg per day, p=0·0080), guar gum (E412; HR 1·11 [1·06–1·17] per increment of 500 mg per day, p<0·0001), gum arabic (E414; HR 1·03 [1·01–1·05] per increment of 1000 mg per day, p=0·013), and xanthan gum (E415, HR 1·08 [1·02–1·14] per increment of 500 mg per day, p=0·013).

Interpretation We found direct associations between the risk of type 2 diabetes and exposures to various food additive emulsifiers widely used in industrial foods, in a large prospective cohort of French adults. Further research is needed to prompt re-evaluation of regulations governing the use of additive emulsifiers in the food industry for better consumer protection.

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Introduction

Food additives are widely used by the food industry for various purposes, such as enhancing and preserving the texture, colour, taste and appearance of products.[1] These additives are generally markers of ultra-processed foods, which constitute a substantial proportion of daily caloric intake and have been associated with an increased risk of chronic conditions in more than 75 prospective studies worldwide.[2] The NutriNet-Santé study was launched in May, 2009, in France, with an ongoing open enrolment of volunteers; the main objective of the study is to investigate the relationships between nutrition and health.[3] Notably, in NutriNet-Santé we observed an association between ultra-processed food intake and an elevated risk of type 2 diabetes.[4] Similar associations were found in other cohort studies conducted in the Netherlands, Spain, and the UK.[5]

Among the various additives that could contribute to these associations, food emulsifiers (food additives with emulsifying properties, referred to as emulsifiers from this point onwards) are the most ubiquitous. They are extensively used by food manufacturers to enhance texture and allow a longer shelf-life in a variety of ultra-processed foods such as chocolate, ice cream, cookies, pastries, ultra-processed fruits, vegetables and cereals, dairy products, mayonnaise, edible oils, and syrups. Globally, the most

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Research in context

Evidence before this study

We did a comprehensive literature search of PubMed from database inception to Sept 25, 2023, for studies published in English and French focusing on the potential effects of food additive emulsifiers on type 2 diabetes. The search terms were "(diabetes or type 2 diabetes or diabetes mellitus)" AND "(food additive emulsifiers or emulsifiers)". A small number of experimental studies (in vitro, animal, and short-term randomised controlled trials) suggested adverse effects of some emulsifiers such as gut microbiota dysbiosis, inflammation, and metabolic perturbations. Two cohort studies from our group showed associations between exposure to various food additive emulsifiers and an increased risk of cardiovascular disease and cancer. No such investigation has, to the best of our knowledge, yet been conducted to assess the risk of type 2 diabetes.

Added value of this study

The present study is the first to quantitatively assess exposure to food additive emulsifiers in a large-scale cohort (n=104 139), thereby providing novel insights into the association of emulsifiers with the risk of type 2 diabetes. Sparse details on the specific industrial food products consumed were available in previous epidemiological studies worldwide, but the variation in additive composition is huge for two different brands of the same food item (eg, a chocolate biscuit can contain zero to eight different additives). Thus, we evaluated the occurrence and dose of exposures to food additive emulsifiers by linking detailed dietary records from the NutriNet-Santé cohort (including commercial names and brands of industrial foods and beverages) to multiple food composition databases, ad-hoc laboratory assays, and dynamic matching to account for reformulations of industrial food items over time. We observed that higher intakes of seven individual emulsifiers (European codes: E407, E340, E472e, E331, E412, E414, and E415) and one emulsifier group (total carrageenans) were associated with an increased risk of type 2 diabetes.

Implications of all the available evidence

These findings could have important public health implications given the ubiquitous nature of these food additives used in thousands of widely consumed ultra-processed products ingested daily by millions of children and adults globally. Although additional long-term observational epidemiological studies as well as short-term interventions (for ethical reasons) are needed to confirm these findings, they align with those of previous in-vitro and in-vivo experiments suggesting adverse effects of several emulsifiers. Altogether, the available evidence supports a re-evaluation of regulations governing the use of food additive emulsifiers by the food industry for a better consumer protection. Indeed, current acceptable daily intakes (ADIs) were set up on the basis of classical cytotoxicity and genotoxicity criteria but neither included clinical epidemiological data on hard endpoints (which are missing so far) nor the latest experimental research (eg, on microbiota dysbiosis). As we advance our understanding of the potential role of additives in the development of diabetes, several public health authorities already recommend minimising the consumption of ultra-processed foods in order to lower exposure to controversial so-called cosmetic food additives.

commonly used emulsifiers are lecithins (E322; found in 14% of food products in the EU according to data from the European Food Safety Authority [EFSA]), monoglycerides and diglycerides of fatty acids (E471; found in 7% of foods), guar gum (E412; found in 6% of foods), xanthan gum (E415; found in 5% of foods), carrageenans (E407; found in 4% of foods), and celluloses (E460–469; found in 2% of foods).[6–13] Recent experimental studies have shown that emulsifiers can directly modulate the composition and function of the intestinal microbiota, driving microbiota encroachment and chronic low-grade intestinal inflammation, thus exacerbating metabolic disorders.[14] In-vitro, animal, and short-term interventional clinical studies have shown that emulsifier consumption induces intestinal microbiota dysbiosis, which stimulates pro-inflammatory signalling, potentially predisposing the consuming host to several diseases such as hypertension, obesity, diabetes, and other cardiometabolic disorders. We previously showed associations between food additive emulsifier intakes and the risk of cardiovascular disease and cancer in the NutriNet-Santé cohort.[15,16]

However, to the best of our knowledge, no epidemiological study has quantified dietary exposures to a wide range of food additive emulsifiers and investigated their associations with the risk of type 2 diabetes. This research gap can be explained by the sparse details of specific industrial food products consumed in previous epidemiological studies. Emulsifier composition indeed varies greatly from one industrial product to another, for the same type of food. A chocolate biscuit, for example, could contain zero to eight different emulsifiers, depending on the brand. The NutriNet-Santé cohort has the potential to advance knowledge in this field, since it has collected extensive brand-specific dietary data through validated repeated 24 h dietary records since 2009. Therefore, in this study, we aimed to investigate the association between emulsifier exposure and type 2 diabetes risk in the NutriNet-Santé prospective cohort study.

For a **publicly available database on the nutritional composition of industrial food products** see https://world.openfoodfacts.org/discover

For the **protocol** see https://info.etude-nutrinet-sante.fr/siteinfo/article/3

Methods

Study population

This study was conducted within the population-based NutriNet-Santé prospective cohort; the protocol is available online. Participants are recruited through vast multimedia campaigns from the general population of French citizens aged older than 15 years with internet access. To enrol,

participants with internet access are required to create a personal account on the NutriNet-Santé web-based platform. Upon enrolment, participants are invited to provide detailed information by completing five questionnaires about their lifestyle and sociodemographic data (eg, date of birth, sex, education level, professional occupation, smoking status, number of children), health status (eg, personal and family medical history, medical treatments), dietary habits (three non-consecutive 24 h dietary records), anthropometric data (eg, self-reported height, bodyweight), and physical activity level (validated 7-day assessment via the International Physical Activity Questionnaire [IPAQ]).[17]

This study is registered with ClinicalTrials.gov (NCT03335644).

For the **web-based platform** see https://etude-nutrinet-sante.fr/

Ethical approval

This study was 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 n°908450/n°909216). Electronic informed consent was provided by each participant included in the NutriNet-Santé cohort before enrolment.

Dietary data collection

At inclusion, and every 6 months thereafter, participants filled out three non-consecutive days of 24 h dietary records, randomly assigned over a 2-week period, including two weekdays and one weekend day (to account for variability in the diet across the week and the seasons). Details on dietary data collection and under-reports identification are provided in the appendix (p 2).

Emulsifier intakes

Intakes of food additives were quantified on the basis of data provided by participants' dietary records, in which the commercial brands or names of the industrial products consumed were recorded. The detailed method for estimation of food additive intakes has been previously described (appendix p 2). Among the available food additives quantified from participants' dietary records, we identified 61 food additives classified as emulsifiers or emulsifying salts in the Codex GFSA database, or according to US or UK regulations when not included in Codex (eg, E404, E418, and E468) and considered the sum of their intakes as the total emulsifier exposure.[18] Their list, with corresponding EU codes, is provided in the appendix (pp 14–15). Additionally, individual emulsifiers with similar chemical structures were summed into eight groups: total phosphates (E339, E340, E341, E343, E450, E451, and E452), total lactylates (E481 and E482), total polyglycerol esters of fatty acids (E475 and E476), total monoglycerides and diglycerides of fatty acids (E471, E472, and E472a-b-c-e), total celluloses (E460, E461, E464, E466, and E468), total carrageenans (E407 and E407a), total alginates (E400, E401, E402, E404, and E405), and total modified starches (E14xx).

Type 2 diabetes ascertainment

Type 2 diabetes was assessed with a multi-source approach. Throughout follow-up, participants could report health events, medical treatment, and examinations via the biannual health questionnaires or at any time directly via the health interface of their personal account. Moreover, the NutriNet-Santé cohort was linked to the national health insurance system database to collect additional information about medical treatments and consultations. The NutriNet-Santé cohort was also linked to the French national mortality registry (CépiDC) to identify occurrence and cause of death. Additional information is provided in the appendix (p 3).

Statistical analyses

Among participants from the NutriNet-Santé cohort who completed at least two 24 h dietary records during their first 2 years of follow-up, we included those who were not under-energy reporters, who did not have any prevalent type 1 or 2 diabetes diagnosed before baseline, and who had a non-null follow-up. A correlation matrix was generated to visualise the Spearman correlations between intakes of individual emulsifiers. The associations between cumulative emulsifier intakes (as a continuous time-dependent exposure) and the risk of type 2 diabetes were assessed with multivariable proportional hazard Cox

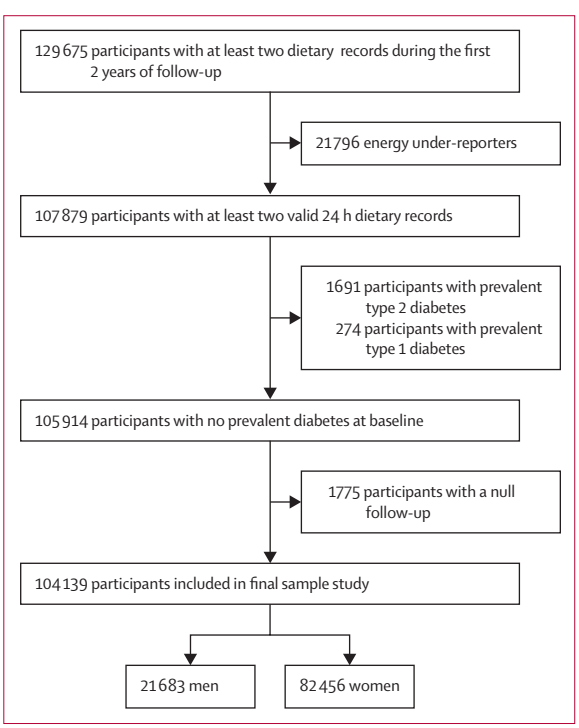

Figure 1: **Flowchart of participants included from the NutriNet-Santé cohort, 2009–23 (n=104 139)**

See **Online** for appendix

	Number of participants (n=104 139)	Mean (SD)	Median (IQR)
Age, years	..	42·7 (14·5)	41·5 (30·1–54·7)
Sex			
Female	82 456 (79·2%)	..	..
Male	21 683 (20·8%)	..	..
BMI, kg/m²*	..	23·6 (4·4)	22·8 (20·7–25·5)
Weight variation during follow-up, kg*		0·8 (5·7)	0·0 (0·0–1·8)
Family history of diabetes†	14 366 (13·8%)	..	..
Education level*			
Less than high school degree	17 032 (16·5%)	..	..
<2 years after high school	16 283 (15·8%)	..	..
≥2 years after high school	69 930 (67·7%)	..	..
Smoking status*			
Never	52 248 (50·2%)	..	..
Former smoker	34 016 (32·7%)	..	..
Occasional smoker	5396 (5·2%)	..	..
Regular smoker	12 397 (11·9%)	..	..
Prevalence of metabolic diseases‡	15 015 (14·4%)	..	..
IPAQ physical activity level*			
Low	29 280 (32·6%)	..	..
Moderate	38 642 (43·0%)	..	..
High	21 890 (24·4%)	..	..
Energy intake without alcohol, kcal per day§	..	1846·2 (451·6)	1790·4 (1538·5–2095·3)
Alcohol intake, g per day	..	7·8 (11·8)	3·3 (0·0–10·8)
Total lipid intake, g per day	..	81·5 (25·2)	78·7 (64·5–95·5)
Saturated fat intake, g per day	..	33·2 (12·1)	31·9 (24·9–40·0)
Sodium intake, mg per day	..	2712·3 (880·9)	2598·8 (2114·2–3179·8)
Fibre intake, g per day	..	19·5 (7·2)	18·4 (14·6–23·1)
Added sugar intake, g per day	..	35·1 (23·7)	35·1 (22·2–50·6)
Refined grains intake, g per day	..	153·6 (84·4)	144·1 (95·2–199·0)
Fruit and vegetable intake, g per day	..	407·1 (220·0)	379·6 (254·1–524·7)
Total dairy intake, g per day	..	197·5 (148·4)	164·0 (87·5–275·5)
Red and processed meat intake, g per day	..	76·5 (52·5)	69·6 (40·0–104·3)
Ultra-processed food intake (% of quantity of daily food intake)	..	17·3% (9·8)	11·0% (10·6–21·6)
Total emulsifier intake, mg per day	..	4191·9 (3163·2)	3531·3 (2017·5–5573·8)

Data are n (%), mean (SD), or median (IQR). IPAQ=International Physical Activity Questionnaire. *Missing values: BMI n=1154; bodyweight variation during follow-up n=1452; education level n=894; smoking status n=82; IPAQ physical activity level n=14 327. †Family history of diabetes in first-degree relatives. ‡Prevalence of metabolic disease was defined as the self-report of diagnosis or treatment, or both, for at least one prevalent cardiometabolic disorder among cardiovascular disease, dyslipidaemia, and hypertension. §All dietary intake data in this table are calculated as the mean intake during the first 2 years of participation in the study.

Table 1: **Baseline characteristics of study participants from the NutriNet-Santé cohort, 2009–23**

models, with age as the timescale, which computed hazard ratios (HRs) and 95% CIs. Participants contributed person-time to the models from their age at enrolment in the cohort (defined as the "start" time, calculated according to their birth date), until their age at the date of type 2 diabetes diagnosis, the date of type 1 diabetes diagnosis, the date of death, the date of the last completed questionnaire, or April 26, 2023, whichever occurred first. HRs were computed for a standardised increment of 1, 10, 100, 500, or 1000 mg per day of emulsifier intake depending on the distribution and order of magnitude of each emulsifier. Increments are specified in the appendix (p 18). A time-to-event data structure was used, with time-dependent dietary variables updated every 2 years. Exposure during a given period was computed with a weighted average of the most recent 2-year period and previous periods. We performed a minimally adjusted model including age (timescale) and sex. Based on a directed acyclic graph (DAG; appendix p 6), the main model was adjusted for age (timescale), sex, BMI (continuous, kg/m²), physical activity (categorical IPAQ variable: high, moderate, or low), smoking status (never smoked, former smoker, occasional smoker, or regular smoker), number of smoked cigarettes in pack-years (continuous), educational level (less than high school degree, <2 years after high school degree, or ≥2 years after high school degree), number of dietary records (continuous), family history of type 2 diabetes (yes or no), daily intakes of alcohol (continuous, g per day), refined grains (continuous, g per day), fruits and vegetables (g per day), dairy products (continuous, mL per day), red and processed meats (continuous, g per day), and proportion of ultra-processed foods in the diet (continuous, %), as the minimally sufficient set of confounders identified by the DAG. We also adjusted for intakes of energy without alcohol (continuous, kcal per day), total saturated fatty acids (continuous, g per day), sodium (continuous, mg per day), total fibre (continuous, g per day), and added sugars (continuous, g per day), to better account for the overall quality of the diet. Additionally, each model was mutually adjusted for the rest of the emulsifiers (mg per day). Restricted cubic splines were also computed. Patterns of emulsifier intake were identified with a principal component analysis, and the associations of the resulting components with type 2 diabetes were assessed. Additional information and sensitivity analyses, including further adjustments for artificial sweeteners, bodyweight change, and prevalent cardiometabolic diseases, are presented in the appendix (pp 3–4).

All statistical analyses were conducted in R (version 4.1.2), except for the restricted cubic spline method, which was conducted in SAS (version 9.4).

Role of the funding source

The funders had no role in study design; the collection, analysis, and interpretation of data; the writing of the report, or the decision to submit the manuscript for publication.

Results

A total of 104 139 participants from the NutriNet-Santé cohort study, enrolled between May 1, 2009, and April 26, 2023, were included in this analysis (figure 1), of whom 82 456 (79·2%) were female, with a mean age of 42·7 years (SD 14·5) at baseline. With an average of 5·7 (SD 3·1) dietary records completed, 99·7% of

participants were exposed to at least one food additive emulsifier. Baseline participants' characteristics, including anthropometric, socioeconomic, health, and dietary data, are detailed in table 1.

Contributions of individual food additive emulsifiers to the total emulsifier intake are shown in figure 2, absolute intakes of emulsifiers (in mg per day) in the first 2 years of follow-up are shown in table 2, and correlations between intakes of individual emulsifiers are presented in the appendix (p 5). Overall, there were limited correlations between intakes of individual emulsifiers (appendix p 5). A total of 34 individual emulsifiers were consumed by less than 5% of included participants, and were therefore not studied individually in relation to type 2 diabetes risk : E332, E335, E343, E400, E402, E404, E405, E406, E418, E425, E433, E435, E444, E445, E461, E468, E472, E472a, E472c, E473, E475, E477, E482, E491, E492, E541, E551, E900, E965, E967, E999, E1200, E1505, and E1520 (table 2). These emulsifiers were, however, included in the calculations of emulsifier intakes overall and by groups. Finally, exposure to food additive emulsifiers occurred through a variety of food products with contrasting nutritional profiles, the main contributors being ultra-processed fruits and vegetables (18·5% of total emulsifier intakes), cakes and biscuits (14·7%), and dairy products (10·0%; figure 3, appendix p 16).

A total of 1056 incident type 2 diabetes cases were detected after inclusion of participants, between 2009 and 2023 (mean follow-up duration 6·8 years [SD 3·7]). Overall, Schoenfeld residuals did not show evidence for violation of the proportional hazard assumptions (appendix p 7). Models adjusted for age and sex only are presented in the appendix (p 17). The associations in the main models between emulsifier intake and type 2 diabetes risk are outlined in figure 4 and detailed for all studied emulsifiers in the appendix (p17). Intakes of the following emulsifiers were positively associated with the risk of developing type 2 diabetes: total carrageenans, carrageenans gum (E407), tripotassium phosphate (E340), acetyl tartaric acid esters of monoglycerides and diglycerides of fatty acids (E472e), sodium citrate (E331), guar gum (E412), gum arabic (E414), and xanthan gum (E415).

Restricted cubic splines plots supported the linearity of the observed associations for total carrageenan, carrageenan gum, tripotassium phosphate, guar gum, and xanthan gum. For acetyl tartaric acid esters of monoglycerides and diglycerides of fatty acids, sodium citrate, and gum arabic, the association showed an overall increasing linear trend and then seemed to plateau in higher intakes (appendix pp 10–13). Overall, sensitivity analyses aligned with results from the main model and all significant associations observed in this study in main and sensitivity analyses went in the same direction, suggesting a low risk of at-random significant associations and indicating the robustness of the results (appendix p 20).

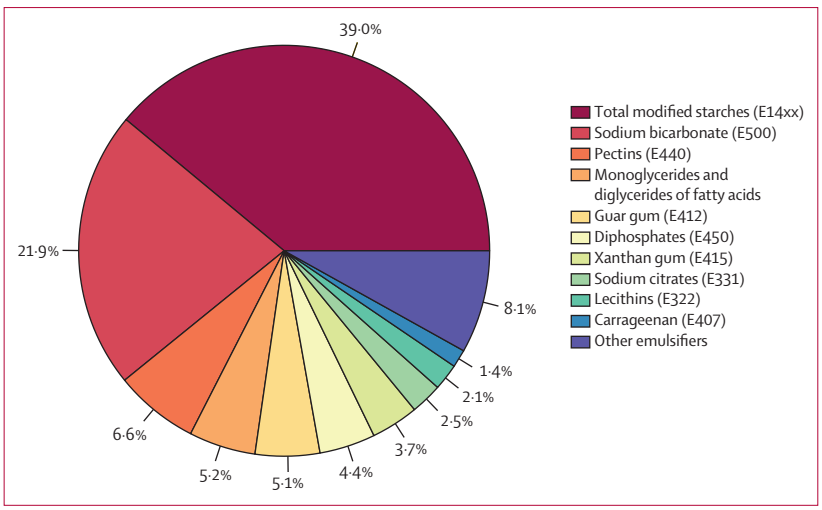

Figure 2: **Contribution of individual emulsifiers to total emulsifier intakes (%) among study participants from the NutriNet-Santé cohort, 2009–23 (n=104 139)**

Other emulsifiers included: triphosphates (E451), gum arabic (E414), polyphosphates (E452), carob bean gum (E410), cellulose (E460), tricalcium phosphate (E341), mono and diacetyl tartaric acid esters of monoglycerides and diglycerides of fatty acids (E472e), hydroxypropyl methyl cellulose (E464), polyglycerol esters of fatty acids (E475), lactic acid esters of monoglycerides and diglycerides of fatty acids (E472b), polydextrose (E1200), sodium stearoyl-2-lactylate (E481), sodium alginate (E401), ammonium salts of phosphatidic acid (E442), esters of monoglycerides and diglycerides of fatty acids (E472), polyglycerol esters of interesterified ricinoleic acid (E476), citric acid esters of monoglycerides and diglycerides of fatty acids (E472c), silicon dioxide (E551), tripotassium phosphate (E340), methyl cellulose (E461), carboxymethylcellulose (E466), trisodium phosphate (E339), acetic acid esters of monoglyceries and diglycerides of fatty acids (E472a), agar (E406), sucrose esters of fatty acids (E473), propylene glycol esters of fatty acids (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).

In principal component analyses (appendix pp 20–21), the first pattern of emulsifier intake, characterised by higher exposures to lecithins (E322), carrageenan (E407), cabob bean gum (E410), guar gum (E412), xanthan gum (E415), diphosphates (E450), sodium tripolyphosphate (E451), polyphosphates (E452), monoglycerides and diglycerides of fatty acids (E471), and sodium bicarbonate (E500) were positively associated with an increased risk of type 2 diabetes (1·14 [95% CI 1·08–1·20] per 1 SD of the component). Components 2 and 3 were characterised simultaneously by high consumption of some emulsifiers and low consumption of others, and thus were not associated with the risk of type 2 diabetes.

Discussion

This large-scale population-based cohort of French adults revealed associations between emulsifier intake and the risk of type 2 diabetes. More specifically, positive associations were observed for seven individual food additive emulsifiers (ie, carrageenans [E407], tripotassium phosphate [E340], acetyl tartaric acid esters of monoglycerides and diglycerides of fatty acids [E472e],

	European code	Mean in mg/kg per day of bodyweight, all participants (SD)	Median in mg/kg per day of bodyweight, all participants (IQR)	Mean in mg per day, all participants (SD)	Median in mg per day, all participants (IQR)	Mean in mg per day, in consumers only (SD)	Median in mg per day, in consumers only (IQR)	Percentage of consumers (%)
Total emulsifiers	..	65·5 (50·2)	54·7 (31·0–87·3)	4191·9 (3163·2)	3531·3 (2017·5–5573·8)	4205·8 (3159·2)	3542·9 (2032·2–5581·6)	99·7%
Total alginates	..	0·1 (0·6)	0·0 (0·0–0·0)	8·8 (37·4)	0·0 (0·0–0·0)	58·6 (79·9)	35·9 (17·2–71·7)	15·1%
Alginic acid	E400	0·0 (0·0)	0·0 (0·0–0·0)	0·0 (0·8)	0·0 (0·0–0·0)	22·5 (28·1)	14·5 (6·0–26·2)	0·1%
Sodium alginate	E401	0·1 (0·6)	0·0 (0·0–0·0)	8·4 (35·7)	0·0 (0·0–0·0)	58·8 (77·4)	36·2 (17·3–71·7)	14·2%
Potassium alginate	E402	0·0 (0·1)	0·0 (0·0–0·0)	0·3 (4·7)	0·0 (0·0–0·0)	34·3 (38·2)	23·2 (11·9–38·5)	0·9%
Calcium alginate	E404	0·0 (0·1)	0·0 (0·0–0·0)	0·1 (10·1)	0·0 (0·0–0·0)	157·4 (292·9)	108·3 (78·6–145·5)	0·1%
Propylene glycol alginate	E405	0·0 (0·0)	0·0 (0·0–0·0)	0·0 (0·0)	0·0 (0·0–0·0)	1·0 (1·0)	1·0 (0·7–1·4)	0·0%
Total carrageenans	..	0·9 (1·2)	0·6 (0·0–1·3)	59·0 (74·6)	36·8 (1·1–86·6)	76·8 (76·7)	56·6 (24·7–104·9)	76·8%
Carrageenan	E407	0·0 (0·2)	0·5 (0·0–1·3)	56·8 (72·5)	35·1 (0·6–82·8)	74·8 (74·7)	54·9 (23·8–101·4)	76·0%
Processed Euchema seaweed	E407a	0·9 (1·1)	0·0 (0·0–0·0)	2·2 (13·2)	0·0 (0·0–0·0)	27·0 (38·8)	17·1 (1·4–37·3)	8·0%
Total phosphates	..	5·5 (8·0)	3·3 (0·4–7·6)	353·2 (501·6)	214·3 (25·4–487·0)	455·3 (527·1)	314·3 (151·6–587·9)	77·6%
Trisodium phosphate	E339	0·1 (0·9)	0·0 (0·0–0·0)	8·6 (57·7)	0·0 (0·0–0·0)	153·4 (192·4)	93·4 (41·5–190·5)	5·6%
Tripotassium phosphate	E340	0·1 (1·4)	0·0 (0·0–0·0)	6·9 (90·5)	0·0 (0·0–0·0)	131·5 (374·8)	48·8 (8·9–138·4)	5·2%
Tricalcium phosphate	E341	0·5 (3·7)	0·0 (0·0–0·0)	28·3 (229·2)	0·0 (0·0–0·0)	151·0 (512·0)	54·6 (21·3–139·7)	18·7%
Magnesium hydrogen phosphate	E343	0·0 (0·0)	0·0 (0·0–0·0)	0·0 (0·0)	0·0 (0·0–0·0)	9·9 (0·0)	9·9 (9·9–9·9)	0·0%
Diphosphates	E450	3·8 (5·6)	2·0 (0·0–5·3)	244·5 (351·7)	131·0 (0·0–337·2)	347·2 (374·2)	238·1 (114·3–446·7)	70·4%
Sodium tripolyphosphate	E451	0·6 (1·8)	0·0 (0·0–0·0)	40·9 (116·9)	0·0 (0·0–0·0)	176·1 (187·2)	119·1 (61·6–228·6)	23·2%
Polyphosphates	E452	0·4 (1·3)	0·0 (0·0–0·0)	24·0 (85·5)	0·0 (0·0–0·0)	111·2 (155·4)	54·0 (15·3–142·9)	21·6%
Total celluloses	..	0·4 (2·1)	0·0 (0·0–0·0)	24·2 (138·3)	0·0 (0·0–0·0)	115·7 (284·4)	32·2 (3·8–119·5)	20·9%
Cellulose	E460	0·2 (1·2)	0·0 (0·0–0·0)	12·0 (79·1)	0·0 (0·0–0·0)	111·3 (217·2)	20·6 (2·8–131·5)	10·8%
Methyl cellulose	E461	0·0 (0·3)	0·0 (0·0–0·0)	2·2 (20·5)	0·0 (0·0–0·0)	91·7 (96·0)	64·9 (37·1–123·8)	2·4%
Hydroxypropyl methyl cellulose	E464	0·1 (0·5)	0·0 (0·0–0·0)	3·3 (33·1)	0·0 (0·0–0·0)	79·4 (143·5)	27·0 (0·1–101·2)	4·1%
Carboxymethylcellulose	E466	0·1 (1·2)	0·0 (0·0–0·0)	6·7 (79·1)	0·0 (0·0–0·0)	59·5 (228·3)	16·4 (6·1–42·8)	11·3%
Cross-linked sodium carboxymethylcellulose	E468	0·0 (0·0)	0·0 (0·0–0·0)	0·0 (0·1)	0·0 (0·0–0·0)	2·1 (3·5)	1·3 (0·5–2·5)	0·1%
Total monoglycerides and diglycerides of fatty acids	..	3·3 (4·6)	1·9 (0·3–4·5)	210·0 (294·1)	123·4 (18·6–286·3)	254·6 (305·8)	168·3 (71·1–333·0)	82·5%
Monoglycerides and diglycerides of fatty acids	E471	2·6 (3·3)	1·6 (0·1–3·7)	165·4 (211·2)	100·1 (9·0 -237·1)	205·8 (217·2)	144·1 (60·5–278·4)	80·3%
Esters of monoglycerides and diglycerides of fatty acids	E472	0·1 (1·5)	0·0 (0·0–0·0)	3·3 (39·2)	0·0 (0·0–0·0)	263·7 (235·5)	185·7 (115·1–371·4)	1·2%
Acetic acid esters of monoglycerides and diglycerides of fatty acids	E472a	0·3 (1·6)	0·0 (0·0–0·0)	7·1 (95·6)	0·0 (0·0–0·0)	219·9 (484·9)	76·5 (41·8–160·9)	3·2%
Lactic acid esters of monoglycerides and diglycerides of fatty acids	E472b	0·1 (0·6)	0·0 (0·0–0·0)	20·5 (105·3)	0·0 (0·0–0·0)	183·2 (263·5)	80·8 (28·6–236·2)	11·2%
Citric acid esters of monoglycerides and diglycerides of fatty acids	E472c	0·1 (0·9)	0·0 (0·0–0·0)	8·5 (58·3)	0·0 (0·0–0·0)	116·7 (184·7)	52·7 (21·6–140·4)	7·3%
Mono and diacetyl tartaric acid esters of monoglycerides and diglycerides of fatty acids	E472e	0·1 (0·5)	0·0 (0·0–0·0)	5·3 (28·8)	0·0 (0·0–0·0)	37·6 (68·6)	20·9 (10·8–41·6)	14·0%
Total polyglycerol esters of fatty acids	..	0·2 (0·9)	0·0 (0·0–0·0)	11·9 (59·5)	0·0 (0·0–0·0)	62·8 (124·7)	21·5 (7·6–59·5)	18·9%
Polyglycerol esters of fatty acids	E475	0·1 (0·9)	0·0 (0·0–0·0)	8·1 (57·2)	0·0 (0·0–0·0)	184·0 (204·0)	111·3 (59·5–231·9)	4·4%
Polyglycerol esters of interesterified ricinoleic acid	E476	0·1 (0·2)	0·0 (0·0–0·0)	3·7 (16·0)	0·0 (0·0–0·0)	24·2 (34·3)	14·3 (5·7–30·0)	15·4%
Total lactylates	..	0·1 (0·4)	0·0 (0·0–0·0)	4·4 (23·7)	0·0 (0·0–0·0)	50·6 (63·8)	31·1 (13·7–62·5)	8·8%
Sodium stearoyl-2-lactylate	E481	0·1 (0·4)	0·0 (0·0–0·0)	4·3 (23·4)	0·0 (0·0–0·0)	50·2 (63·5)	30·9 (13·7–62·5)	8·6%
Calcium stearoyl-2-lactylate	E482	0·0 (0·1)	0·0 (0·0–0·0)	0·1 (3·1)	0·0 (0·0–0·0)	44·9 (48·2)	28·6 (17·1–59·9)	0·2%
Total modified starches	..	20·1 (18·1)	16·0 (7·2–28·0)	1290·0 (1143·5)	1032·5 (461·7–1803·8)	1407·6 (1123·0)	1143·8 (609·4–1896·3)	91·6%
Modified starches	E14xx	19·0 (17·7)	14·9 (6·4–26·6)	1220·3 (1120·2)	964·3 (412·2–1711·6)	1347·4 (1101·9)	1077·1 (564·3–1813·8)	90·6%

(Table 2 continues on next page)

	European code	Mean in mg/kg per day of bodyweight, all participants (SD)	Median in mg/kg per day of bodyweight, all participants (IQR)	Mean in mg per day, all participants (SD)	Median in mg per day, all participants (IQR)	Mean in mg per day, in consumers only (SD)	Median in mg per day, in consumers only (IQR)	Percentage of consumers (%)
(Continued from previous page)								
Total polysorbates	..	0·0 (0·1)	0·0 (0·0–0·0)	0·3 (5·0)	0·0 (0·0–0·0)	29·9 (37·4)	17·9 (8·9–35·7)	1·1%
Polyoxyethylene sorbitan monooleate	E433	0·0 (0·1)	0·0 (0·0–0·0)	0·3 (4·9)	0·0 (0·0–0·0)	29·9 (37·6)	17·9 (8·9–35·7)	1·0%
Polyoxyethylene sorbitan monostearate	E435	0·0 (0·0)	0·0 (0·0–0·0)	0·0 (0·9)	0·0 (0·0–0·0)	27·8 (32·7)	19·2 (9·1–35·9)	0·0%
Total sorbitan	..	0·0 (0·2)	0·0 (0·0–0·0)	0·8 (13·7)	0·0 (0·0–0·0)	133·0 (121·7)	97·4 (64·1–171·4)	0·6%
Sorbitan monostearate	E491	0·0 (0·1)	0·0 (0·0–0·0)	0·1 (4·2)	0·0 (0·0–0·0)	101·8 (71·1)	74·1 (57·1–150·0)	0·1%
Sorbitan tristearate	E492	0·0 (0·2)	0·0 (0·0–0·0)	0·7 (13·0)	0·0 (0·0–0·0)	139·9 (128·9)	98·2 (65·5–178·6)	0·5%
Other emulsifiers								
Lecithins	E322	1·0 (1·3)	0·6 (0·2–1·3)	62·2 (79·0)	38·2 (10·3–85·3)	71·3 (80·7)	47·2 (20·1–94·7)	87·3%
Sodium citrate	E331	1·7 (4·1)	0·0 (0·0–1·8)	112·8 (271·4)	0·0 (0·0–118·4)	235·8 (353·4)	128·4 (55·8–267·9)	47·8%
Potassium dihydrogen citrate	E332	0·0 (0·0)	0·0 (0·0–0·0)	0·0 (0·0)	0·0 (0·0–0·0)	0·0 (0·0)	0·0 (0·0–0·0)	0·0%
Sodium tartarates	E335	0·0 (0·0)	0·0 (0·0–0·0)	0·0 (0·4)	0·0 (0·0–0·0)	22·1 (17·2)	21·1 (8·9–30·0)	0·0%
Agar	E406	0·1 (0·6)	0·0 (0·0–0·0)	4·3 (40·1)	0·0 (0·0–0·0)	158·1 (186·1)	104·1 (47·6–209·5)	2·7%
Carob bean gum	E410	0·5 (1·1)	0·0 (0·0–0·6)	33·1 (72·3)	0·0 (0·0–39·8)	72·8 (92·7)	44·3 (22·7–84·4)	45·5%
Guar gum	E412	2·6 (3·6)	1·3 (0·0–3·7)	166·8 (232·5)	83·9 (0·0–236·8)	234·7 (245·3)	163·1 (67·9–314·3)	71·1%
gum arabic (acacia gum)	E414	0·8 (6·6)	0·0 (0·0–0·0)	53·1 (428·5)	0·0 (0·0–0·0)	502·1 (1228·8)	160·1 (59·5–439·6)	10·6%
Xanthan gum	E415	2·1 (3·5)	0·7 (0·1–2·6)	133·5 (220·9)	47·1 (7·3–169·2)	164·9 (234·8)	75·8 (26·8–215·0)	80·9%
Gellan gum	E418	0·0 (0·1)	0·0 (0·0–0·0)	0·4 (4·4)	0·0 (0·0–0·0)	19·9 (24·9)	12·0 (5·2–25·0)	2·0%
Konjac flour	E425	0·0 (0·0)	0·0 (0·0–0·0)	0·0 (0·8)	0·0 (0·0–0·0)	121·8 (108·4)	125·0 (68·5–176·8)	0·0%
Pectins	E440	3·4 (4·8)	2·0 (0·4–4·5)	218·9 (307·3)	129·6 (28·3–286·7)	268·9 (320·2)	172·9 (81·8–339·3)	81·4%
Ammonium salts of phosphatidic acid	E442	0·1 (0·7)	0·0 (0·0–0·0)	5·9 (42·1)	0·0 (0·0–0·0)	60·7 (121·9)	8·6 (2·9–66·8)	9·8%
Sucrose acetate isobutyrate	E444	0·0 (0·0)	0·0 (0·0–0·0)	0·0 (0·8)	0·0 (0·0–0·0)	15·8 (17·0)	10·7 (6·7–20·6)	0·1%
Glycerol esters of rosin	E445	0·0 (0·0)	0·0 (0·0–0·0)	0·1 (1·2)	0·0 (0·0–0·0)	6·1 (8·2)	3·8 (2·1–7·1)	1·4%
Sucrose esters of fatty acids	E473	0·0 (0·2)	0·0 (0·0–0·0)	1·3 (14·7)	0·0 (0·0–0·0)	51·7 (76·3)	29·4 (16·0–57·1)	2·6%
Propylene glycol esters of fatty acids	E477	0·0 (0·1)	0·0 (0·0–0·0)	0·4 (7·1)	0·0 (0·0–0·0)	23·4 (48·1)	6·6 (3·4–15·7)	1·8%
Sodium bicarbonate	E500	23·0 (33·0)	10·9 (0·0–32·9)	1463·1 (2087·0)	694·4 (0·0–2099·1)	2014·1 (2210·4)	1326·8 (516·8–2730·0)	72·6%
Sodium aluminium phosphate	E541	0·0 (0·0)	0·0 (0·0–0·0)	0·0 (0·0)	0·0 (0·0–0·0)	3·8 (3·7)	1·9 (1·3–6·0)	0·0%
Silicon dioxide	E551	0·1 (2·6)	0·0 (0·0–0·0)	6·2 (152·9)	0·0 (0·0–0·0)	250·7 (941·1)	88·0 (41·9–165·0)	2·5%
Dimethyl polysiloxane	E900	0·0 (0·0)	0·0 (0·0–0·0)	0·0 (0·0)	0·0 (0·0–0·0)	0·1 (0·1)	0·0 (0·0–0·1)	0·0%
Beeswax	E901	0·0 (0·0)	0·0 (0·0–0·0)	0·1 (0·6)	0·0 (0·0–0·0)	1·2 (2·2)	0·5 (0·2–1·3)	5·5%
Maltitol	E965	0·1 (1·4)	0·0 (0·0–0·0)	6·3 (94·3)	0·0 (0·0–0·0)	317·3 (591·6)	103·7 (52·6–311·2)	2·0%
Xylitol	E967	0·0 (0·6)	0·0 (0·0–0·0)	2·3 (33·7)	0·0 (0·0–0·0)	186·0 (244·3)	104·1 (52·1–211·7)	1·2%
Quillaia extract	E999	0·0 (0·0)	0·0 (0·0–0·0)	0·0 (0·1)	0·0 (0·0–0·0)	7·5 (4·1)	6·0 (4·5–11·0)	0·0%
Polydextrose	E1200	0·4 (5·5)	0·0 (0·0–0·0)	27·9 (340·3)	0·0 (0·0–0·0)	1697·3 (2054·5)	1051·8 (473·2–2131)	1·6%
Triethyl citrate	E1505	0·0 (0·1)	0·0 (0·0–0·0)	0·4 (3·7)	0·0 (0·0–0·0)	16·7 (18·7)	10·5 (6·3–20·0)	2·2%
Propylene glycol	E1520	0·0 (0·0)	0·0 (0·0–0·0)	0·0 (0·3)	0·0 (0·0–0·0)	32·4 (28·3)	34·1 (9·7–56·8)	0·0%

Data are mean (SD), median (IQR), or %. All emulsifier intake data in this table are calculated as the mean intake during the first 2 years of participation in the study.

Table 2: **Daily emulsifier intakes among study participants from the NutriNet-Santé cohort, 2009–23 (n=104 139)**

sodium citrate [E331], guar gum [E412], gum arabic [E414], xanthan gum [E415]), and one group of emulsifiers (ie, total carrageenans; E407–407a).

To the best of our knowledge, this study is the first to evaluate and detect positive associations between a wide range of emulsifier intakes and the risk of type 2 diabetes in a large prospective cohort of adults. The qualitative and quantitative exposures to food additives were assessed in the NutriNet-Santé cohort by considering the different commercial brands of the products, to provide a high level of accuracy about the food composition of each food or beverage consumed at the individual level. Thus, it is not possible to directly compare our findings with previous epidemiological literature. Authorised emulsifiers are deemed safe for human consumption, and acceptable daily intakes (ADIs), such as for all other

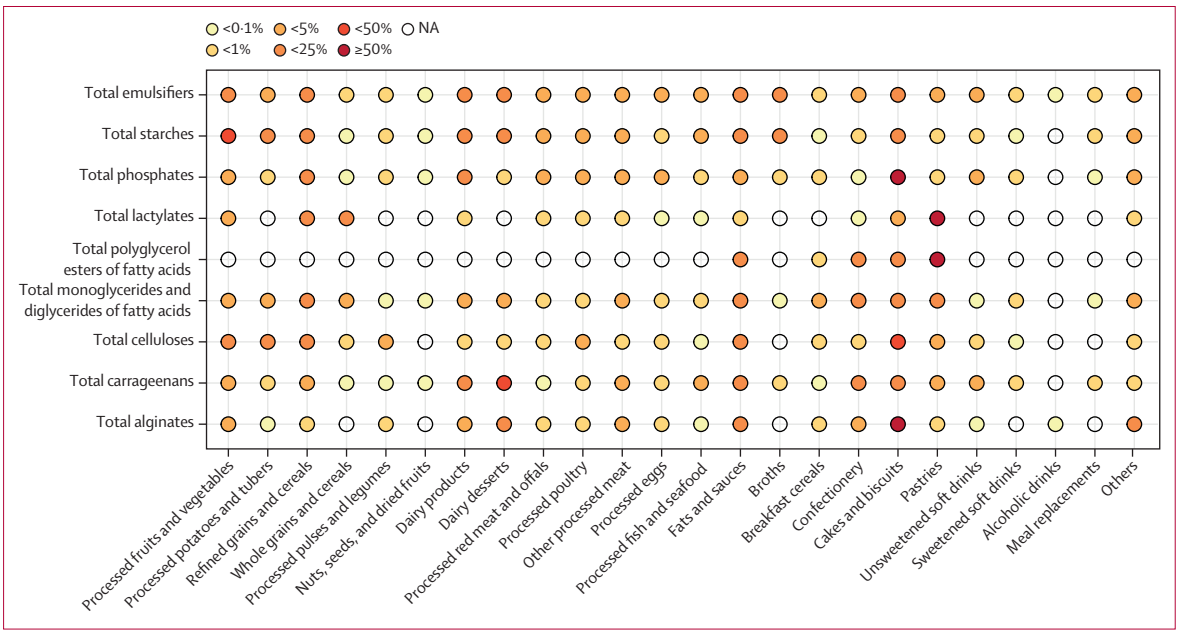

Figure 3: **Dietary sources of total emulsifier intakes and groups of emulsifier intakes among study participants from the NutriNet-Santé cohort, 2009–23 (n=104 139)**

Groups of emulsifiers were defined as follows (European codes): 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, 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). Detailed percentages are provided in the appendix (p 16).

food additives, have been set up for some of these emulsifiers by EFSA and the Joint Food and Agriculture Organization (FAO)/WHO Expert Committee on Food Additives (WHO-FAO JECFA) at the international level.[19] ADIs are theoretically intended to protect consumers against the potential adverse effects of each individual substance in a given food product. In that context, EFSA and WHO-FAO JECFA perform a thorough review on all available literature at the time, discussed within expert groups. However, these reports neither include clinical epidemiological data on hard endpoints (which are missing so far) nor the latest experimental research on outcomes beyond cytotoxicity and genotoxicity (eg, microbiota dysbiosis). The present large-scale study, as well as mounting evidence from recent experimental studies that explored new outcomes, such as alteration of gut microbiota, raise concerns about the need to revise ADIs for several food additives, including emulsifiers.[20,21] For instance, in the present study, no participant exceeded the ADI of 75 mg/kg bodyweight per day for total carrageenans (E-407–407a), but a positive association with type 2 diabetes was observed for these extensively used additives. Recent animal-based experimental studies suggest evidence of intestinal inflammation with greater exposures to carrageenan.[22,23] Consequently, the JECFA has restricted the use of carrageenan in infant foods and formulas.[24] For many other emulsifiers, no ADIs have been defined so far, while recent studies on gut microbiota have revealed potential adverse effects due to their exposure.[25] Dysbiosis induced by chronic exposure to emulsifiers can drive chronic intestinal as well as systemic inflammation, which could affect other organs.[18] Low-grade inflammatory signalling can induce metabolic syndrome and potentially type 2 diabetes by desensitising insulin receptor signalling.[26] We previously observed positive associations between higher intakes of total and specific emulsifier groups and the risk of cardiovascular disease.[15] Interestingly, the emulsifiers linked to cardiovascular disease (cellulose, monoglycerides and diglycerides of fatty acids, E460, E466, E472b, and E472c) were distinct from those associated with the risk of type 2 diabetes in the present study (total carrageenans, E407, E340, E472e, E331, E412, E414, and E415), indicating unique risk profiles for each condition. One potential reason for this difference, which remains a hypothesis, might lie in the differential biological pathways affected by these compounds. Emulsifiers linked to cardiovascular disease might influence cholesterol metabolism and endothelial function, while those related to type 2 diabetes might interact with insulin signalling and glucose homeostasis, reflecting unique mechanisms of action for each condition.

Further multidisciplinary research is needed to unravel the biological mechanisms underpinning the observed associations between emulsifier exposure and type 2 diabetes risk. Mechanistic epidemiology, investigating mediation via biomarkers of inflammation, oxidative stress, metabolomics, and gut microbiota profiles, is

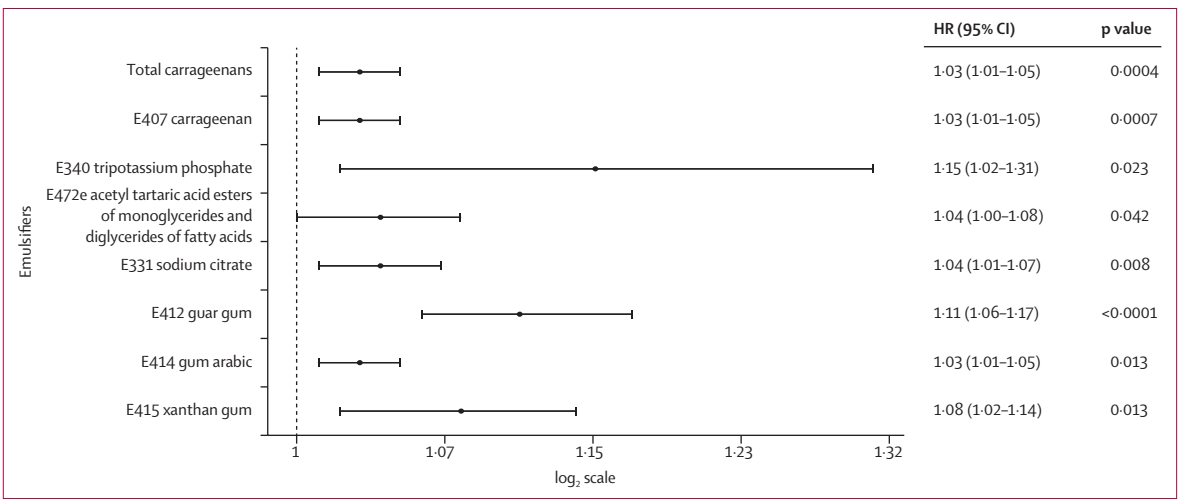

Figure 4: **Associations between selected emulsifier intakes and type 2 diabetes risk among study participants from the NutriNet-Santé cohort, 2009–23 (n=104 139 participants; 1056 incident cases).**

Details of all investigated associations between emulsifier intakes and type 2 diabetes risk with corresponding HRs and 95% CIs are provided in the appendix (p 17). HRs were computed for increments of 1 mg per day for E332 and E901; 100 mg per day for total alginates, E401, total carrageenans, E407, E407a, E472e, E476, total lactylates, E481, total polysorbates, E410, and E322; 500 mg per day for total alginates, E401, total phosphates, E339, E340, E341, E450, E451, E452, total celluloses, E460, E466, total monoglycerides and diglycerides of fatty acids, E471, E472b, E472c, total polyglycerol esters of fatty acids, E331, E412, E415, E440, and E442; and 1000 mg per day for total emulsifiers, total modified starches, E14xx, E414, E500, based on the order of magnitude of intake. Multivariable Cox proportional hazard models were adjusted for age (timescale), sex, BMI (continuous, kg/m^2), physical activity (categorical IPAQ variable: high, moderate, or low), smoking status (never smoked, former smoker, occasional smoker, or 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 type 2 diabetes (yes or no), daily intakes of alcohol (continuous, g per day), added sugars (continuous, g per day), refined grains (continuous, g per day), fruits and vegetables (g per day), dairy products (continuous, mL per day), red and processed meats (continuous, g per day), and proportion of ultra-processed food in the diet (continuous, %). Additionally, each model was mutually adjusted for the rest of other emulsifiers consumed (mg per day). False discovery rate-adjusted p-trend values were calculated for the associations between the risk of type 2 diabetes and intakes of total carrageenans (p=0·0071), carrageenans (p =0·0079), tripotassium phosphate (p=0·10), acetic acid esters of monoglycerides and diglycerides of fatty acids (p=0·17), sodium citrate (p=0·067), guar gum (p=0·0018), gum arabic (p=0·068), and xanthan gum (p=0·068). HR=hazard ratio.

promising (and is ongoing in NutriNet-Santé). Experimental research in vitro and in vivo on individual emulsifiers and their mixtures, along with short-term randomised controlled trials (to avoid jeopardising participants' safety) on early metabolic outcomes will also offer key insights in this field. Another perspective will be to explore the potential mediating role of emulsifiers and other additives in the association between ultra-processed food intake and type 2 diabetes risk.

The strengths of this study lie in its prospective design, large sample size, and meticulous assessment of dietary exposures. The NutriNet-Santé study is the first to precisely evaluate both qualitative and quantitative exposures to food additives, using detailed and repeated 24 h dietary records, links to multiple food composition databases (the French Observatory of Food Quality [OQALI], Open Food Facts, the Global New Products Database [GNPD], EFSA, and General Standard For Food Additives [GSFA]), ad-hoc laboratory assays, and dynamic matching to account for reformulations of industrial food items over time.[27] Associations remained stable across various sensitivity analyses. Although the study has robust strengths, it is not without limitations. The observational nature of the design introduces inherent constraints. Despite extensive adjustments for confounding variables, including dietary, lifestyle, anthropometric, and sociodemographic factors, the potential for unmeasured and residual confounding persists, particularly due to the inherent limitations of self-reported data, such as smoking status and alcohol intake. A single observational epidemiological study is not sufficient per se to establish causality. Second, measurement errors in emulsifier exposure might also be present—for instance, in products exempt from labelling requirements. Dietary records were validated against interview responses by a trained dietitian and against blood and urinary biomarkers for energy and key nutrients (appendix p 2). However, specific exposure to emulsifiers has not been validated against blood or urine assays because of the absence of specific biomarkers so far. The validation of exposure biomarkers for additives for which metabolites could be specific enough would be useful to strengthen exposure assessment. Additionally, to the best of our knowledge, there is no comprehensive food composition database available to ascertain the dietary content of naturally occurring emulsifiers such as lecithin. Therefore, our study focused solely on food additive emulsifiers. Besides, several emulsifiers were not ingested by a sufficient number of individuals for individual investigation. Intakes of emulsifiers in our study were lower than those reported in EFSA's opinions with simulation scenarios based on maximum permitted

For more on **EFSA's opinions** see https://www.efsa.europa.eu/fr/topics/topic/food-additives

levels, and no brand-specific data, but were of the same order of magnitude as those reported in the American Cancer Prevention Study-3 (CPS-3) Diet Assessment Sub-Study, which used brand-specific qualitative data coupled with simulations for quantitative data.[28] Another intricate challenge is disentangling the independent effects of emulsifiers from those of other food additives. However, adjusting for ultra-processed food intake and for intake of artificial sweeteners did not substantially modify the findings. Next, the generalisability of our findings could be influenced by the cohort's demographic characteristics, such as a higher proportion of women and a health-conscious population. Therefore, caution is warranted when extrapolating our results to broader populations. The potential biases embedded in the estimation of HRs, particularly those related to selection processes, must also be acknowledged.[29] Last, the cause-specific approach for handling competing events requires the assumption of conditional exchangeability of censoring to be met. Even though this method is the most optimal in this design, this assumption might have not been fully respected in real-world settings, as emulsifiers and high consumptions of ultra-processed foods could be shared risk factors for type 2 diabetes and death.[30]

In conclusion, this study highlighted positive associations between various food additive emulsifiers and an increased risk of type 2 diabetes in a large prospective cohort of French adults. These findings provide the first epidemiological insight about the potential involvement in the development of type 2 diabetes of emulsifier additives that are ubiquitous in western diets and consumed daily by millions of children and adults worldwide. Additional long-term observational epidemiological studies as well as short-term interventions (for ethical reasons) and preclinical experimental research are required to strengthen the evidence basis on this subject. If confirmed, these findings could prompt a re-evaluation of regulations governing the use of food additive emulsifiers by the food industry for better consumer protection.

Contributors

CS, BS, and MT designed the study. FSE, CA, ADS, and MT developed the additives composition database and matched consumption and composition data. CA coordinated dietitian work. FSE was responsible for data management. CS and GJ performed the statistical analysis. BS and MT supervised the statistical analysis. CS drafted the manuscript; MT supervised the writing. BS participated in supervising the writing. All authors contributed to data interpretation and revised each draft for important intellectual content. BS and MT contributed equally and are joint last authors. All authors read and approved the final manuscript. CS, BS, and MT had full access to all the data in the study. MT takes responsibility for the integrity of the data and the accuracy of the data analysis, and is the guarantor. BS attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. MT (the guarantor; m.touvier@eren.smbh.univ-paris13.fr) affirms 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.

Declaration of interests

We declare no competing interests.

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.

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