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CLINICAL RESEARCH
Epidemiology, prevention, and health care policies

Preservative food additives, hypertension, and cardiovascular diseases: the NutriNet-Santé study

Anaïs Hasenböhler [1,2,*], Guillaume Javaux [1,2], Marie Payen de la Garanderie [1,2], Fabien Szabo de Edelenyi [1], Paola Yvroud-Hoyos [1], Cédric Agaësse [1], Alexandre De Sa[1], Inge Huybrechts [2,3], Fabrice Pierre [2,4], Xavier Coumoul [2,5], Léopold K. Fezeu [1], Pilar Galan [1], Jacques Blacher [1,6], Chantal Julia [1,7], Benjamin Allès [1], Serge Hercberg [1,2,7], Benoit Chassaing [2,8], Mélanie Deschasaux-Tanguy [1,2], Bernard Srour [1,2], and Mathilde Touvier [1,2]

[1]Université Sorbonne Paris Nord and Université Paris Cité, INSERM, INRAE, CNAM, Centre for Research in Epidemiology and StatisticS (CRESS), Nutritional Epidemiology Research Team (EREN), 74 rue Marcel Cachin, 93017 Bobigny, Seine-Saint-Denis, France; [2]Nutrition and Cancer Research Network (NACRe network, https://www.reseaunacre.eu/nacre-network), 78352 rue de la Manufacture, 78350 Jouy-en-Josas, Yvelines, France; [3]International Agency for Research on Cancer, World Health Organization, Lyon, Rhône, France; [4]Toxalim (Research Centre in Food Toxicology), Université de Toulouse, INRAE, ENVT, INP-Purpan, UPS, Toulouse, Haute-Garonne, France; [5]INSERM T3S, UMR-S 1124, Université Paris Cité, Paris, France; [6]Diagnosis and Therapeutic Centre, Hôtel-Dieu University Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris Cité University, Paris, France; [7]Public Health Department, Groupe Hospitalier Paris-Seine-Saint-Denis, Assistance Publique-Hôpitaux de Paris (AP-HP), Bobigny, Seine-Saint-Denis, France; and [8]Microbiome-Host Interactions, Institut Pasteur, INSERM U1306, CNRS UMR6047, Université Paris Cité, Paris, France

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Abstract

Background and Aims Experimental studies suggest that some preservative food additives may exert adverse cardiovascular effects, yet human data are lacking. The associations between exposure to these compounds and incidence of hypertension and cardiovascular diseases (CVD) were investigated in the NutriNet-Santé cohort (France, 2009–2024).

Methods Dietary intakes were assessed using repeated 24-h dietary records (up to 96), including commercial brands. Exposure to food additives was evaluated through multiple composition databases and *ad hoc* laboratory assays in food matrices. Associations between cumulative time-dependent exposures to preservative food additives during follow-up and outcomes were characterized using multi-adjusted Cox models.

Results Overall, 112 395 participants were included (78.7% women, mean age 42.8 ± 14.7 years) with a median follow-up of 7.9 years. The sum of total preservatives encompassed 58 substances consumed by at least one participant. Total non-antioxidant preservatives were positively associated with higher incidences of hypertension [n = 5544; hazard ratio (HR) higher vs. lower consumers: 1.29, 95% confidence interval (CI) 1.20–1.39] and CVD (*n* = 2450; HR 1.16, 95% CI 1.04–1.29), while total antioxidant preservatives were associated with higher incidence of hypertension (HR 1.22, 95% CI 1.13–1.31). Out of the 17 individual preservative food additives consumed by at least 10% of the study population, eight were associated with higher incidence of hypertension and one with higher incidence of CVD, after multiple test correction.

Conclusions Multiple associations between exposure to preservative food additives widely used in industrial foods and higher incidence of hypertension or CVD were observed in this large prospective cohort. Experimental research is needed to gain insight into underlying mechanisms. If confirmed, these new data call for the re-evaluation of regulations governing the use of these additives to improve consumer protection.

Trial Registration ClinicalTrials.gov NCT03335644.

* Corresponding author. Email: anais.hasenbohler@eren.smbh.univ-paris13.fr; Dr Mathilde Touvier, Email: m.touvier@eren.smbh.univ-paris13.fr
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Structured Graphical Abstract

Key Question

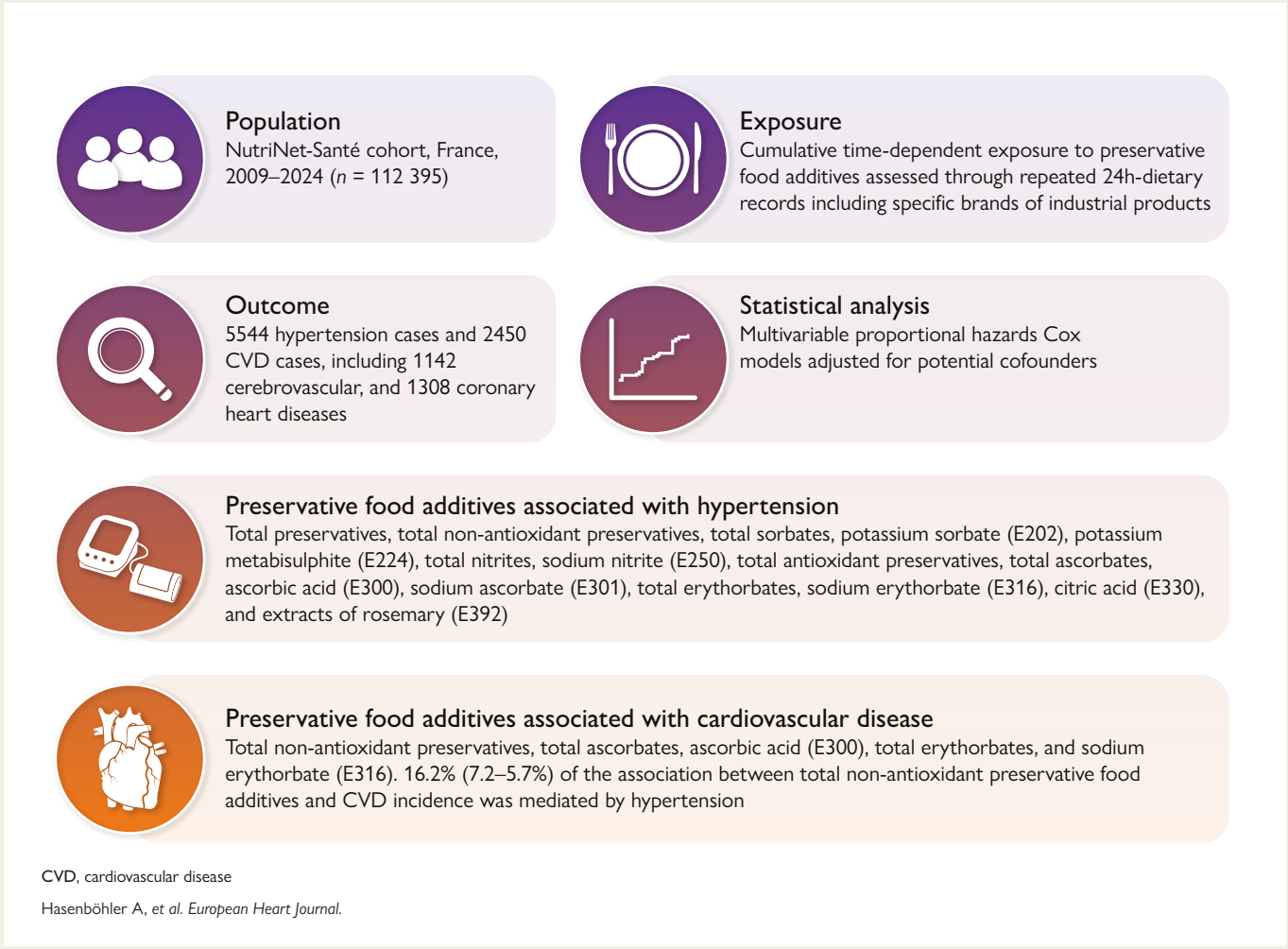
Is chronic exposure to preservative food additives associated with hypertension and cardiovascular disease incidence?

Key Finding

This large prospective cohort revealed multiple positive associations between exposure to widely consumed preservative food additives and higher incidence of hypertension and/or cardiovascular disease, including cerebrovascular and coronary heart diseases, after careful adjustment for potential confounders.

Take Home Message

This study provides new insights for the assessment of benefit/risk balance between food preservation and cardiovascular health, supporting utilization of freshly-made, minimally-processed foods.



CVD, cardiovascular disease

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Keywords Food additives • Preservatives • Hypertension • Cardiovascular disease • Prospective cohort

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Introduction

Preservative food additives are substances added to prolong packaged products' shelf life, protecting them against deterioration caused by micro-organisms and/or growth of pathogens and alterations caused by oxidation, such as fat rancidity and colour changes.[1] More than 20% of industrial foods and drinks referenced on the Open Food Facts World database contained at least one of these food additives in 2024.[2]

Over the past 10 years, 25 food additive re-evaluations conducted by the European Food Safety Authority (EFSA) focused on preservatives. Among these, 16 resulted in establishing acceptable daily intake (ADI) reference values for specific additives or their respective groups.[3] ADIs were derived from

experimental data, based on a broad spectrum of toxicological endpoints, including behavioural, carcinogenic, developmental, haematological, reproductive, and thyroid toxicity, growth retardation, elevated blood methaemoglobin level, and increased mortality. A recent *in vitro* study based on four human cell models suggested cytotoxic properties of several preservatives.[4] Recent experimental data suggest potential effects and properties of food additive preservatives that may impact blood pressure and cardiovascular health. While antihypertensive properties have been suggested for some of them (e.g. sulphur dioxide, citric or carnosic acids),[5–8] others were suggested to promote oxidative damage (e.g. nitrites[9,10]) or cytotoxicity (e.g. potassium sorbate, sodium nitrite, sodium ascorbate, sodium erythorbate,[4]) or to be advanced glycation end product activators *in vitro* (e.g. potassium sorbate[11]). Besides, several preservative additives' corresponding substances also naturally occur in foods and beverages (e.g. antioxidant vitamins C/ascorbic acid and E/alpha-tocopherol). Epidemiological studies generally associated their consumption through natural dietary sources (e.g. fruits, vegetables) with lower cardiovascular disease (CVD) risk.[12] While one may expect such beneficial properties to apply to the corresponding food additives, other studies detected little to no overall effects of their supplementation (at physiological or supraphysiological doses) in the general population regarding CVD or hypertension,[13] and none of these studies investigated food additive sources so far. Indeed, except for a few preservatives, such as nitrites and nitrates,[14–16] mainly used in processed meats, previous cohort studies lacked food additive exposure data, due to the absence of brand-specific information and variability in additive composition across products of the same type but different brands. Thus, this study aimed, for the first time, to comprehensively quantify the cumulative time-dependent exposures to total preservatives, total non-antioxidant and total antioxidant preservative food additives (main analyses), and specific substances (secondary analyses) and examine their associations with the incidence of CVD [including cerebrovascular accident (CVA) and coronary heart disease (CHD)] and hypertension, in a large prospective cohort with detailed dietary data.

Methods

Study population

This study relied on the data from the French NutriNet-Santé population-based prospective e-cohort, launched in 2009, to investigate the association between nutrition and health.[17] All French-speaking individuals aged at least 15 years with access to the Internet are eligible. Participants are recruited continuously since May 2009, following multimedia campaigns, and enrol voluntarily by registering online on our secure platform (www.etude-nutrinet-sante.fr). There is no preselection of eligible participants from a database, hence no 'response rate during recruitment'. Fully aware of the study design and objectives, participants are invited to regularly answer questionnaires on their dietary intakes, health, anthropometric,[18,19] physical activity,[20,21] lifestyle, and sociodemographic data.[22]

Dietary data collection

Upon registration and every 6 months, participants were invited to complete sequences of three validated[23–25] web-based 24-h dietary records (24HDRs). At each period, 24HDRs were randomly assigned to three nonconsecutive days over 2 weeks (two weekdays and one weekend day). Details on the dietary data collection and identification of under-/over-energy reports can be found in Supplementary Method 1. Dietary intakes in energy, fibre, and macro- and micronutrients (including vitamins C and E) were assessed by merging with the NutriNet-Santé food composition table.[26] Using multiple sources, participants' intakes of naturally occurring acetic and citric acids, nitrites, nitrates, and sulphites were quantified. Details are available in Supplementary Method 2.

Preservative food additive intakes

Assessment of food additive intake in the NutriNet-santé cohort through brand-specific data of the 24HDRs has been previously described.[27-29] Detailed information is provided in Supplementary Method 2. Briefly, three composition databases were merged with the NutriNet-Santé database to determine the presence of any specific food additive in a given industrial product. Potential reformulations were accounted for through dynamic matching: products were matched date-to-date, and each participant's date of consumption of each food or beverage was used to match the product to the closest composition data available, thus accounting for potential reformulations. Doses were determined by *ad hoc* laboratory analyses in food matrices and doses retrieved from other sources, such as the EFSA, following an official Public Access to Document request (doses available in Supplementary materials of another article from our research group[28]). The 80 preservative food additives listed in the Codex General Standard for Food Additives database[30] or the UK Food Standards Agency[31] were eligible for the present study. However, the occurrence of some of them was very low in the French/European markets; thus, the proportion of consumers was null; their list is provided in the footnote to *Table 2* and Supplementary data online, *Table S1*. We decided to include as food additive preservatives both preservatives *per se* as defined by Regulation (EC) No. 1333/2008[1] and antioxidant food additives, as both prevent the spoilage of food (food additive antioxidants preserving food via an antioxidant mode of action). In this paper, the term 'preservative food additives' includes both 'preservative non-antioxidant food additives' and 'preservative antioxidant food additives'. Some preservative food additives possess additional key properties (e.g. emulsifiers). All food additives with preservative properties are included in the present paper. Primary analyses were conducted on total preservative, total non-antioxidant, and total antioxidant preservative exposures. Secondary analyses investigated the summed individual preservative food additives with similar chemical structures into the following groups: sorbates (European codes E200, E202, E203), benzoates (E210, E211, E212), sulphites (E220, E221, E222, E223, E224, E225, E228), nitrites (E249, E250), nitrates (E251, E252), acetates (E260, E261, E262, E263), propionates (E280, E281, E282), ascorbates (E300, E301, E302, E304), tocopherols (E306, E307, E307b, E307c), erythorbates (E315, E316), butylates (E319, E320, E321), citrates (E330, E332, E333), and EDTA (E385, E386). Besides, all individual preservatives consumed by a least 10% were also investigated in association with studied outcomes. We compared the magnitudes of means of intake of food additive preservatives in NutriNet-Santé with the estimates of form EFSA reports[3] (in which SD are not provided).

Cardiovascular disease and hypertension ascertainment

A multisource approach was used to ascertain CVD and hypertension cases. 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 account. A physician expert committee validated each major health event after reviewing the participants' medical records and collecting additional

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information from the participants' doctors or medical facilities. Moreover, the NutriNet-Santé cohort was linked to the national health insurance system database to collect additional information regarding medical treatments and consultations and to the French national mortality registry to identify the occurrence and cause of death. Cases were then classified using the International Classification of Diseases-10th Revision.[32] In this study, we considered as cases all primary CVD [which included CHD (myocardial infarction, acute coronary syndrome, angioplasty, and angina pectoris), along with CVA (stroke and transient ischaemic attack)] and hypertension cases diagnosed between enrolment and 31 December 2024. Further details are available in Supplementary Method 3.

Statistical analyses

Participants from the NutriNet-Santé cohort who completed at least two 24HDRs during their first 2 years of participation, who were not considered as under- or overreporting for energy, and who did not report any prevalent CVD or hypertension at their inclusion (depending on the studied outcome) were included in the analysis (flowchart of participants presented in Supplementary data online, *Figure S1*). Baseline participants' characteristics were described as mean [standard deviation (SD)] for quantitative variables and *n* (%) for qualitative variables for the overall population before exclusion of prevalent cases of CVD/hypertension and per baseline sex-specific tertiles of total preservative food additive exposure (*Table 1*). Baseline daily intakes of preservative food additives were reported as mean (SD) and median (25th to 75th percentiles), including per kilogram of body weight (*Table 2* and Supplementary data online, *Table S1*). A correlation matrix was generated to visualize the Spearman correlations between intakes of individual food additives and between continuous covariates (see Supplementary data online, *Figures S3* and *S4*, respectively). Correlations between categorical covariates were tested using the Cramer method. For each studied additive or group of additives, the mean daily intake (continuous variable in mg/d) for each 2-year period of follow-up was calculated, accounting for all available dietary records in this time frame. Participants were then categorized into lower, medium, and higher consumers, defined as sex-specific tertiles if the additive was consumed by at least two-thirds of participants, and as nonconsumers, and lower/higher consumers separated by the sex-specific median otherwise (cut-offs provided in Supplementary data online, *Table S2*). These categories of exposure represent intake of specific preservatives and not just broader dietary patterns. Studied exposures were total preservative food additives, total non-antioxidant, and total antioxidant preservatives (main analyses), as well as each preservative additive consumed by at least 10% of the population study (secondary exploratory analyses), coded as cumulative time-dependent variables. The relationships between these exposures and CVD/hypertension incidence were investigated using multivariable cause-specific proportional hazard Cox models to account for competing risks[33] (e.g. death as a competing event) with age as the time scale. Hazard ratios (HR) and 95% confidence intervals (95% CI) were calculated. Participants contributed person-time to the models from their age at enrolment in the cohort until their age at the date of CVD/hypertension ascertainment, death, last contact, or 31 December 2024, whichever occurred first. A counting process structure was used with cumulative time-dependent dietary variables updated every 2 years (food additive exposures and dietary covariates). Exposure during a specific period was computed using an exponential decay weighted average of the most recent 2-year period and prior periods (see Supplementary method *S4*), thereby using all available dietary record data and allowing for trajectories of all dietary data. Based on the directed acyclic graph presented in Supplementary data online, *Figure S2*, the main model was adjusted for sociodemographic, baseline anthropometric, baseline lifestyles and behavioural, baseline proxies of genetic predisposition, and number of dietary records (structural) and dietary factors corresponding to known or suspected risk or protective factors for cardiometabolic health (detail and coding in footnote to *Figure 2*). In addition, when applicable, each model (one preservative exposure per model) was adjusted for the intake of the corresponding substance coming from natural sources. Primary analyses were also run per sex. The proportional hazard assumption was tested using the Schoenfeld residual method (see Supplementary data online, *Figure S6*). Restricted cubic splines were computed to assess the potential nonlinearity of dose–response associations (see Supplementary method 4 for details on restricted cubic splines models; main model, Supplementary data online, *Figure S7*). *P*-trend values across exposure tertiles (obtained in a model coding exposure as an ordinal categorical variable 1, 2, 3) were retained only when the spline analysis did not reject the log-linearity assumption (*P* for nonlinearity $\geq$ .05 in the restricted cubic splines models). Otherwise, when the assumption of log-linearity was not met (*P* for nonlinearity <.05), it was not correct/possible to use the *P* for linear trend; thus, the likelihood ratio overall *P*-value was retained (obtained by coding the exposure as a non-ordinal categorical variable and calculating likelihood ratio test between models with and without the studied food additive exposure variable, not assuming a linear trend). For exploratory analyses of specific preservative additives, *P*-values with and without correction for multiple testing by the false discovery rate[34] were computed; CIs were not corrected. We computed *E*-values[35] to estimate the necessary strength for unmeasured confounding to have to negate the observed results. We also tested the associations between food preservative additive exposures and hip fracture (i.e. outcome with no expected causal relationship) as a negative outcome control model. Hypertension and type 2 diabetes being intermediate risk factors for CVD, we tested the proportion of the association between preservative food additive exposure and CVD incidence that was mediated by hypertension and type 2 diabetes, using the CMAverse R package[36] and the same adjustment variables as the main model. Additional information and sensitivity analyses are presented in Supplementary methods *S4* and *S5*. All methods are reported following STROBE guidelines for cohort studies.[37]

Results

Descriptive characteristics

The overall population before exclusion of prevalent cases of the studied pathologies (*n* = 112 395) had a mean age at baseline of 42.8 (SD 14.7), with 78.7% of women. The median of completed 24HDRs is 18 (25th to 75th percentile = 6–35). Compared to lower consumers (Tertile 1), higher consumers of total preservative food additives (Tertile 3) tended to be younger, with a higher education level and a lower physical activity level and less family history of cardiometabolic disorder or hypertension and personal history of metabolic diseases. They were more likely to consume less alcohol but more ultra-processed foods and drinks (see *Table 1* for descriptive unadjusted comparison of participants' profile across categories of exposure to preservatives). Intakes of preservative food additives are presented in *Table 2* and Supplementary data online, *Table S1*. A total of 99.5% of participants had a non-null intake of preservative food additives in the first 2 years of follow-up. Out of the 58 preservative food additives detected and quantified in this population study, 17 were consumed by at least 10% of the participants and thus were

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individually investigated in association with CVD and hypertension incidence. In terms of proportion of consumers, the main preservative food additives were citric acid (91.3% consumers), lecithins (86.4%), total sulphites (83.5%), ascorbic acid (83.0%), sodium nitrite (73.3%), potassium sorbate (65.3%), sodium erythorbate (52.5%), sodium ascorbate (49.7%), potassium metabisulphite (44.2%), and potassium nitrate (32.3%). No strong correlation between intakes of preservative food additives was identified (see Supplementary data online, *Figure S3*). We verified the absence of collinearity issues between

Table 1 Baseline characteristics of participants from the NutriNet-Santé cohort, 2009–24 (*n* = 112 395)

Characteristic	overall (*n* = 112 395)	Sex-specific tertiles of total preservative food additive exposure			*P-value*[a]
		Tertile 1 (*n* = 37 466)	Tertile 2 (*n* = 37 464)	Tertile 3 (*n* = 37 465)	
Age (years), mean (SD)	42.8 (14.7)	46.0 (14.7)	43.3 (14.5)	39.0 (13.9)	<.001
Women, *n* (%)	88 405 (78.7)	29 469 (78.7)	29 468 (78.7)	29 468 (78.7)	NA
Height (cm)[e], mean (SD)	166.7 (8.1)	166.2 (8.0)	166.6 (8.1)	167.4 (8.2)	<.001
BMI (kg/m^2) *, mean (SD)	23.7 (4.5)	23.5 (4.3)	23.6 (4.3)	23.9 (4.8)	<.001
Family history of cardiometabolic disorder [b, *], *n* (%)	67 167 (61.0)	22 985 (62.7)	22 577 (61.4)	21 605 (58.8)	<.001
Family history of hypertension [b, *], *n* (%)	37 017 (34.4)	12 514 (35.0)	12 463 (34.7)	12 040 (33.6)	<.001
Educational level*, *n* (%)					<.001
Less than a high school degree	19 579 (17.7)	7186 (19.5)	6463 (17.5)	5930 (16.0)	
≤3 years after high school	53 065 (47.8)	16 995 (46.1)	17 450 (47.2)	18 620 (50.3)	
>3 years after high school	38 271 (34.5)	12 705 (34.4)	13 075 (35.3)	12 491 (33.7)	
Smoking status*, *n* (%)					<.001
Never	56 218 (50.2)	17 693 (47.5)	19 065 (51.0)	19 460 (52.0)	
Former smoker	36 887 (32.9)	13 323 (35.7)	12 361 (33.1)	11 203 (30.0)	
Current smoker	18 923 (16.9)	6273 (16.8)	5935 (15.9)	6715 (18.0)	
IPAQ physical activity level*, *n* (%)					<.001
Low	21 361 (23.4)	6539 (21.4)	7174 (23.5)	7648 (25.4)	
Moderate	39 338 (43.1)	12 836 (42.0)	13 464 (44.0)	13 038 (43.4)	
High	30 521 (33.5)	11 193 (36.6)	9949 (32.5)	9379 (31.2)	
Personal history of cardiometabolic disorders[c], *n* (%)	12 199 (10.9)	4491.0 (12.0)	4214.0 (11.2)	3494.0 (9.3)	<.001
Personal history of cardiovascular disease, *n* (%)	2039.0 (1.8)	803.0 (2.1)	716.0 (1.9)	520.0 (1.4)	<.001
Personal history of type 2 diabetes, *n* (%)	1939.0 (1.7)	696.0 (1.9)	643.0 (1.7)	600.0 (1.6)	.026
Personal history of dyslipidaemia, *n* (%)	1863.0 (1.7)	570.0 (1.5)	619.0 (1.7)	674.0 (1.8)	.012
Personal history of hypertension, *n* (%)	9009.0 (8.0)	3406.0 (9.1)	3121.0 (8.3)	2482.0 (6.6)	<.001
Energy intake excluding alcohol (kcal/d)[d], mean (SD)	1848.6 (454.6)	1726.2 (417.2)	1846.2 (423.0)	1973.5 (486.2)	<.001
Alcohol intake, mean (SD)	7.7 (11.8)	8.1 (12.3)	7.9 (11.8)	7.1 (11.4)	<.001
Saturated fat intake (g/d), mean (SD)	33.1 (12.1)	29.8 (11.0)	33.4 (11.3)	36.3 (13.1)	<.001
Sodium intake (mg/d), mean (SD)	2725 (895)	2590 (881)	2735 (854)	2851 (929)	<.001
Potassium intake (mg/d), mean (SD)	3002 (901)	2985 (942)	2996 (865)	3025 (895)	<.001
Fibre intake (g/d), mean (SD)	20.2 (10.0)	20.5 (11.0)	20.1 (9.7)	19.8 (9.3)	<.001
Sugar intake (g/d), mean (SD)	92.6 (33.7)	82.6 (31.3)	91.7 (30.0)	103.5 (36.1)	<.001
Fruit and vegetable intake (g/d), mean (SD)	465.6 (232.0)	477.4 (245.1)	466.5 (216.3)	452.8 (232.9)	<.001
Dairy product intake (g/d), mean (SD)	158.1 (147.1)	150.5 (147.9)	159.8 (144.0)	164.0 (149.0)	<.001
Red and processed meat intake (g/d), mean (SD)	75.7 (52.9)	70.1 (53.8)	75.7 (50.0)	81.4 (54.2)	<.001

Continued

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Table 1 *Continued*

Characteristic	overall (*n* = 112 395)	Sex-specific tertiles of total preservative food additive exposure			*P-value*[a]
		Tertile 1 (*n* = 37 466)	Tertile 2 (*n* = 37 464)	Tertile 3 (*n* = 37 465)	
Ultra-processed food intake (% of weight intake), mean (SD)	17.3 (9.9)	14.3 (8.2)	16.2 (8.3)	21.4 (11.4)	<.001
Total preservative food additive exposure (mg/d), mean (SD)	536.4 (613.9)	156.2 (81.6)	407.9 (76.1)	1045.3 (835.5)	<.001

IPAQ, International Physical Activity Questionnaire; SD, standard deviation.
[a]Kruskal–Wallis rank sum test for continuous variables; Pearson's Chi-squared test for categorical variables. Crude (unadjusted) comparisons.
[b]Family history of cardiometabolic disorder (i.e. myocardial infarction, angina, stroke, hypercholesterolaemia, diabetes, and hypertension)/hypertension in first-degree relatives.
[c]Personal history of metabolic disease was defined as the diagnosis and/or treatment for at least one prevalent metabolic disorder among: type 2 diabetes, dyslipidaemia, cardiovascular disease and hypertension.
[d]All dietary intake data in this table were calculated as the mean daily intake across all records during the first two years of participation in the study (mean number of 24 h records per person = 5.8 (SD 3.2)).
[e]Missing values: height *n* = 3155 (low consumers, 952; medium consumers, 997; high consumers: 1206); BMI *n* = 3155 (952; 997; 1206); family history of cardiometabolic disorder *n* = 2249 (814; 690; 745); family history of hypertension *n* = 4814 (1669; 1538; 1607); education level *n* = 1480 (580; 476; 424); smoking status *n* = 367 (177; 103; 87); IPAQ physical activity level *n* = 21 175 (6898; 6877; 7400).

categorical covariates (min–max correlations = 0.04–0.09, data not tabulated) and between continuous covariates (see Supplementary data online, *Figure S4*).

Preservative food additives are ubiquitously found across various food groups (*Figure 1* and Supplementary data online, *Table S3*). Some are nonetheless more specific to given food groups, e.g. 83.7% of sulphite intake came from alcoholic drinks; 54.0% of nitrites, 76.8% of nitrates, and 42.1% of erythorbates, from processed meat; 43.4% and 30.6% of propionates from refined and whole grains and cereals, respectively; 51.0% of ascorbates and 25.9% of citrates from processed fruits and vegetables; and 29.6% of tocopherols from breakfast cereals. For food additive substances that also naturally occurred in the diet, the relative contribution of the food additive source varied depending on the compound: from 1% for tocopherols or 5% for acetates to 16% for citric acid, 29% for ascorbates, and 63% for sulphites on average.

No participant exceeded the ADI set by EFSA[3] for sorbates, erythorbates, or nitrates. However, 96 participants exceeded the ADI (=0.7 mg of sulphur dioxide equivalent/kg body weight per day) set for sulphites with a mean intake of 0.89 mg of sulphur dioxide equivalent/kg body weight per day (SD 0.32, median 0.81, 25th to 75th percentiles: 0.75–0.93) and 54 exceeded the ADI (=0.07 mg nitrite ion equivalent/kg body weight per day) for nitrites with a mean intake of 0.09 mg nitrite ion/kg body weight per day (SD 0.03, median 0.08, 25th to 75th percentiles: 0.08–0.10).

For some preservative food additives, EFSA data were available to compare intake levels in the European Union with those observed in our population study; the order of magnitude was consistent overall (further details available in Supplementary data online, *Table S10*).

Associations between preservative food additive intakes and incidence of cardiovascular disease and hypertension

Participants' median follow-up time was 7.9 years (25th to 75th percentiles: 3.2–12.3; *n* = 110 356; 870 898 person-years) for the CVD analysis tailored population and 7.6 years (2.9–11.8; *n* = 103 386; 784 955 person-years) for the hypertension analysis tailored population. Between 2009 and 2024, 2450 CVD (including 33 fatal events), 1142 CVA, and 1308 CHD, as well as 5544 hypertension incident cases, were detected. Schoenfeld residuals did not refute the proportional hazard assumption (see Supplementary data online, *Figure S6*).

Restricted cubic spline plots (see Supplementary data online, *Figure S7*) generally did not indicate a departure from linearity (*P*-values for nonlinearity ≥0.05); in this case, *P*-values for trend are provided in the following paragraph and in *Figure 2*, Supplementary data online, *Figure S5*, and Supplementary data online, *Table S4*. For some associations, restricted cubic splines suggested a dose–response relationship with plateau effect or inverted U-shape (*P*-values for nonlinearity <0.05); in this case, the likelihood ratio overall *P*-values (requiring no underlying hypothesis of linearity) are displayed thereafter and in *Figure 2*, Supplementary data online, *Figure S5* and Supplementary data online, *Table S4*. Both *P*-trends and overall *P*-values are provided for all tested additives in Supplementary data online, *Table S4* for the main model and in Supplementary data online, *Table S5* for sensitivity analyses.

Results of Cox models are presented in *Figure 2*, Supplementary data online, *Figure S5* and in Supplementary data online, *Table S4* (all studied outcomes). *Figure 3* presents the predicted cumulative hazard curves for exposure tertiles, estimated from the Cox models. Higher intakes of total non-antioxidant preservatives were associated with a higher incidence of CVD [$HR_{\text{higher vs. lower intakes}}$ = 1.16 (95% CI 1.04–1.29), *P* = .004] and CHD [1.26 (1.10–1.46), *P* = .005]. Higher intakes of the following additives were associated with a higher incidence of hypertension: total preservatives [1.24 (1.16–1.34), *P* < .001], total non-antioxidant preservatives [1.29 (1.20–1.39), *P* < .001], and total antioxidant preservatives [1.22 (1.13–1.31), *P* < .001]. *Figure 4* presents the sex-guided analysis for the main model. Positive associations of non-antioxidant and antioxidant food additive preservatives with hypertension were statistically significant for both sexes, while the positive association of non-antioxidant preservatives with CVD and CHD was

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Table 2 Daily preservative food additive exposures among study participants from the NutriNet-santé cohort, 2009–24 (n = 112 395)

Food additive	European code	Type of food additive	Mean in mg/d/kg of body weight, all participants (SD)	Median in mg/d/kg of body weight, all participants [25th–75th percentile]	Mean in mg/d, all participants (SD)	Median in mg/d, all participants [25th–75th percentile]	Mean in mg/d, in consumers only (SD)	Median in mg/d, in consumers only [25th–75th percentile]	Proportion of consumers (%)
Total preservatives			8.3 (9.5)	6.2 [3.5–10.2]	536.4 (613.9)	403.4 [226.3–656.4]	539.3 (614.3)	405.6 [228.9–658.2]	99.5
Total non-antioxidant preservatives		Preservative	0.8 (1.5)	0.3 [0.1–1.0]	54.2 (95.3)	22.7 [5.9–62.3]	56.0 (96.4)	24.3 [7.0–64.5]	96.7
Total sorbates		Preservative	0.3 (0.5)	0.1 [0.0–0.4]	19.3 (31.6)	7.1 [0.0–25.7]	28.4 (34.8)	17.1 [6.6–37.1]	67.9
Total benzoates		Preservative	0.0 (0.0)	0.0 [0.0–0.0]	0.2 (2.1)	0.0 [0.0–0.0]	5.6 (9.0)	2.9 [1.0–6.6]	4.0
Total sulphites		Preservative	0.1 (0.1)	0.0 [0.0–0.1]	4.0 (5.8)	1.9 [0.2–5.5]	4.8 (6.0)	2.8 [0.9–6.5]	83.5
Nisin	E234	Preservative	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]	2.3
Natamycin	E235	Preservative	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]	0.8
Hexamethylene tetramine	E239	Preservative	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]	0.3
Dimethyl dicarbonate	E242	Preservative	0.0 (0.0)	0.0 [0.0–0.0]	0.0 (0.7)	0.0 [0.0–0.0]	19.1 (28.1)	8.9 [5.0–22.3]	0.04
Total nitrites		Preservative	0.0 (0.0)	0.0 [0.0–0.0]	0.2 (0.3)	0.1 [0.0–0.3]	0.3 (0.3)	0.2 [0.1–0.4]	73.3
Total nitrates		Preservative	0.0 (0.0)	0.0 [0.0–0.0]	0.2 (0.5)	0.0 [0.0–0.1]	0.5 (0.7)	0.3 [0.2–0.6]	32.3
Total acetates		Preservative	0.3 (1.1)	0.0 [0.0–0.0]	17.7 (71.7)	0.0 [0.0–0.0]	97.8 (143.2)	46.0 [14.2–125.0]	18.1
Total propionates		Preservative	0.2 (0.5)	0.0 [0.0–0.1]	12.3 (32.3)	0.0 [0.0–3.8]	48.4 (48.6)	33.6 [17.9–61.8]	25.4
Sodium tetraborate (borax)	E285	Preservative	0.0 (0.0)	0.0 [0.0–0.0]	0.0 (0.0)	0.0 [0.0–0.0]	3.6 (1.1)	3.8 [3.1–4.2]	0.003
Lysozyme	E1105	Preservative	0.0 (0.0)	0.0 [0.0–0.0]	0.2 (2.1)	0.0 [0.0–0.0]	7.2 (10.1)	3.0 [1.0–9.1]	2.8
Total antioxidant preservatives		Antioxidant	7.5 (9.2)	5.4 [2.9–9.1]	482.3 (597.0)	353.0 [191.7–586.1]	488.6 (598.4)	357.6 [197.7–590.5]	98.7
Total ascorbates		Antioxidant	1.1 (1.5)	0.5 [0.1–1.5]	67.3 (90.1)	34.6 [7.3–94.6]	75.9 (92.1)	44.6 [14.1–104.8]	88.7
Total tocopherols		Antioxidant	0.0 (0.0)	0.0 [0.0–0.0]	0.8 (2.9)	0.0 [0.0–0.0]	3.3 (5.3)	1.6 [0.6–3.8]	23.1
Propyl gallate	E310	Antioxidant	0.0 (0.0)	0.0 [0.0–0.0]	0.1 (1.3)	0.0 [0.0–0.0]	11.8 (10.5)	7.6 [5.1–14.3]	0.7
Total erythorbates		Antioxidant	0.1 (0.3)	0.0 [0.0–0.2]	8.2 (16.4)	1.3 [0.0–9.9]	15.7 (19.8)	9.2 [4.4–19.4]	52.5
Total butylates		Antioxidant	0.0 (0.0)	0.0 [0.0–0.0]	0.1 (1.5)	0.0 [0.0–0.0]	4.8 (8.1)	0.8 [0.2–7.1]	2.5
Lecithins	E322	Antioxidant	0.9 (2.3)	0.5 [0.1–1.1]	56.3 (151.4)	34.2 [9.2–72.7]	65.2 (161.1)	42.5 [18.9–80.6]	86.4
Total citrates		Antioxidant	5.0 (8.3)	3.1 [1.1–6.0]	322.5 (539.0)	199.6 [70.6–387.1]	353.4 (554.4)	224.2 [105.0–413.7]	91.3

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Table 2 *Continued*

Food additive	European code	Type of food additive	Mean in mg/d/kg of body weight, all participants (SD)	Median in mg/d/kg of body weight, all participants [25th–75th percentile]	Mean in mg/d, all participants (SD)	Median in mg/d, all participants [25th–75th percentile]	Mean in mg/d, in consumers only (SD)	Median in mg/d, in consumers only [25th–75th percentile]	Proportion of consumers (%)
Tartaric acid (L(+)-)	E334	Antioxidant	0.1 (0.5)	0.0 [0.0–0.0]	4.9 (31.4)	0.0 [0.0–0.0]	76.5 (100.2)	44.6 [8.6–104.2]	6.4
Phosphoric acid	E338	Antioxidant	0.2 (0.7)	0.0 [0.0–0.0]	13.4 (44.8)	0.0 [0.0–0.0]	65.7 (80.0)	40.9 [19.8–79.7]	20.4
Total EDTA		Antioxidant	0.0 (0.0)	0.0 [0.0–0.0]	0.0 (0.1)	0.0 [0.0–0.0]	0.3 (0.5)	0.2 [0.1–0.3]	6.0
Extracts of rosemary	E392	Antioxidant	0.0 (0.0)	0.0 [0.0–0.0]	0.4 (1.5)	0.0 [0.0–0.0]	1.9 (2.7)	1.0 [0.4–2.3]	22.1
Citric acid esters of mono- and diglycerides of fatty acids	E472c	Antioxidant	0.1 (0.9)	0.0 [0.0–0.0]	8.2 (57.8)	0.0 [0.0–0.0]	115.5 (185.5)	53.9 [21.6–138.4]	7.1

SD: standard deviation.
All food additive intake data in this table were calculated as the mean intake during the first 2 years of participation in the study.
The number of consumers was null for the following authorized preservatives: calcium benzoate (E213), ethyl p-hydroxybenzoate (E214), sodium ethyl p-hydroxybenzoate (E215), methyl p-hydroxybenzoate (E218), sodium methyl p-hydroxybenzoate (E219), potassium acetate (E261), calcium acetate (E263), carbon dioxide (E290), gamma-tocopherol (E308), delta tocopherol (E309), sodium lactate (E325), potassium lactate (E326), potassium citrate (E332), calcium citrate (E333), 4-hexylresorcinol (E586), and nitrous oxide (E942). The type of the food additive is defined by the Codex General Standard for Food Additives (https://www.fao.org/gsfaonline/additives/index.html).
Detailed intakes for each preservative food additive are available in Supplementary data online, *Table S1*.

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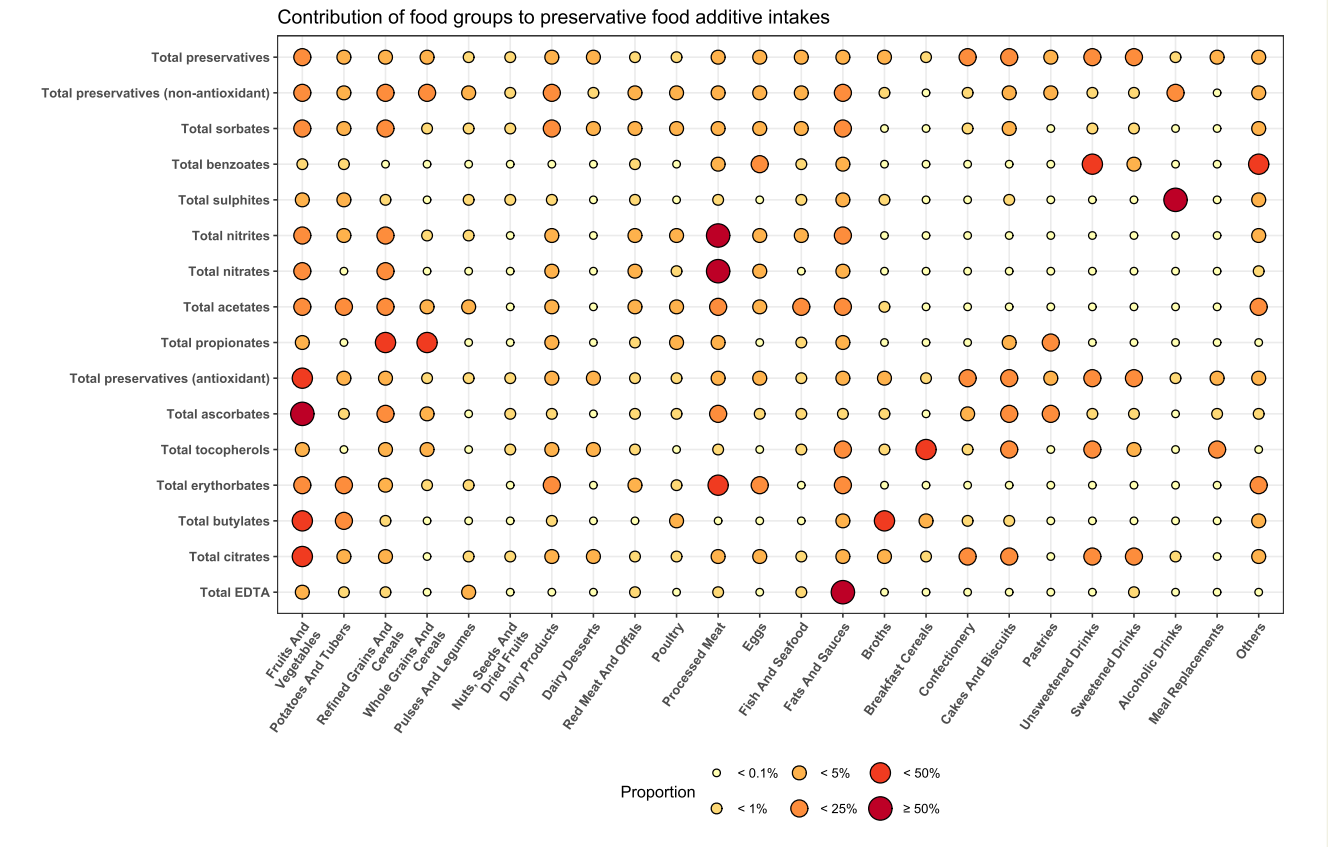


Figure 1 Dietary sources of total and groups of preservative intakes among study participants from the NutriNet-Santé cohort, 2009–24 (n = 112 395) [a]. [a]Groups of preservative food additives were defined as follows (European codes): total sorbates (E200, E202, E203), total benzoates (E210, E211, E212), total sulphites (E220, E221, E222, E223, E224, E225, E228), total nitrites (E249, E250), total nitrates (E251, E252), total acetates (E260, E261, E262, E263), total propionates (E280, E281, E282), total ascorbates (E300, E301, E302, E304), total tocopherols (E306, E307, E307b, E307c), total erythorbates (E315, E316), total butylates (E319, E320, E321), and total EDTA (E385, E386). Detailed % are presented in Supplementary data online, *Table S3*

statistically significant only in women. However, no interaction was detected between these exposures and sex (see Supplementary data online, *Table S12*). Several individual preservative additives were associated with higher incidence of the studied outcomes, in particular the following ones that remained statistically significant after FDR correction, with hypertension: total sorbates [1.39 (1.29–1.49), $P < .001$, $P_{FDR} < 0.001$], potassium sorbate (E202) [1.39 (1.28–1.50), $P < .001$, $P_{FDR} < 0.001$], total sulphites [1.11 (1.02–1.22), $P = .02$, $P_{FDR} = 0.04$], potassium metabisulphite (E224) [1.16 (1.08–1.25), $P < .001$, $P_{FDR} < 0.001$], total nitrites [1.16 (1.08–1.25), $P < .001$, $P_{FDR} < 0.001$], sodium nitrite (E250) [1.16 (1.08–1.25), $P < .001$, $P_{FDR} < 0.001$], total ascorbates [1.13 (1.05–1.21), $P < .001$, $P_{FDR} = 0.001$], ascorbic acid (E300) [1.14 (1.06–1.22), $P < .001$, $P_{FDR} = 0.001$], sodium ascorbate (E301) [1.12 (1.04–1.20), $P = .002$, $P_{FDR} = 0.003$], total erythorbates [1.13 (1.06–1.22), $P = .001$, $P_{FDR} = 0.002$], sodium erythorbate (E316) [1.14 (1.06–1.22), $P = .001$, $P_{FDR} = 0.002$], citric acid (E330) [1.25 (1.16–1.34), $P < .001$, $P_{FDR} < 0.001$], and extracts of rosemary (E392) [1.10 (1.02–1.18), $P = .003$, $P_{FDR} = 0.01$], with CVD: ascorbic acid (E300) with CVD [1.15 (1.04–1.28), $P = .005$, $P_{FDR} = 0.05$] (detail of all associations in Supplementary data online, *Figure S5* and Supplementary data online, *Table S4*).

These results were similar across all sensitivity analyses (see Supplementary data online, *Tables S5* and *S7*, *Figure S8*). All results of our primary analyses followed the same trends when excluding transient ischaemic attack, angina, and angioplasty from incidences and in the hypertensive subpopulation; some individual food additives lost statistical significance, probably due to the loss of statistical power (see Supplementary data online, *Tables S6 and S8*). Higher intakes of sodium were associated with a higher incidence of hypertension [$HR_{\text{tertile 3 vs. tertile 1}}$ 1.13 (1.04 –1.23), $P < .001$]; no significant association was detected with CVD [0.91 (0.80–1.03), $P = .15$].[41] As expected, no association was detected with the hip fracture negative control model (613 incident cases, all $P > .05$).

None of the three identified mixtures of preservative food additives reached statistical significance for the associations with CVD, CVA, or CHD. Mixture 2 (mainly represented by acetic and tartaric acids, citric acid esters of mono- and diglycerides of fatty acids, potassium metabisulphite, and potassium sorbate) and Mixture 3 (mainly characterized by citric and phosphoric acids, sodium nitrite, sodium erythorbate, and potassium sorbate) were associated with higher hypertension incidence (see Supplementary data online, *Table S9*).

No interaction with age nor with diet quality was detected. An interaction was detected between prevalent metabolic

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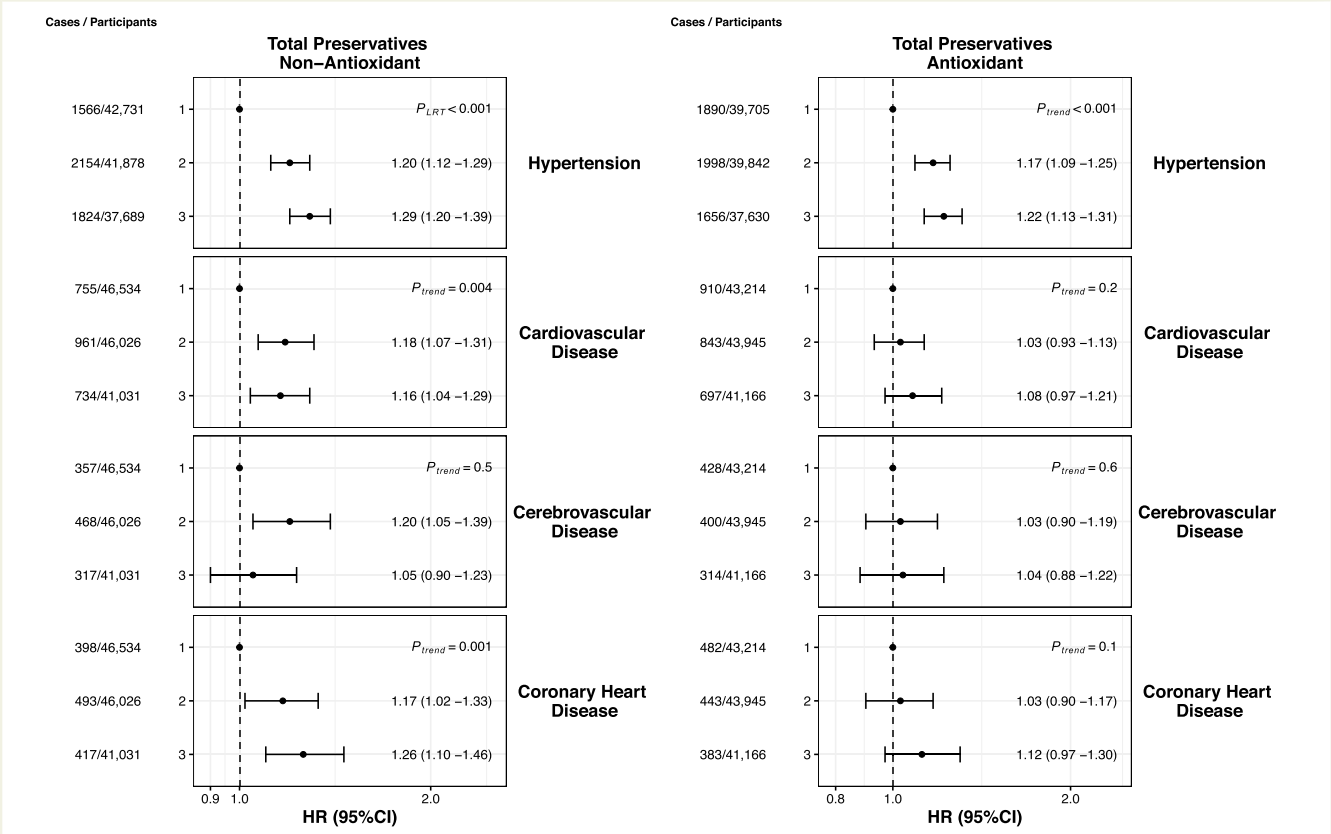


Figure 2 Associations between exposure to preservative food additives and cardiovascular disease (2450 incident cardiovascular disease cases, including 1142 cerebrovascular and 1308 CHD cases/110 356 participants) and hypertension (5544 incident hypertension cases/103 386 participants) incidence among study participants from the NutriNet-santé cohort, 2009–24[a,b,c]. Abbreviations: HR, hazard ratio; CI, confidence interval. [a] The three food additive categories of exposure were defined as follows: sex-specific tertiles for total non-antioxidant preservatives and total antioxidant preservatives. Cut-offs were recalculated for each period and are available in Supplementary data online, *Table S2*. [b] The detail of all investigated associations between food additive preservative intakes and pathology incidence with corresponding HRs, 95% Cis, and number of cases/participants per category is provided in Supplementary data online, *Table S4*. Based on the linearity test from restricted cubic splines presented in Supplementary data online, *Figure S7*, the *P-value* displayed in the present forest plot is either the *P-trend* (when *P* for nonlinearity was ≥ 0.05) or the overall *P-value* (when *P* for nonlinearity was <0.05). Both *P-values* are provided for all additives in Supplementary data online, *Table S4*. As recommended for the presentation of Cox model results,[38–40] the overall LRT *P-value* is provided by the same model as the one used to obtain HR and their confidence intervals, while the *P-trend* is obtained via a different model, in which exposure categories were coded 1, 2, and 3 and considered ordinal. [c] Multivariable Cox proportional hazard models adjusted for age (time scale), sex, height (continuous, m), BMI (continuous, kg/m^2), physical activity (categorical IPAQ variable: high, moderate, low), smoking status (never smoked, former smoker, current smoker), number of smoked cigarettes in pack-years (continuous), educational level (less than high school degree, ≤ 3 y after high school degree, > 3 y after high school degree), family history of cardiometabolic disorder/hypertension (yes/no), number of dietary records (continuous), daily intakes of energy without alcohol (continuous, kcal/d), alcohol (continuous, g/d), saturated fats (continuous, g/d), sodium (continuous, mg/d), dietary fibre (continuous, g/d), sugars (continuous, g/d), fruits and vegetables (continuous, g/d), dairy products (continuous, g/d), red and processed meats (continuous, g/d)

disorders and total non-antioxidant preservatives regarding CVD and CHD incidences. Thus, corresponding stratified analyses are now presented in Supplementary data online, *Table S12*. Associations tended to be stronger in participants with prevalent metabolic disorder, although direction of the associations was similar in both strata.

Total non-antioxidant food additive preservatives being associated both with hypertension (risk factor for CVD) and CVD incidence in this study, and with type 2 diabetes in a previous study in the same cohort,[38] we computed mediation analyses. In all, 16.2% (95% CI 7.2–55.7%) of the association between total non-antioxidant preservative food additive exposure and CVD incidence was mediated by hypertension, and 4.7% (95% CI 1.7–24.8%) was mediated by type 2 diabetes (see Supplementary data online, *Table S11*).

All *E*-values (see Supplementary data online, *Table S4*) of statistically significant associations were above or equal to 1.5, the only exception being the association between extracts of rosemary (E392) and incidence of hypertension (*E*-value = 1.43). It is therefore unlikely for detected associations to be entirely ruled out by residual confounding.

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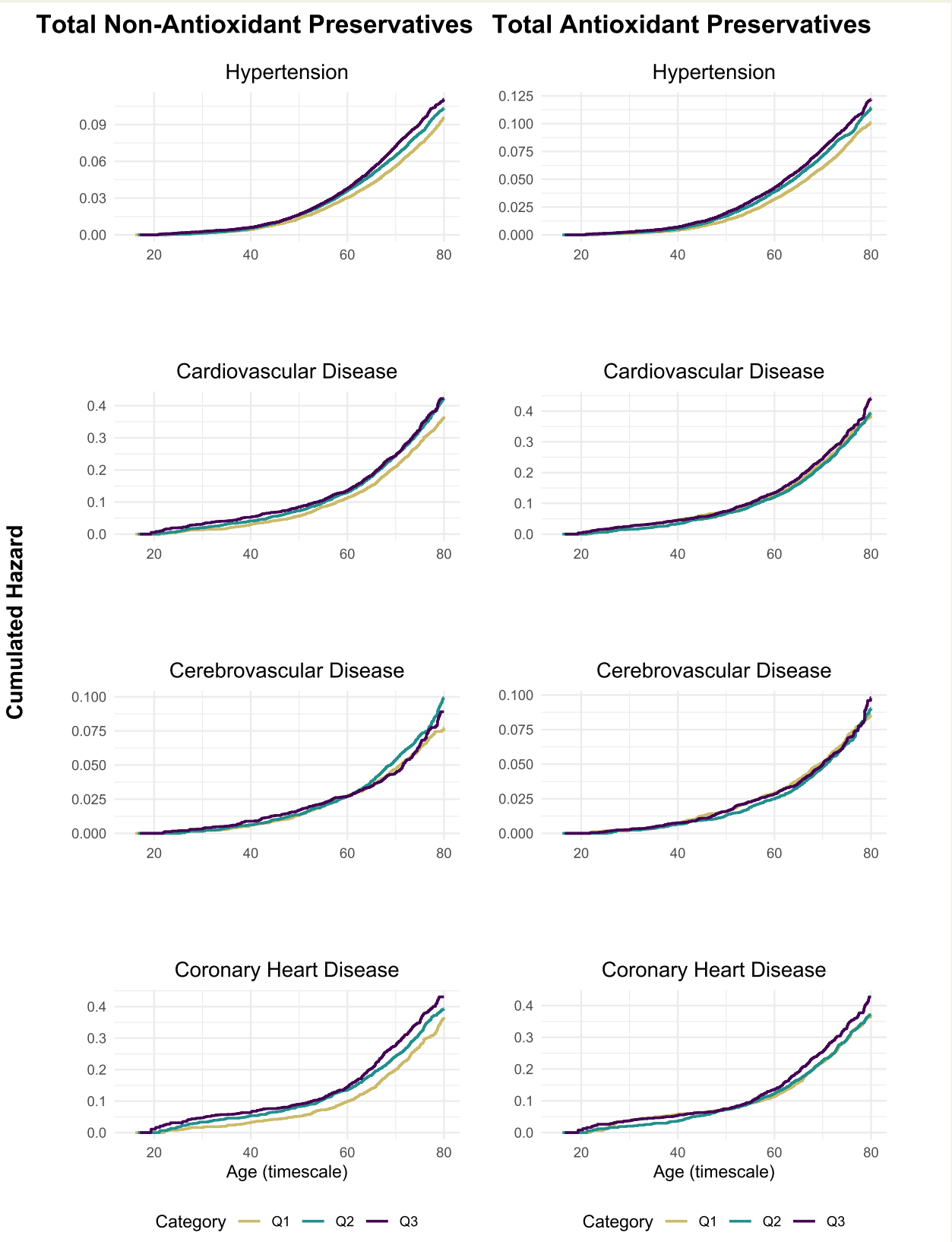


Figure 3 Predicted cumulative hazard curves for the associations between exposure to preservative food additives and cardiovascular disease (2450 incident cardiovascular disease cases, including 1142 cerebrovascular and 1308 CHD cases/110 356 participants) and hypertension (5544 incident hypertension cases/103 386 participants) incidence among study participants from the NutriNet-Santé cohort, 2009–24.[a,b,c] HR, hazard ratio; CI, confidence interval. [a] The three food additive categories of exposure were defined as follows:

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Discussion

In this large prospective cohort, exposure to several widely used preservative food additives was associated with increased incidence of hypertension and/or major CVD outcomes, including CVA and CHD. No inverse association was observed, suggesting a possible involvement of these compounds in cardiovascular aetiology (*Structured Graphical Abstract*).

Comparison with other population studies

So far, except for the specific case of nitrite/nitrate food additives in processed meat, no other cohort study has investigated the associations between exposures to preservative food additives and CVD or hypertension incidence, probably due to a lack of data on specific industrial foods consumed by participants, while their additive content varies greatly from one brand to another, rendering comparison with epidemiological literature challenging.

Our group previously published a study on nitrites and nitrates, in association with CVD, CVA, CHD, and hypertension risks in NutriNet-Santé.[14] Using a different methodology (time-dependent cumulative exposure) with longer follow-up (>2 years), we found stable results, suggesting that higher food additive nitrite exposure is associated with higher incidence of hypertension while food additive nitrates showed no associations with cardiometabolic outcomes. While some interventional studies suggest a beneficial role of dietary nitrate naturally present in vegetables or derived solutions (e.g. in beetroot juice) on the cardiovascular function,[42,43] our results do not support cardiovascular benefits from food additive nitrites or nitrates. Consistently, a recent study within the prospective US Nurses' Health Study found no independent effect of nitrate dietary intake (food additive and mostly naturally occurring) on CHD risk.[15] Results from the US NIH-AARP Diet and Health Study prospective cohort showed positive associations between nitrites and nitrates from processed meat (corresponding almost exclusively to the additives used in meat processing) and all-cause and heart disease mortality.[16] A 2025 systematic review and meta-analysis observed lower nitrate and nitrite plasma concentrations in individuals with cardiometabolic risk, whereas salivary nitrate showed a significant positive association with diastolic blood pressure.[44] However, these biomarkers reflect overall exogenous exposure (including from natural nitrates/nitrites in plant-based foods) and endogenous metabolism, limiting their relevance to food additives specifically.

No epidemiological study investigated the associations between sorbate additives and CVD or hypertension. Potassium sorbate is a *trans* fatty acid.[3] The deleterious impact of *trans* fat on cardiovascular health is well documented,[45] including on blood pressure elevation and hypertension risk,[46,47] which is consistent with our findings on hypertension.

In our study, food additives ascorbic acid and erythorbates (isomer of ascorbic acid) were associated with elevated incidence of CVD and hypertension, while tocopherols showed no such associations. Systematic reviews and meta-analyses of prospective studies concluded that, while higher natural food intake and/or blood concentrations of ascorbic acid and alpha-tocopherol tended to be associated with reduced risk of CVD[12] or hypertension,[48] no evidence supports preventive effects of these substances from other sources. An umbrella review found no overall effects of vitamin C supplementation on arterial stiffness and other biomarkers of CVD.[13] A randomized controlled trial showed no effect of alpha-tocopherol supplementation on cardiovascular events in high-risk patients.[49] Some studies even suggested an increased risk of CVD or mortality associated with vitamin C/ascorbic acid supplementation.[50,51] However, none of these studies provided data specifically on preservative antioxidant food additives. Despite food additive ascorbic acid and alpha-tocopherol having identical structures to their naturally occurring forms,[3] their effects can differ based on factors such as food matrix (composition, structure, etc.), dosage, and interactions with other food compounds affecting bioavailability.[52]

To our knowledge, there was no epidemiological study with which we could compare our results on other preservative food additives and CVD/hypertension risk.

Mechanistic evidence

As shown in Supplementary data online, *Figure S9*, many mechanisms may explain the observed associations. A recent *in vitro* study suggested no cytotoxicity or genotoxicity for lecithins, but cytotoxicity (potentially playing a role in atherosclerosis[53]) for potassium sorbate, sodium nitrite, sodium ascorbate, and sodium erythorbate and enhanced cell proliferation by potassium metabisulphite, ascorbic acid, and citric acid in different locations, including the liver for the two latter.[4] In a human microbiota-associated mouse model, the combined consumption of 10% fructose (weight/volume) and potassium sorbate for 11 weeks may increase the risk of development and progression of metabolic dysfunction-associated steatotic liver disease (MASLD).[54] The liver and cardiovascular system are closely linked,[55] and the *trans* configuration of potassium sorbate[3] may play a role. Moreover, *in vitro* studies suggest *trans* C18:1

Figure 3 Continued

sex-specific tertiles for total non-antioxidant preservatives and total antioxidant preservatives. Cut-offs were recalculated for each period and are available in Supplementary data online, *Table S2*. [b] The detail of all investigated associations between food additive preservative intakes and pathology incidence with corresponding HRs, 95% Cis, and number of cases/participants per category is provided in Supplementary data online, *Table S4*. Based on the linearity test from restricted cubic splines presented in Supplementary data online, *Figure S7*, the *P-value* displayed in the present forest plot is either the *P-trend* (when *P* for nonlinearity was ≥ .05) or the overall *P-value* (when *P* for nonlinearity was <.05). Both *P-values* are provided for all additives in Supplementary data online, *Table S4*. As recommended for the presentation of Cox model results,[38–40] the overall LRT *P-value* is provided by the same model as the one used to obtain HR and their confidence intervals, while the *P-trend* is obtained via a different model, in which exposure categories were coded 1, 2, and 3 and considered ordinal. [c] See footnote of *Figure 2* for the adjustment strategy for multivariable Cox proportional hazard models

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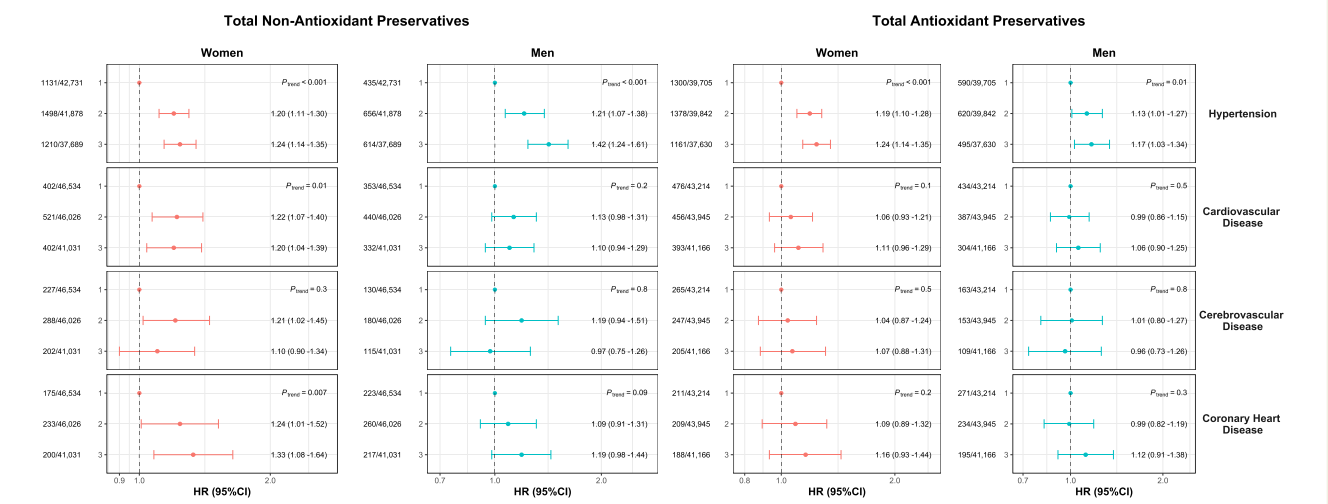


Figure 4 Sex-guided analysis on the associations between exposure to preservative non-antioxidant and preservative antioxidant food additives and cardiovascular disease (2450 incident cardiovascular disease cases, including 1142 cerebrovascular and 1308 CHD cases/110 356 participants) and hypertension (5544 incident hypertension cases/103 386 participants) incidence among study participants from the NutriNet-santé cohort, 2009–24.[a,b,c] HR, hazard ratio; CI, confidence interval. [a] The three food additive categories of exposure were defined as follows: sex-specific tertiles for total non-antioxidant preservatives and total antioxidant preservatives. Cut-offs were recalculated for each period and are available in Supplementary data online, *Table S2*. [b] The detail of all investigated associations between food additive preservative intakes and pathology incidence with corresponding HRs, 95% Cis, and number of cases/participants per category is provided in Supplementary data online, *Table S4*. Based on the linearity test from restricted cubic splines presented in Supplementary data online, *Figure S7*, the *P-value* displayed in the present forest plot is either the *P-trend* (when *P* for nonlinearity was ≥ .05) or the overall *P-value* (when *P* for nonlinearity was <.05). Both *P-values* are provided for all additives in Supplementary data online, *Table S4*. As recommended for the presentation of Cox model results,[38–40] the overall LRT *P-value* is provided by the same model as the one used to obtain HR and their confidence intervals, while the *P-trend* is obtained via a different model, in which exposure categories were coded 1, 2, and 3 and considered ordinal. [c] Multivariable Cox proportional hazard models adjusted for age (time scale), sex, height (continuous, m), BMI (continuous, kg/m^2), physical activity (categorical IPAQ variable: high, moderate, low), smoking status (never smoked, former smoker, current smoker), number of smoked cigarettes in pack-years (continuous), educational level (less than high school degree, ≤ 3 y after high school degree, > 3 y after high school degree), family history of cardiometabolic disorder/hypertension (yes/no), number of dietary records (continuous), daily intakes of energy without alcohol (continuous, kcal/d), alcohol (continuous, g/d), saturated fats (continuous, g/d), sodium (continuous, mg/d), dietary fibre (continuous, g/d), sugars (continuous, g/d), fruits and vegetables (continuous, g/d), dairy products (continuous, g/d), red and processed meats (continuous, g/d). No interaction was detected between these exposures and sex (see Supplementary data online, *Table S12*)

fatty acids are more potent than their *cis* isomers at stimulating glucagon[56] and insulin secretion[57] and not inhibiting glucose oxidation as much,[57] potentially altering pancreatic functions and increasing the risk of type 2 diabetes and consequently of hypertension or CVD.

Sulphites can trigger allergic or pseudo-allergic reactions in sensitive individuals (mandatory declaration of allergen),[58] leading to vasodilation and hypertension at high exposure levels. The evidence of sulphites elevating blood pressure is lacking, with some studies suggesting potential hypotensive effects.[5] Similarly, citric and carnosic acid (from extracts of rosemary) showed potential antihypertensive effects in hypertensive animal models.[6,7] Low-level exposure in humans might lead to long-term adaptation balancing initial hypotensive reactions with hypertensive responses. Further research is needed on how these additives affect vascular function.

Mechanisms involving nitrites and nitrates have been discussed previously.[14] Briefly, the positive associations with hypertension might relate to nitrites promoting oxidative damage[9,10] and *N*-nitroso compounds (essentially formed during meat processing), which increase the risk of insulin resistance,[59] and itself exacerbating hypertension risk.[60]

Type 2 diabetes is an important risk factor for CVD and hypertension. Studies showed that potassium sorbate activates advanced glycation end products *in vitro*,[11] nitrites can increase insulin resistance in rats,[59,61] propionate impairs insulin action via glucagon and FABP4 production in mice and humans,[62] and chronic pharmacological doses of vitamins C and E in rodents increased fasting blood glucose, insulin, and homeostasis model assessment index for insulin resistance (HOMA).[63] However, authorized doses of additives are physiological and not pharmacological.

Hypertension is a risk factor for CVD. In this study, total non-antioxidant preservative exposure was associated with higher incidences of both CVD and hypertension, with a substantial proportion of the CVD association mediated by hypertension.

Restricted cubic splines revealed that some tested associations presented a *P*-value for nonlinearity <0.05. Plots for the following associations suggested a plateau effect, indicating the possibility of a receptor saturation[64]: total preservative

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food additives with hypertension (turning point = 609.07 mg/d), total non-antioxidant preservative food additives with CHD (60.45 mg/d) and hypertension (60.86 mg/d), total sorbates and potassium sorbate (E202) with hypertension (30.29 mg/d and 26.29 mg/d, respectively), total antioxidant preservative food additives with hypertension (543.24 mg/d), ascorbic acid (E300) with hypertension (87.45 mg/d), total erythorbates and sodium erythorbate (E316) with hypertension (14.97 and 14.97 mg/d, respectively), and citric acid (E330) with hypertension (366.87 mg/d). In turn, plots for associations of total propionates and calcium propionate (E282) with hypertension suggested inverted U-shaped associations (turning points = 40.00 and 111.43 and 40.00 and 111.32 mg/d, respectively). This could suggest that at low doses of exposure to these additives (i.e. Category 2, since Category 1 are nonconsumers), detoxification systems may not be activated yet but become so when reaching a certain threshold.[65] An additive could have several targets, some of which are activated at low concentrations (triggering deleterious effects) and others at higher concentrations, including the receptors that trigger the adaptive response, favouring their elimination. The potential nonlinearity of some associations should be further investigated in future studies to confirm or refute these trends.

Strengths and limitations

To our knowledge, this is the first prospective epidemiological study investigating the links between a wide range of preservative food additives and cardiovascular health. It relied on a large cohort with highly detailed, brand-specific, and repeatedly collected 24HDRs over 15 years of follow-up, enabling time-dependent cumulative exposure assessment. These data were linked to multiple food composition databases, *ad hoc* laboratory assays in food matrices, and dynamic matching accounting for reformulations, providing access to unique information on exposure to preservative food additives.

Several limitations should nevertheless be acknowledged. First, the observational design precludes causal inference based on this study alone, and residual confounding cannot be entirely ruled out. However, models were adjusted for a wide range of potential confounders and remained robust across multiple sensitivity analyses. Although some preservatives are more prevalent in certain food groups, most are ubiquitous rather than specific to a single category. Models were therefore adjusted for major food groups associated with cardiovascular risk or protection (e.g. fruits and vegetables, red and processed meats, ultra-processed foods), and associations remained statistically significant. This limits the likelihood that the observed associations are solely driven by the foods themselves rather than by the preservatives studied. In addition, although information on industrial processing methods is not systematically available, results were similar after adjustment for the proportion of ultra-processed foods (Nova classification), and preservatives are used across products with diverse processing levels. Mechanistic evidence from *in vivo* and *in vitro* studies further supports a potential causal role for several of these compounds. Second, as in other volunteer-based nutritional cohorts, participants were more often women and more highly educated and had healthier lifestyles than the general French population,[66,67] and between 11.5% and 11.9% (depending on the studied population) of the participants dropped out during follow-up, main motive being burden related to questionnaires. The proportion of participants who received nutritional advice from a healthcare professional was unknown. Ethnic, racial, and religious data were unavailable due to strict French regulations. Caution is therefore warranted when generalizing the findings. However, energy intake, proportion of energy from ultra-processed foods, and geographical distribution were comparable to national estimates.[28,68–70] Importantly, for aetiological research, exposure contrast and population diversity are more critical than strict representativeness. NutriNet-Santé captured substantial contrasts in preservative exposure across a wide range of lifestyle profiles. Moreover, the preservatives studied are authorized across the European Union but also widely used in other regions, including North America. Third, demographic characteristics of the cohort and the young minimum enrolment age likely contributed to the relatively low proportion of participants with hypertension (5% in this study against 30% in France[71]). Although the combination of multisource case ascertainment from proactive participant declaration and monitoring via medico-administrative databases reduced the risk of missing diagnosed cases, undiagnosed hypertension cannot be excluded. This limitation should be interpreted in light of national data indicating a substantial prevalence of undiagnosed hypertension in France (6 million in 2023),[71] but with higher diagnostic awareness among women,[72] who comprised the majority of the cohort. Besides, the observation of well-established associations with major risk factors (e.g. sodium intake and smoking) supports the validity of case ascertainment in this cohort. Moreover, if differential healthcare access had substantially biased the results, a higher incidence of diagnosed hypertension would be expected among participants with healthier lifestyles[73]; this was not observed. Any remaining misclassification would more likely have attenuated associations rather than generated spurious positive findings. Finally, although exposure assessment was highly detailed, some degree of misclassification is possible. Nonetheless, dietary intake assessment in NutriNet-Santé is among the most accurate in large cohort studies, based on validated,[23–25] repeatedly collected, brand-specific 24HDRs linked to multiple food composition databases and laboratory analyses, with dynamic updates for reformulations. While validation against biomarkers of preservative exposure was not feasible due to the lack of specific biomarkers for most additives, estimated intakes were generally consistent with EFSA data. Some limitations remain regarding the estimation of naturally occurring compounds for some substances (e.g. natural lecithins), and the inability to study rarely consumed preservatives; however, these reflect their low prevalence on the market and limited potential public health impact.

Conclusions

This large prospective cohort revealed multiple positive associations between exposure to widely consumed preservative food additives, which were long considered safe under current regulation, and higher incidence of hypertension and/or CVD, CVA, and CHD. These findings may have important public health implications as consumers are exposed to these compounds via thousands of foods and drinks. These results need to be

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confirmed by other epidemiological studies, and additional experimental data are needed to depict the mechanisms underlying potential adverse CVD- and hypertension-related effects of these substances. These results do not call into question food-based dietary guidelines or results based on scores for compliance to these diets (DASH, Mediterranean diet) but rather complement them. It is not only important to consume sufficient amounts of fruit and vegetables, fish, legumes, and fibre and to limit intake of processed meats, salt, etc., to prevent hypertension and CVD, but it would also seem preferable to favour 'fresh and minimally processed' versions of these products as officially recommended for consumers and patients in the French nutritional health programme.[74] These are two complementary dimensions that are not opposed to each other but are rather complementary.[75] This study provides new insights for revisiting the evaluation of the safety of these food additives, which should consider the benefit/risk balance between food preservation with these additives and their potential impact on cardiovascular health.

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Authors' contributions

The authors' contributions were as follows to A.H. and M.T.: designed the study; F.S.E., C.A., A.D.S., and M.T. developed the additive composition database and matched consumption/composition data. P.Y. led the validation of pathology cases. A.H.: performed statistical analysis; M.T. and G.J. supervised statistical analysis; A.H.: drafted the manuscript; M.T.: supervised the writing. All authors contributed to the data interpretation and revised each draft for important intellectual content. All authors read and approved the final manuscript. A.H. and M.T. had full access to all the data in the study, M.T. takes responsibility for the integrity of the data and the accuracy of the data analysis —she is the guarantor. The corresponding authors (A.H. and M.T.) attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Transparency statement

Dr. Touvier (the guarantor) 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.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of interest

Nothing to declare.

No support from any for-profit organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Data Availability

Researchers from public institutions can submit a request to have access to the data for strict reproducibility analysis (systematically accepted) or for a new collaboration, 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 authorizations from the competent administrative authorities may be needed. In accordance with existing regulations, no personal data will be accessible.

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Ethical Approval

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 n°908450/n°909216). Each participant signs an electronic informed consent form before enrolment in the NutriNet-Santé cohort and is informed of the study design. The NutriNet-Santé protocol is available in both French and English on the study website: https://info.etude-nutrinet-sante.fr/siteinfo/article/3.

Pre-registered Clinical Trial Number

Clinicaltrials.gov: NCT03335644

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