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Artificial sweeteners and risk of cardiovascular diseases: results from the prospective NutriNet-Santé cohort

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ABSTRACT

OBJECTIVES

To study the associations between artificial sweeteners from all dietary sources (beverages, but also table top sweeteners, dairy products, etc), overall and by molecule (aspartame, acesulfame potassium, and sucralose), and risk of cardiovascular diseases (overall, coronary heart disease, and cerebrovascular disease).

DESIGN

Population based prospective cohort study (2009-21).

SETTING

France, primary prevention research.

PARTICIPANTS

103 388 participants of the web based NutriNet-Santé cohort (mean age 42.2±14.4, 79.8% female, 904 206 person years). Dietary intakes and consumption of artificial sweeteners were assessed by repeated 24 h dietary records, including brand names of industrial products.

MAIN OUTCOMES MEASURES

Associations between sweeteners (coded as a continuous variable, log10 transformed) and

cardiovascular disease risk, assessed by multivariable adjusted Cox hazard models.

RESULTS

Total artificial sweetener intake was associated with increased risk of cardiovascular diseases (1502 events, hazard ratio 1.09, 95% confidence interval 1.01 to 1.18, P=0.03); absolute incidence rate in higher consumers (above the sex specific median) and non-consumers was 346 and 314 per 100 000 person years, respectively. Artificial sweeteners were more particularly associated with cerebrovascular disease risk (777 events, 1.18, 1.06 to 1.31, P=0.002; incidence rates 195 and 150 per 100 000 person years in higher and non-consumers, respectively). Aspartame intake was associated with increased risk of cerebrovascular events (1.17, 1.03 to 1.33, P=0.02; incidence rates 186 and 151 per 100 000 person years in higher and non-consumers, respectively), and acesulfame potassium and sucralose were associated with increased coronary heart disease risk (730 events; acesulfame potassium: 1.40, 1.06 to 1.84, P=0.02; incidence rates 167 and 164; sucralose: 1.31, 1.00 to 1.71, P=0.05; incidence rates 271 and 161).

CONCLUSIONS

The findings from this large scale prospective cohort study suggest a potential direct association between higher artificial sweetener consumption (especially aspartame, acesulfame potassium, and sucralose) and increased cardiovascular disease risk. Artificial sweeteners are present in thousands of food and beverage brands worldwide, however they remain a controversial topic and are currently being re-evaluated by the European Food Safety Authority, the World Health Organization, and other health agencies.

TRIAL REGISTRATION

ClinicalTrials.gov NCT03335644

Introduction

The harmful effects of added sugars on various health outcomes including cardiometabolic disorders have been extensively studied, meta-analysed^{1 2} and are currently recognised as major risk factors by public health authorities. In particular, the World Health Organization recommends that less than 5% daily energy intake should come from free sugar.³ Artificial sweeteners emerged as an alternative to added sugar that enabled the sweet taste to be reproduced without using sugar and therefore reduced calorie content from free sugar, which was highly appreciated by

WHAT IS ALREADY KNOWN ON THIS TOPIC

The harmful effects of added sugars have been established for several chronic diseases, leading food industries to use artificial sweeteners as alternatives in a wide range of foods and beverages

The safety of artificial sweeteners is debated and study findings remain divided about their role in the cause of various diseases

The negative influence of these food additives on cardiovascular disease has been suggested in experimental studies, but data from human studies remain limited and previous observational studies have focused solely on artificially sweetened beverages used as a proxy

WHAT THIS STUDY ADDS

In this large scale, prospective cohort of French adults, artificial sweeteners (especially aspartame, acesulfame potassium, and sucralose) were associated with increased risk of cardiovascular, cerebrovascular, and coronary heart diseases

The results suggest that artificial sweeteners might represent a modifiable risk factor for cardiovascular disease prevention

The findings indicate that these food additives, consumed daily by millions of people and present in thousands of foods and beverages, should not be considered a healthy and safe alternative to sugar, in line with the current position of several health agencies

consumers.⁴ Artificial sweeteners currently represent a \$7200m (£5900m; €7000m) market globally, with a 5% annual growth projected to attain \$9700m by 2028.⁵ An extensive number of brands worldwide contain these food additives, especially ultra-processed foods such as artificially sweetened beverages, some snacks, and low calorie ready-to-go meals or dairy products; overall more than 23 000 products worldwide contain artificial sweeteners.⁶ Artificial sweeteners are also directly used by consumers as table top sweeteners instead of sugar. Acceptable daily intakes for each artificial sweetener have been set by the European Food Safety Authority (EFSA), the United States Food and Drug Administration, or the Joint Expert Committee on Food Additives. Nonetheless, they remain a topic of controversy and are currently undergoing a re-evaluation by several health authorities, including the EFSA⁷ and WHO.⁸

Some experimental in vivo and in vitro studies, observational studies, and human randomised controlled trials investigated early markers of cardiovascular health, for example, weight status,⁹⁻¹² hypertension,¹³ inflammation,¹⁴ vascular dysfunction,^{15 16} or gut microbiota perturbation¹⁷⁻²⁰ in association with consumption of artificial sweeteners or artificially sweetened beverages. Most of these studies suggested adverse effects,¹¹⁻²⁰ and few suggested neutral or beneficial properties.^{9 10} Although the results were mixed, this literature generally supports a potential involvement of artificial sweeteners in cardiovascular health, with plausible mechanisms.²¹⁻²³

Cardiovascular diseases (CVDs) are the leading cause of death worldwide.²⁴ Randomised controlled trials have not directly assessed the impact of artificial sweetener intake on hard endpoints such as CVD risk for ethical reasons. Similarly, observational prospective studies have not directly investigated the association between artificial sweetener intake (mg/day) and CVD risk, but several have used artificially sweetened beverage consumption (millilitres or servings/day) as a proxy to explore these associations with conflicting results.^{22 23 25-34} One of these studies was performed in the NutriNet-Santé cohort²⁸ and found that sugary drinks and artificially sweetened beverages were associated with increased CVD risk. Systematic reviews and meta-analyses^{35 36} have suggested direct associations between artificially sweetened beverages and CVD risk. The WHO 2022 report on the health effects of artificial sweeteners notably observed associations between consumption of beverages with artificial sweeteners (used as a proxy) and some intermediate markers of CVD,⁸ including a modest increase in the unfavourable total cholesterol to HDL cholesterol ratio (meta-analysis of four randomised control trials), and an increased risk of hypertension (meta-analysis of four prospective studies). The international health authority also identified an increase in CVD mortality, and in the incidence of cardiovascular events and strokes associated with greater intake of soft drinks containing artificial sweeteners (meta-analysis of four randomised control trials). However, prospective

studies remain limited and the level of evidence for these associations is still considered low by WHO.⁸ Additionally, because artificially sweetened beverages only represent part of the total artificial sweetener intake, it is crucial to consider all dietary sources in causal studies.

In this context, our objective was to conduct a large scale prospective study using quantitative data to investigate the associations between consumption of artificial sweeteners (mg/day) from all dietary sources (beverages but also table top sweeteners, dairy products, etc), overall and by type (aspartame, acesulfame potassium, and sucralose), and risk of CVD (overall, coronary, and cerebrovascular). Our study was performed within the population based NutriNet-Santé cohort, which includes detailed information on commercial names and brands of industrial food consumed.

Methods

Study population and data collection

This study was based on the prospective NutriNet-Santé e-cohort, launched in France in May 2009, with an open ongoing enrolment of volunteers. The main objective was to investigate the relations between nutrition and health.³⁷ Participants are French adults, aged 18 years or older, with internet access, recruited from the general population by means of multimedia campaigns. They are followed through their personal account created at inclusion on the study website (<https://etude-nutrinet-sante.fr/>). Immediately after enrolment, each person completes five online questionnaires about diet (24 h dietary records, detailed below), health (eg, personal and familial history, prescription drug use), anthropometric data (height and weight^{38 39}), lifestyle and sociodemographic data (eg, date of birth, sex, education level, professional occupation, smoking status, number of children⁴⁰), and physical activity. Physical activity levels were defined based on the validated seven day assessment International Physical Activity Questionnaire (IPAQ).⁴¹ All activities declared by participants were converted into metabolic equivalent of task (MET) minutes per week according to the compendium of physical activities.⁴² Three levels of physical activity were defined: low (<600 MET-min/week), moderate (600-1500 MET-min/week), and high (>1500 MET-min/week) using standardised IPAQ processing guidelines.⁴¹ For instance, 600 MET-min/week is equivalent to 150 min/week of moderate intensity (4 METs) physical activity or 75 min/week of high intensity (8 METs) physical activity.

Each person included in the NutriNet-Santé cohort provides informed consent electronically. The study is registered at ClinicalTrials.gov (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).

Table 1 | Baseline characteristics of the study population, NutriNet-Santé cohort, France, 2009-21 (n=103 388)

Characteristics	All participants	Categories of artificial sweetener intakes*			P value†
		Non-consumers	Lower consumers	Higher consumers	
No of participants (%)	103 388	65 028 (62.90)	19 221 (18.59)	19 139 (18.51)	—
Age, years (mean (SD))	42.22 (14.41)	42.96 (14.64)	41.94 (14.42)	39.97 (13.35)	<0.001
Female sex	82 485 (79.78)	50 160 (77.14)	16 200 (84.28)	16 125 (84.25)	<0.001
Body mass index (mean (SD))	23.59 (4.33)	23.21 (4.06)	23.68 (4.29)	24.79 (4.99)	<0.001
Family history of CVD	28 053 (27.44)	17 788 (27.69)	5312 (27.84)	4953 (26.2)	<0.001
Prevalent hypercholesterolemia	7696 (7.44)	4525 (6.96)	1676 (8.72)	1495 (7.81)	<0.001
Prevalent hypertriglyceridemia	1321 (1.28)	709 (1.09)	280 (1.46)	332 (1.73)	<0.001
Prevalent hypertension	7125 (6.89)	4297 (6.61)	1448 (7.53)	1380 (7.21)	<0.001
Education level					<0.001
No	16 652 (16.24)	10 814 (16.78)	2935 (15.37)	2903 (15.3)	—
Yes, <2 years	16 282 (15.88)	10 324 (16.02)	2897 (15.18)	3061 (16.13)	—
Yes, ≥2 years	69 577 (67.87)	43 309 (67.20)	13 258 (69.45)	13 010 (68.57)	—
Smoking status					<0.001
Current	14 894 (14.42)	9387 (14.45)	2292 (11.93)	3215 (16.81)	—
Former	41 302 (39.98)	25 533 (39.30)	7895 (41.09)	7874 (41.16)	—
Never	47 121 (45.61)	30 052 (46.25)	9028 (46.98)	8041 (42.03)	—
Physical activity level‡					<0.001
Low	21 823 (21.11)	13 374 (20.57)	4167 (21.68)	4282 (22.37)	—
Moderate	38 376 (37.12)	23 937 (36.81)	7420 (38.60)	7019 (36.67)	—
High	28 868 (27.92)	18 807 (28.92)	5070 (26.38)	4991 (26.08)	—
Number of 24 h dietary records (mean (SD))	5.59 (3.05)	5.31 (3.01)	6.81 (3.10)	5.28 (2.83)	<0.001
Energy intake without alcohol, kcal/day (mean (SD))	1898.02 (469.80)	1911.4 (477.34)	1888.42 (432.76)	1862.19 (477.55)	<0.001
Alcohol intake, g/day (mean (SD))	7.71 (11.71)	8.05 (12.19)	7.51 (10.79)	6.79 (10.88)	<0.001
SFA intake, g/day (mean (SD))	33.18 (12.13)	33.59 (12.29)	33.16 (11.19)	31.81 (12.39)	<0.001
PUFA intake, g/day (mean (SD))	11.5 (4.94)	11.63 (5.17)	11.31 (4.30)	11.25 (4.75)	<0.001
Sodium intake, mg/day (mean (SD))	2705.38 (880.94)	2698.58 (897.29)	2711.43 (812.38)	2722.43 (890.75)	0.003
Dietary fibre intake, g/day (mean (SD))	19.4 (7.19)	19.75 (7.48)	18.93 (6.26)	18.69 (7.00)	<0.001
Total sugar intake, g/day (mean (SD))	92.69 (33.11)	92.11 (33.49)	94.62 (30.56)	92.73 (34.16)	<0.001
Added sugar intake, g/day (mean (SD))	38.76 (23.73)	38.5 (23.54)	40.3 (22.46)	38.12 (25.51)	<0.001
Percentage of energy from added sugar (mean (SD))	8.20 (4.18)	8.12 (4.16)	8.58 (3.95)	8.10 (4.45)	<0.001
Sugary drinks, mL/day (mean (SD))	47.84 (106.70)	42.77 (103.87)	55.15 (97.73)	57.72 (122.53)	<0.001
Non-alcoholic beverages with no added sugars, mL/day (mean (SD))	1088.67 (536.6)	1063.93 (529.25)	1092.54 (517.02)	1168.85 (571.66)	<0.001
Fruit and vegetable intake, g/day (mean (SD))	404.83 (220.04)	409.35 (222.68)	397.73 (196.93)	396.59 (232.24)	<0.001
Red and processed meat intake, g/day (mean (SD))	76.41 (52.70)	74.53 (53.23)	76.10 (46.75)	83.09 (55.89)	<0.001
Whole-grain food intake, g/day (mean (SD))	34.16 (45.97)	35.71 (49.16)	31.42 (38.40)	31.66 (41.29)	<0.001
Ultra-processed foods intake, % of the diet in g/day (mean (SD))	17.40 (9.90)	15.96 (9.12)	17.42 (8.61)	22.27 (11.92)	<0.001
Weight loss diet during the first two years of follow-up	17 585 (17.01)	7729 (11.89)	3654 (19.01)	6202 (32.41)	<0.001
Artificial sweetener intake, mg/day (mean (SD))	15.76 (48.57)	0.00 (0.00)	7.46 (4.95)	77.62 (89.33)	<0.001
Aspartame (E951) intake, mg/day (mean (SD))	9.13 (30.95)	0.00 (0.00)	3.16 (3.96)	46.13 (58.91)	<0.001
Acesulfame potassium (E950) intake, mg/day (mean (SD))	4.60 (14.90)	0.00 (0.00)	2.71 (2.79)	22.14 (28.43)	<0.001
Sucralose (E955) intake, mg/day (mean (SD))	1.59 (16.17)	0.00 (0.00)	1.08 (1.94)	7.49 (36.95)	<0.001

CVD=cardiovascular disease; PUFA=polyunsaturated fatty acid; SD=standard deviation; SFA=saturated fatty acid.

Values are numbers (percentages) unless stated otherwise. 1 kcal=4.18 kJ=0.00418 MJ.

*Categories of consumption were defined as non-consumers, lower consumers, and higher consumers, separated by the sex specific median among consumers, that is, 16.44 mg/day in men and 18.46 mg/day in women.

†P values for crude comparison between the three categories of sweetener intake by analysis of variance or χ^2 test when appropriate.

‡Available for 89 067 participants, categorised into high, moderate, and low categories according to International Physical Activity Questionnaire guidelines.

Dietary assessment

Three non-consecutive days of 24 h dietary records were randomly assigned over a two week period, at baseline, and every six months thereafter. During those recording days (two weekdays and one weekend day) participants indicated all foods and beverages consumed during the three main meals and any other eating occasions, and in what quantities, using validated photographs and standard serving containers⁴³ or by directly entering the amount (in grams or millilitres). All 24 h dietary records provided during the first two years of each person's follow-up were averaged to obtain baseline diet. This represents a reliable estimate of consumption habits, while respecting the prospective

design and guaranteeing sufficient delay between consumption and CVD outcomes. Intakes of energy, alcohol, and nutrients were assessed using the NutriNet-Santé food composition table (≈ 3500 food/beverage items⁴⁴). Nutritional contributions of mixed dishes were estimated by standard French recipes defined by nutrition professionals. Dietary assessment through these 24 h dietary records were validated against interviews by a trained dietitian⁴⁵ and against blood and urinary biomarkers.⁴⁶⁻⁴⁷ The basal metabolic rate and the Goldberg cut-off method enabled any under reporting to be identified⁴⁸⁻⁵⁰; participants who under reported were excluded from the analyses. Supplementary method 1 gives details of methods used to identify under reporting.

Table 2 | Associations between intake of total artificial sweeteners, aspartame, acesulfame potassium, and sucralose and overall cardiovascular diseases, coronary heart diseases and cerebrovascular diseases, NutriNet-Santé cohort, France, 2009-21 (n=103 388)

Outcome and exposure	Hazard ratio (95% CI)	P value
Cardiovascular diseases (n=1502)		
Total artificial sweeteners	1.09 (1.01 to 1.18)	0.03
Aspartame	1.03 (0.94 to 1.14)	0.49
Acesulfame potassium	1.18 (0.98 to 1.41)	0.08
Sucralose	1.11 (0.92 to 1.34)	0.28
Coronary heart diseases (n=730)		
Total artificial sweeteners	1.02 (0.91 to 1.14)	0.79
Aspartame	0.91 (0.78 to 1.06)	0.22
Acesulfame potassium	1.40 (1.06 to 1.84)	0.02
Sucralose	1.31 (1.00 to 1.71)	0.05
Cerebrovascular diseases (n=777)		
Total artificial sweeteners	1.18 (1.06 to 1.31)	0.002
Aspartame	1.17 (1.03 to 1.33)	0.02
Acesulfame potassium	1.01 (0.79 to 1.29)	0.93
Sucralose	0.99 (0.76 to 1.29)	0.93

Median follow-up times for overall cardiovascular, coronary heart, and cerebrovascular diseases were all 9.0 years; person years were 904 205, 904 270, and 904 259, respectively. Exposure was coded as log10 of artificial sweetener intake in mg/day+1. Main models were adjusted for age (time scale), sex, physical activity (categorical: International Physical Activity Questionnaire variable: high, moderate, low, missing value), smoking status (categorical: never, former, current smoker), number of smoked cigarettes in pack years (continuous), higher educational level (categorical: less than high school degree, <2 years after high school degree, ≥2 years after high school degree), family history of cardiovascular disease (categorical: yes, no), energy intake without alcohol (continuous: kcal/day), daily intakes (continuous: g/day) of alcohol, sodium, saturated fatty acids, polyunsaturated fatty acids, fibre, sugar, fruit and vegetables, red and processed meat. Models were also mutually adjusted for sweetener intake other than the one studied (continuous).

Artificial sweetener intakes

Chazelas and colleagues described the quantitative evaluation of food additive consumption in participants of the NutriNet-Santé cohort.⁵¹ Briefly, food additive intakes, including artificial sweeteners, were assessed through the interactive online 24 h dietary record tool, in which commercial names and brands of industrial products consumed could be recorded. The presence of food additives was first determined for each food and beverage using ingredients lists available from three large scale food composition databases: Open Food Facts (<https://world.openfoodfacts.org/>); the French food safety agency database Oqali (https://www.oqali.fr/oqali_eng/)⁵²; and Mintel's Global New Products Database.⁵³ Doses of additives were determined by around 2700 assays performed by accredited laboratories, requested by the Nutritional Epidemiology Research Team or by a consumer association (UFC Que Choisir). These quantitative data were completed by average doses per food group provided by EFSA and the Joint FAO/WHO Expert Committee on Food Additives.⁵⁴ Food additive composition data were matched by date to account for possible industrial reformulations and changes in additive composition (date of consumption was considered to match the product to the closest consumption data). Supplementary method 2 gives additional information on food additive and artificial sweetener intake assessment.

For this study, we were able to estimate intakes of aspartame (European food additive identification number E951), acesulfame potassium (E950), sucralose (E955), cyclamates (E952), saccharin (E954), thaumatin (E957), neohesperidine dihydrochalcone (E959), steviol glycosides (E960), and salt of

aspartame-acesulfame potassium (E962) and to create a sum variable labelled total artificial sweeteners.

Cardiovascular disease determination

Throughout follow-up, biannual health questionnaires and a permanently open personal health interface on the study account allowed participants to report any new health events, medical treatments, and examinations. For each incident CVD event declared, participants were contacted by a physician of the team and asked to provide any relevant medical records (eg, radiological reports, electrocardiogram, angioplasty). When necessary, the study physicians contacted the patient's physician or any hospitals providing treatment to collect additional information. These medical data were reviewed by physician experts. An investigation was also conducted by the physicians of the NutriNet-Santé study by contacting the participant's family or their physician when no connection to the study website was made for more than a year. Beyond this proactive health follow-up, data were paired with the medico-administrative databases of the national health insurance system database (SNIIRAM) and the national mortality registry (CépiDC), thereby limiting potential bias due to people with CVD not reporting their disease to the study investigators (further information available in supplementary method 3). International classification of diseases clinical modification, 10th revision, was used to classify CVD.⁵⁵ For this study, first incidence of CVD, coronary heart disease (myocardial infarction, code I21; acute coronary syndrome, code I21.4; angioplasty, code Z95.8; angina pectoris, code I20.0), or cerebrovascular disease (stroke, code I64; transient ischaemic attack, codes G45.8 and G45.9) diagnosed between inclusion and 5 October 2021 were considered as events and investigated in the analyses.

Statistical analyses

Participants with at least two valid dietary records during the first two years of follow-up were included in the analysis. Those with prevalent CVD or pre-existing diabetes were excluded. To limit reverse causality bias (particularly sensitive when sugar was substituted by artificial sweeteners), participants with CVD diagnosed during the first two years of follow-up were also excluded. Supplementary figure 1 presents a flowchart showing detailed selection of the study population.

We classified participants into three categories of artificial sweetener consumption: non-consumers, lower consumers (participants with artificial sweetener intake below the sex specific median among consumers), and higher consumers. Baseline characteristics (sociodemographic, health, lifestyle, dietary intakes) were assessed for each category and compared using χ^2 tests for categorical variables and analysis of variance tests for continuous variables (table 1).

Associations between artificial sweeteners, overall and the most represented (aspartame, acesulfame potassium, and sucralose, consumed by more than 5% of participants), and CVD (overall, coronary

heart disease, and cerebrovascular disease) were investigated using multivariable adjusted Cox proportional hazard models (table 2). Participants contributed person time from their inclusion in the cohort until the date of CVD, date of last follow-up, date of death, or 5 October 2021, whichever occurred first. We first tested dose-response analyses using the restricted cubic spline (RCS) functions with the SAS macro developed by Desquilbet and Mariotti.⁵⁶ Given the logarithmic profile of the associations suggested by the RCS curves (supplementary fig 2) and to account for the large proportion of non-consumers (especially for each specific artificial sweetener), artificial sweetener intakes were log transformed (log10 of sweetener consumption in mg/g+1) to compute continuous models (+1 was uniformly added to all consumptions because log(0) is not allowed). The continuous model was used as the primary analyses to obtain hazard ratios and 95% confidence intervals. Supplementary tables 1 and 2 present models using three categories (non-consumers, lower consumers, and higher consumers, separated by the sex specific median) and four categories (non-consumers and sex specific consumers in thirds) of sweetener consumption.

The main models were adjusted for several variables suspected or known to be associated with diet and with CVD risk: sociodemographic (age, sex, educational level), lifestyle (smoking status, number of smoked cigarettes, physical activity), and health (family history of CVD) factors, and food groups and nutrients for which a role in CVD cause has been strongly suggested⁵⁷⁻⁶⁵: energy intake without alcohol, alcohol, sugar, sodium, saturated fatty acids, polyunsaturated fatty acids, fibre, fruit and vegetables, and red and processed meat. We added a table showing the rationale for selection of each covariate and information on how they were collected and measured (supplementary method 4). Analyses by specific artificial sweeteners (aspartame, acesulfame potassium, and sucralose) were additionally adjusted for other artificial sweetener intakes. Multiple imputation by chained equations⁶⁶ was applied to handle any missing values for covariates (15 imputed datasets; supplementary method 5). Cox proportional hazard assumption was verified using the rescaled Schoenfeld type residual method (supplementary fig 3). Competing risks were accounted for in all analyses using cause specific Cox models,⁶⁷ with death considered a competing risk for CVDs, coronary heart diseases, and cerebrovascular diseases. Additionally, cerebrovascular events were considered competing risks for coronary heart diseases and vice versa. Supplementary table 3 presents results from competing events. Cumulative incidence graphs were also plotted using the Fine and Gray model (presented in supplementary fig 4).

Associations were computed separately for each type of cerebrovascular or coronary disease event: myocardial infarction, acute coronary syndrome, angioplasty, angina pectoris, stroke and transient ischaemic event (supplementary table 4), and for all CVDs except transient ischaemic events. We also

investigated associations between CVD risk and artificial sweeteners from beverages and from solid food (supplementary table 5). Substitution analyses were performed by entering added sugars and artificial sweeteners into the model. Hazard ratios and 95% confidence intervals for substituting artificial sweeteners for added sugars were estimated using the difference in coefficients obtained from this model. Supplementary method 6 presents these analyses. Formal interactions between body mass index (<25 or ≥25) and artificial sweeteners were tested for each outcome by entering the product of the two variables into Cox models.

We performed a sensitivity analysis in which we doubled the requested minimal number of 24 h dietary records (excluding participants with less than four records; supplementary table 6). Additionally, we computed models with artificial sweetener intakes coded as time dependent variables across the whole follow-up period (supplementary table 6). Other sensitivity analyses were also performed, with further adjustments for prevalent dyslipidaemia, for healthy and western dietary patterns (derived by principal components analysis) instead of food groups, added sugar intakes instead of sugar, proportion of ultra-processed foods in the diet, weight loss or calorie restricted diet, weight variation during follow-up, number of 24 h dietary records, body mass index, and social desirability score⁶⁸; and analyses without excluding prevalent diabetes (details presented in supplementary table 6). All tests were two sided, and $P < 0.05$ was considered statistically significant. We used the statistical analysis software SAS, version 9.4 for analyses.

Patient and public involvement

The research question developed in this article corresponds to a concern expressed by some participants involved in the NutriNet-Santé cohort, and by the public in general. Participants in the study are thanked in the Acknowledgments section.

Results

Descriptive characteristics

Overall, 103 388 participants were selected from the NutriNet-Santé cohort. Mean age at baseline was 42.2 years (standard deviation 14.4), 79.8% were women, and the mean number of 24 h dietary records during the first two years of follow-up was 5.6 (standard deviation 3.1). Supplementary figure 5 shows the distribution of the number of 24 h dietary records per person. Among the overall cohort, 0.94% (n=1639) participants have died since their inclusion (981 in the present population study) and 9.4% (n=16 306) dropped out because they did not want to receive any more questionnaires. A total of 37.1% of participants consumed artificial sweeteners. The average intake of artificial sweeteners was 15.76 mg/day among all participants and 42.46 mg/day among consumers only, which corresponds to approximately one individual packet of table top sweetener or 100 mL

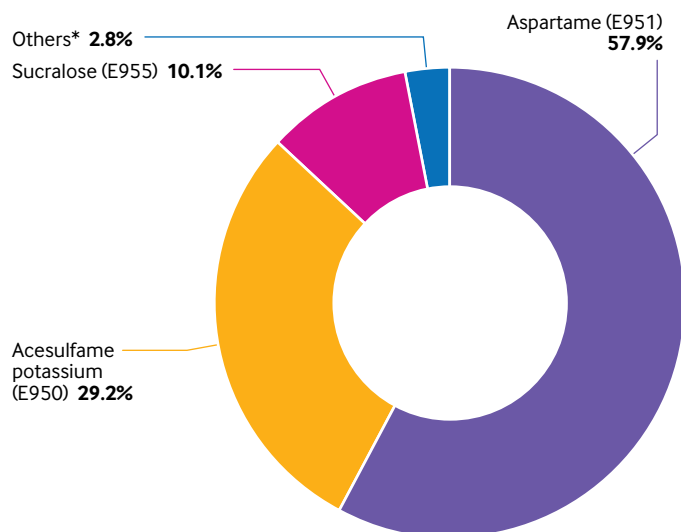


Fig 1 | Relative contribution of each specific artificial sweetener to the total intake of artificial sweeteners (%), NutriNet-Santé cohort, France, 2009-21 (n=103 388).

*Cyclamates (E952), saccharin (E954), thaumatin (E957), neohesperidine dihydrochalcone (E959), steviol glycoside (E960), aspartame-acesulfame salt (E962)

of diet soda.^{69 70} Among participants who consumed artificial sweeteners, mean intakes for lower and higher consumer categories were 7.46 and 77.62 mg/day, respectively. Compared with non-consumers, higher consumers (unadjusted comparisons) tended to be younger, have a higher body mass index, were more likely to smoke, be less physically active, and to follow a weight loss diet; they had lower total energy intake, and lower alcohol, lipid (saturated and polyunsaturated), fibre, carbohydrate, fruit and

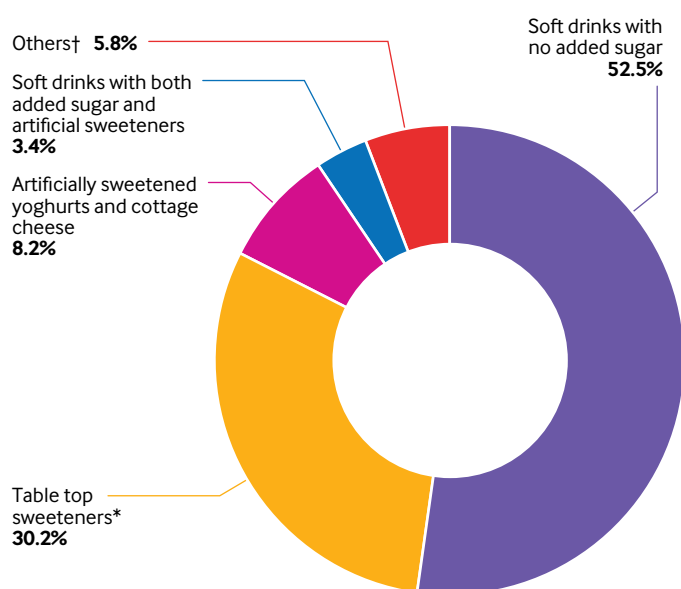


Fig 2 | Relative contribution of each food group to the total intake of artificial sweeteners (%), NutriNet-Santé cohort, France, 2009-21 (n=103 388). *Used as tablets, liquid, or powder, added by the participants in yoghurts, hot drinks and so on, or for cooking. †High protein food substitutes, sugary foods, cookies, biscuits, cakes, pastries, breakfast cereals, sauces, savoury foods, ultra-processed fish products

vegetable intakes, and higher intakes of sodium, red and processed meat, dairy products, and beverages with no added sugar (table 1). Aspartame, acesulfame potassium, and sucralose contributed to 58%, 29%, and 10% of total artificial sweetener intakes, respectively (fig 1). Soft drinks with no added sugar accounted for 53% of artificial sweeteners; table top sweeteners were also an important vector (30%), as well as artificially sweetened flavoured dairy products (eg, yoghurts, cottage cheese, 8%; fig 2). As shown in supplementary figure 6, food group contributions varied for each artificial sweetener; for example, table top sweeteners contributed to 48% of aspartame intake, followed by soft drinks with no added sugar (41%), whereas acesulfame potassium and sucralose were both mainly provided by the consumption of soft drinks with no added sugar (76% and 78%, respectively). Participants who consumed artificial sweeteners tended to consume more than one type of the main artificial sweeteners, and 7.23% of the total participants consumed all three of the main types (supplementary fig 7).

Associations between artificial sweetener intakes and cardiovascular diseases

During follow-up (904 206 person years; median follow-up duration 9.0 years, interquartile range 7.5-10.1 years), 1502 incident cardiovascular events occurred, among which there were 730 coronary heart disease events (143 myocardial infarction, 75 acute coronary syndrome, 477 angioplasty, and 277 angina pectoris events) and 777 cerebrovascular disease events (203 strokes and 598 transient ischaemic events). Mean age at CVD event was 62.7 years (standard deviation 12.9). The RCS analyses suggested a log shaped association (increased risk followed by a plateau; P for non-linearity=0.067, 0.494, 0.016, and 0.021 for total artificial sweetener, aspartame, acesulfame potassium, and sucralose, respectively, for the overall CVD model; supplementary fig 2).

Total artificial sweetener intake was associated with increased risk of CVD (hazard ratio 1.09, 95% confidence interval 1.01 to 1.18, P=0.03; table 2); absolute incidence rate in higher consumers (above the sex specific median) was 346 per 100 000 person years, and in non-consumers it was 314 per 100 000 person years. Artificial sweeteners were more particularly associated with cerebrovascular disease risk (1.18, 1.06 to 1.31, P=0.002; incidence rates 195 and 150). Aspartame intake was associated with increased risk of cerebrovascular events (1.17, 1.03 to 1.33, P=0.02; incidence rates 186 and 151), and acesulfame potassium and sucralose were associated with increased coronary heart disease risk (acesulfame potassium: 1.40, 1.06 to 1.84, P=0.02; incidence rates 167 and 164; sucralose: 1.31, 1.00 to 1.71, P=0.05; incidence rates 271 and 161). Results were similar when artificial sweetener intakes were coded as time dependent variables (supplementary table 6). For each type of cerebrovascular disease or coronary heart disease, direct associations were observed

between sucralose and risk of angioplasties ($n=477$; 1.60, 1.17 to 2.21, $P=0.004$) and between total artificial sweeteners and transient ischaemic events ($n=598$; 1.18, 1.05 to 1.33, $P=0.006$). For artificial sweeteners from beverages or solid food, associations were statistically significant between sweeteners from beverages and CVD risk ($P=0.02$) and between aspartame from beverages and coronary heart disease risk ($P=0.03$). Associations were borderline between acesulfame potassium and sucralose from beverages and coronary heart diseases ($P=0.06$ and $P=0.08$, respectively), and between aspartame, acesulfame potassium, and sucralose from solid food sources and cerebrovascular diseases ($P=0.006$, $P=0.01$, and $P=0.002$, respectively; supplementary table 5). Substitution analyses did not suggest a benefit for substituting artificial sweeteners for added sugars for CVD risk (hazard ratio 1.00, 95% confidence interval 0.99 to 1.01, $P=0.28$), cerebrovascular disease risk (1.00, 0.99 to 1.01, $P=0.89$), or coronary heart disease risk (1.00, 0.99 to 1.01, $P=0.13$; supplementary method 6). The results were stable across all sensitivity analyses tested (supplementary table 6). The artificial sweetener by body mass index variable was not statistically significant for overall cardiovascular disease, coronary heart disease, and cerebrovascular disease (all $P>0.05$), suggesting no interaction on the multiplicative scale.

Discussion

Principal findings

In the NutriNet-Santé cohort, total artificial sweetener intake was associated with increased risk of overall CVD and cerebrovascular disease. Aspartame intake was associated with increased risk of cerebrovascular events, and acesulfame potassium and sucralose were associated with increased coronary heart disease risk. Our results suggest no benefit from substituting artificial sweeteners for added sugar on CVD outcomes.

Strengths and limitations of this study

This study was based on a large sample size ($n=103\,388$) and prospectively investigated the associations between artificial sweetener intake from all dietary sources and CVD risk. There is no perfect measure of dietary consumption, therefore classification bias cannot be ruled out. However, the assessment of artificial sweetener consumption performed in this study was a comprehensive assessment at the individual level in a large scale population based cohort. The NutriNet-Santé study is an epidemiological cohort with precise and high quality dietary data. Dietary records have previously been validated by interviews with a trained dietitian³³ and against blood and urinary biomarkers for energy and nutrient intakes.^{34 35} Epidemiological studies worldwide generally use food frequency questionnaires (known to be less precise than repeated 24 h dietary records⁷¹) or a limited number of records or recalls at baseline.

The main vectors of artificial sweeteners are products that are generally consumed on a regular basis as part of daily dietary habits, including artificially sweetened beverages, table top sweeteners, and dairy products. Occasional artificial sweetener consumption is not likely to have a strong impact on CVD risk, and so even if some consumption might have been missed, it would probably have had a low impact on the study results. If there was a classification bias, it was non-differential due to the prospective design. Additionally, a sensitivity analysis was performed in the subgroup of participants with at least four records (mean 7.8, standard deviation 2.4, $n=57\,668$), which doubled the minimal number of 24 h dietary records needed to be included in the analysis, and the results remained similar. Twenty four hour dietary recording days were decided in advance, which might have influenced the behaviour of participants on these days; however, adjustment for social desirability bias did not modify the findings, and the comprehensive recording enabled memory bias to be limited. In contrast to previous observational studies, artificially sweetened beverages were not used as a proxy to estimate artificial sweetener intakes. Detailed information on the brands of food or beverage consumed are collected as part of the NutriNet-Santé study. The dynamic date-to-date matching performed between the interactive web based 24 h dietary records and specific ingredient lists allowed the additive composition of industrial products to be identified, accounting for potential reformulations.⁵¹

Some limitations should be discussed. Residual confounding cannot be totally excluded and no causal relation can be established with results from a unique observational study. However, models were adjusted for a wide range of potential sociodemographic, anthropometric, dietary, and lifestyle confounders. Further adjustment for the proportion of ultra-processed food in the diet was conducted, ensuring that the associations observed were not entirely driven by following an ultra-processed diet in general.⁷² Additionally, reverse causality could lead to higher artificially sweetened food and beverage consumption among participants who were overweight or obese, and already had poorer cardiovascular health at baseline before CVD diagnosis.^{73 74} However, this factor probably does not entirely explain the observed associations because we excluded CVD events occurring during the first two years of follow-up and we also tested models adjusted for baseline body mass index, weight loss diet, and weight change during follow-up, which did not substantially change the results.

Caution is needed to generalise these results to the whole French population. As generally observed in volunteer based cohorts, participants from the NutriNet-Santé study were more often women, with higher educational and socio-professional levels, and they were more likely to have a health conscious lifestyle and good dietary behaviours.⁷⁵ Therefore, artificial sweetener intake among NutriNet-Santé participants could be lower compared with French adults in general.

Mean intakes of aspartame and acesulfame potassium for consumers in the cohort were 0.49 and 0.22 mg/kg body weight/day, respectively versus 1.29 and 0.73 mg/kg body weight/day, respectively estimated in the French population.⁷⁶ These intakes suggest that the associations found in our study between artificial sweetener consumption and risk of CVD might be underestimated. However, our assessment was more accurate than the one previously performed for the general French population,⁷⁶ which was based on three days of dietary records by participants at most, and brand specific composition was not accounted for.

The order of magnitude obtained for the associations in this study is in line with the one traditionally observed in nutritional epidemiology studies for commonly consumed dietary factors,^{72 77 78} and with the findings of WHO in its recent report,⁸ which was based on meta-analyses of prospective cohort studies investigating intake of beverages containing artificial sweeteners.²⁵⁻³² Furthermore, in terms of public health perspectives, the opportunity of preventing even a moderate proportion of CVD events through reduced artificial sweetener intake is of high interest given the extensive use of these substances in products on the global market. Associations were consistent across the many sensitivity analyses we performed; they were also consistent with previous epidemiological literature on proxies of sweetener intakes (eg, artificially sweetened beverages) and in line with mechanistic insights from experimental studies. All observed associations between sweetener intakes and CVD events went in the same (positive) direction, which is not in favour of random findings observed by chance.

The two complementary methods (self-reporting and medico-administrative databases) ensured good identification of CVD outcomes. However, the possibility of missing some events cannot be entirely ruled out. Additionally, despite efforts to identify transient ischaemic attacks as objectively as possible (based on medical or hospital reports, if possible a specialised neurological diagnosis, computed tomography or magnetic resonance imaging scan, or symptoms precisely described by the participant or a person close to them), these CVD events could not be diagnosed with the same certainty as for strokes or myocardial infarctions because they generally do not reveal sequelae on brain imaging. Finally, limited statistical power might have prevented us from detecting some associations for specific CVD pathologies.

Comparison with other studies

Observational prospective studies on the associations between artificial sweeteners, assessed from the whole diet (in mg/day), and CVD risk are lacking; therefore, no direct comparison was possible. However, several studies have been conducted²⁵⁻³⁴ and meta-analysed^{8 22 35 36 73 79} using artificially sweetened beverage consumption as a proxy (in mL or serving/day) and CVD risk. In line with recent results from the NutriNet-Santé study,²⁸ multiple cohorts found

associations between artificially sweetened beverages and CVD. Higher artificially sweetened beverage consumption was associated with increased risks of stroke and cardiovascular events in the Women's Health Initiative,^{26 29} which is consistent with prospective investigations from the Nurses' Health Study, the Health Professional Follow-up Study (HPFS),^{25 30} the Framingham Offspring cohort,³¹ and the Northern Manhattan Study.²⁷ Similarly, meta-analyses reported increased risks of stroke, vascular events, coronary heart diseases, CVDs, and CVD mortality.^{35 36 73 79} Consistent with our findings, no association was observed for coronary heart diseases in the HPFS.³³ These studies mostly took place in the United States³⁵ and have not been as extensively explored in European populations. In line with our results, the recent WHO meta-analyses⁸ reported positive associations between the intake of beverages containing artificial sweeteners and cardiovascular events overall (hazard ratio 1.32, 95% confidence interval 1.17 to 1.50, three prospective studies²⁶⁻²⁸) and more specifically for the incidence of stroke (1.19, 1.09 to 1.29, five prospective studies^{25 27 29 31 32}), but not for coronary heart disease (1.16, 0.97 to 1.39, four prospective studies^{27 29 33 80}).

Meta-analyses performed by Azad and colleagues²² also suggested associations between high intake of drinks with non-nutritive sweeteners and higher risk of strokes²⁵ and cardiovascular events,^{26 27} but no significant associations were found for coronary heart diseases.^{33 80} However, other studies suggested associations between artificially sweetened beverages and stroke but also coronary heart diseases.²⁹ Differences between results for coronary heart and cerebrovascular diseases could be because these pathologies have different causes and therefore, although they might share common nutritional determinants, others might play a different role in the development of these diseases. Each type of artificial sweetener might not have the same metabolic effect.¹⁴ For instance, after ingestion, acesulfame potassium is absorbed from the small intestine and distributed to the blood and tissues through the systemic circulation and then excreted in urine. However, sucralose passes through digestion and is almost entirely excreted in the stools; only a small part is absorbed from the gastrointestinal tract. The aspartame molecule is broken down in different amino acids: aspartic acid and phenylalanine are sent to the systemic circulation while methanol is metabolised by the liver.¹⁴ Because this study quantified the intake of each specific sweetener and investigated the association with CVD risk, overall and by type, future epidemiological studies and experimental data will be needed to further investigate a potential differential effect of artificial sweeteners according to cerebrovascular or coronary CVD types.

Furthermore, according to WHO⁸ and as mentioned in the systematic reviews by Toews and colleagues and Zhang and colleagues,^{23 73} randomised controlled trials investigating the long term effects of artificial sweeteners on the risk of hard endpoints such as CVD

are lacking. However, some have studied early markers of cardiovascular health, such as weight variations, hypertension, or blood glucose level.^{81 82} Most of these studies were conducted among participants with particular conditions (eg, people who were overweight or those with prevalent hypertension)²² and were of short duration (follow-up around six months), with a level of evidence ranging from very low to moderate.^{23 83} Additionally, it should be noted that many studies investigating the health effects of artificial sweeteners are funded by the industry, notably several randomised control trials included in reviews and meta-analyses. Azad and colleagues reported that industry sponsored randomised controlled trials suggest greater weight loss results compared with studies not financed by industry.²² For instance, a systematic review has specifically studied the issue of conflict of interest in this field⁸⁴ and revealed that reviews sponsored by the artificial sweetener industry were more inclined to show beneficial weight loss effects. Therefore, no firm conclusion could be drawn from randomised controlled trials about the cardiometabolic impact of artificial sweeteners. However, several of these randomised controlled trials observed increased associations with several cardiometabolic outcomes, suggesting mechanistic plausibility for an impact of artificial sweeteners on cause of CVD.

Mechanistic plausibility from experimental studies

In some prospective cohort studies, associations have been reported between artificially sweetened beverage consumption and increased risk of obesity or weight gain.^{8 22 85 86} Low calorie sweeteners (from beverages, table top sweeteners, and foods) were associated with obesity in the National Health and Nutrition Examination Survey⁸⁷ and abdominal obesity in the Baltimore Longitudinal Study of Ageing.⁸⁸ A cross-sectional study also found that consumers of diet soft drinks had greater waist circumference.⁸⁹ In the PREDIMED study (multicentre randomised trial) there was a positive association between artificially sweetened beverages and abdominal obesity.⁹⁰ Therefore, part of the associations between artificial sweeteners and CVD risk observed in our study might be because of weight gain. However, the associations observed here are probably not entirely driven by increased body weight. The impact of artificial sweeteners on weight gain is debated.^{8 9 22 23} Some randomised controlled trials found no effect on body weight when replacing sugar sweetened beverages with artificially sweetened versions,⁹¹ and others suggested decreased body weight, body mass index, fat mass, and waist circumference.^{83 85} Adjustment for baseline body mass index and weight gain during follow-up did not modify the findings.

Other underlying mechanisms could be causally involved.^{92 93} Meta-analyses suggest associations between artificially sweetened beverages and metabolic syndrome,^{94 95} a cardiometabolic risk factor defined by dyslipidaemia, abdominal obesity, high blood glucose, insulin resistance, and hypertension.⁹⁶

Artificially sweetened beverages were associated with increased risk of metabolic syndrome^{89 90 97} in a cohort study,⁹⁷ a cross-sectional study,⁸⁹ and a multicentre randomised trial.⁹⁰ More specifically, associations were observed with increased hypertension,^{8 98 99} type 2 diabetes,^{8 87 100} and hypertriglyceridemia.^{8 90} Another potential pathway could involve the interaction of artificial sweeteners with intestinal sweet taste receptors,⁹² which play a part in insulin secretion and glucose absorption. Experimental studies (rodent models) suggest that glucose and energy homeostasis could be altered by artificial sweeteners.^{11 101} Ingestion of sugar by animals accustomed to artificial sweeteners could lead to low glucagon like peptide 1 levels (which normally stimulate insulin secretion) and induce hyperglycaemia,¹⁰¹ which could also be observed in humans.⁹² Additionally, the alteration of gut microbiota by some artificial sweeteners could increase glucose intolerance,¹⁷ but the results remain conflicting.²⁰ Vascular dysfunction, which contributes to CVD onset and development, after the ingestion of artificial sweeteners, has been observed in experimental studies (rodent models)¹⁵ and in vitro (human cellular model),¹⁶ and could also play a part in the risk of CVD. Finally, Basson and colleagues¹⁴ suggest that artificial sweetener consumption might be associated with increased inflammation, a risk factor for CVD.⁹⁶

Policy implications and conclusions

In conclusion, these findings suggest that higher artificial sweetener consumption might be associated with increased risk of CVDs. Further well designed, large scale prospective studies need to confirm these results and experimental studies should be conducted to clarify biological pathways. In the meantime, this study provides key insights into the context of artificial sweetener re-evaluation by the EFSA, WHO, and other health agencies worldwide. Our results indicate that these food additives, consumed daily by millions of people and present in thousands of foods and beverages, should not be considered a healthy and safe alternative to sugar, in line with the current position of several health agencies.^{23 102}

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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.

The lead author 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.

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 and by a press release from the Journal or the French Medical Institute for Health and Medical

Research, in association with Inrae, Cnam and Sorbonne Paris Nord communication and direction boards. This press release will be posted on their website and sent to their journalist contact book in France, Europe, and abroad (translated in English) as well as through their social medias Facebook and Twitter.

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Web appendix: online data supplements