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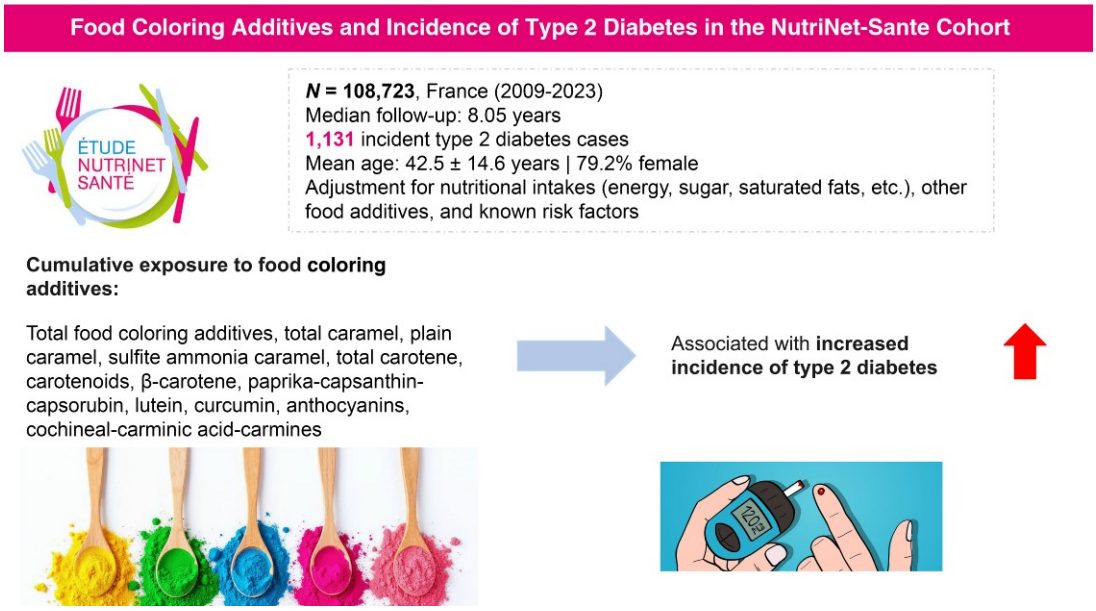

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Experimental studies have demonstrated deleterious effects of some food coloring additives on cytotoxic, genotoxic, and metabolic end points. However, no prospective study has examined their association with type 2 diabetes.
- **What is the specific question we wanted to answer?**
  Are dietary exposures to food coloring additives associated with type 2 diabetes incidence?
- **What did we find?**
  Using data from >108,000 participants of the NutriNet-Santé cohort, we found that several food coloring additives (natural or artificial) were associated with higher type 2 diabetes incidence, after adjusting for nutritional quality of diet and other confounders.
- **What are the implications of our findings?**
  Food coloring additives may represent a modifiable risk factor for type 2 diabetes prevention and support recommendations to limit exposure to these nonessential additives.

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Sanam Shah,[1,2] Anaïs Hasenböhler,[1,2] Guillaume Javaux,[1] Marie Payen de la Garanderie,[1,2] Fabien Szabo de Edelenyi,[1] Paola Yvroud,[1] Cédric Agaësse,[1] Alexandre De Sa,[1] Inge Huybrechts,[2,3] Fabrice Pierre,[2,4] Marc Audebert,[2,4] Xavier Coumoul,[2,5] Chantal Julia,[1,6] Emmanuelle Kesse-Guyot,[1,2] Benjamin Allès,[1] Valérie Deschamps,[7] Serge Hercberg,[1,2,6] Benoit Chassaing,[2,8] Emmanuel Cosson,[1,9] Sopio Tatulashvili,[1,9] Mélanie Deschasaux-Tanguy,[1,2] Bernard Srour,[1,2] and Mathilde Touvier[1,2]

[1]*Centre for Research in Epidemiology and StatisticS (CRESS), Nutritional Epidemiology Research Team (EREN), Université Sorbonne Paris Nord and Université Paris Cité, INSERM, Institut National de la Recherche pour l'agriculture, l'alimentation et l'environnement (INRAE), Conservatoire National des Arts et Métiers (CNAM), Bobigny, France*
[2]*Nutrition And Cancer Research Network , Jouy-en-Josas, France*
[3]*International Agency for Research on Cancer, World Health Organization, Lyon, France*
[4]*Toxalim (Research Centre in Food Toxicology), INRAE, Ecole Nationale Vétérinaire de Toulouse (ENVT), Ecole d'Ingénieurs de Purpan (INP-Purpan), Université de Toulouse 3 Paul Sabatier (UPS), Toulouse, France*
[5]*INSERM T3S, UMR-S 1124, Université Paris Cité, Paris, France*
[6]*Public Health Department, Groupe Hospitalier Paris-Seine-Saint-Denis, Assistance Publique-Hôpitaux de Paris, Bobigny, France*
[7]*Nutritional Epidemiology Surveillance Team (ESEN), Santé Publique France, The French Public Health Agency, Bobigny, France*
[8]*Microbiome-Host Interactions, Institut Pasteur, Université Paris Cité, INSERM U1306, Paris, France*
[9]*Diabetology, Endocrinology and Nutrition Department, Avicenne Hospital, Assistance Publique-Hôpitaux de Paris, Bobigny, France*

Corresponding authors: Sanam Shah, sanam.shah@eren.smbh.univ-paris13.fr, and Mathilde Touvier, m.touvier@eren.smbh.univ-paris13.fr

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OBJECTIVE

To investigate potential association between exposure to food coloring additives and type 2 diabetes incidence.

RESEARCH DESIGN AND METHODS

The study followed 108,723 participants (79.2% female, mean age 42.5 [SD 14.6] years) from the French NutriNet-Santé cohort (2009–2023). Dietary data were assessed using repeated 24-h dietary records, including industrial food brands. Cumulative time-dependent exposure to food additives was evaluated through multiple composition databases and ad hoc laboratory assays in food matrices. Associations between exposures to food coloring additives (sex-specific tertiles if proportion of exposed participants was more than two-thirds, or nonexposed/lower/higher exposed based on sex-specific median otherwise) and type 2 diabetes incidence were assessed using multivariable Cox proportional hazards models.

RESULTS

There were 1,131 incident type 2 diabetes cases diagnosed (median follow-up, 8.05 years). After false discovery rate correction, intakes of the following colors were associated with higher type 2 diabetes incidence: total food coloring additives (hazard ratio [HR]$_{\text{higher vs. non/lower consumers}}$ 1.38 [95% CI 1.17–1.63], *P* = 0.0002), total caramel (1.43 [1.21–1.67], *P* = 0.0002), plain caramel (1.46 [1.26–1.70], *P* = 0.0002), sulfite ammonia caramel (1.30 [1.07–1.59], *P* = 0.007), total carotene (1.27 [1.08–1.48], *P* = 0.007), carotenoids (1.39 [1.19–1.62], *P* = 0.0002), β-carotene (1.44 [1.23–1.68], *P* = 0.0002), paprika-capsanthin-capsorubin (1.26 [1.08–1.46], *P* = 0.004), lutein (1.20 [1.02–1.40], *P* = 0.0002), curcumin (1.49 [1.29–1.73], *P* = 0.0002), cochineal-carminic acid-carmines (1.27 [1.10–1.48], *P* = 0.003), and anthocyanins (1.40 [1.17–1.68], *P* = 0.0002).

CONCLUSIONS

Several positive associations were observed between exposure to natural and synthetic food coloring additives and type 2 diabetes incidence. Further studies are needed to gain insights into underlying mechanisms, and if confirmed, call for reevaluation of food coloring additives to protect consumer health.

Type 2 diabetes is a leading global public health challenge accounting for >95% of diabetes cases. Lifestyle-related factors contribute to its growing prevalence (1), in

particular, ultraprocessed foods (UPFs), comprising >60% of daily energy intake in some countries, have been associated with increased type 2 diabetes incidence independent of energy intake and adiposity (2,3).

Food coloring additives, key markers of UPFs, are introduced to enhance or restore the color of food following exposure to light, temperature changes, and moisture, and to increase consumer appeal. Certain coloring additives showed adverse health effects in preclinical studies and short-term human trials, particularly azoic dyes (allura red, tartrazine, and sunset yellow) (4,5). These colors, along with carmoisine, ponceau 4R, and quinoline yellow, the "Southampton Six" colors, have been implicated in childhood behavioral effects (6). The European Food Safety Authority (EFSA) has lowered permitted levels for quinolone yellow, sunset yellow, and ponceau 4R (5), while titanium dioxide has been banned for use in food in the European Union. Furthermore, by the end of 2026, a number of synthetic coloring additives will be phased out from the U.S. market. In Europe, although some coloring additives, such as caramel colors are widespread, most synthetic additives are used sparingly, while natural colors are more frequently used. Public perception, accentuated by marketing that often uses this argument, tends to associate substances of natural origin with lower health risks, but the natural nature of a substance does not inherently guarantee its safety (7), as evidenced by numerous naturally occurring toxic substances. However, scientific data on the health impacts of natural food colors are lacking.

To date, evidence on metabolic effects of coloring additives is limited. Research suggests that coloring additives may alter key molecular pathways involved in insulin signaling and inflammation. For instance, in vivo studies have linked certain synthetic colors to elevated blood glucose levels, hepatic and gastrointestinal tissue damage, and potential alterations in gut microbiota composition (8–12). However, despite the rapid and manifold increase in use of coloring additives (>139,000 food products listed in Open Food Facts), no epidemiological study has quantified dietary exposures to these additives or investigated their association with diabetes incidence. This gap may be explained by limited detail on specific industrial food products consumed in previous cohort studies lacking brand-specific data and by variability in additive content between industrial food products and between countries. In this regard, the NutriNet-Santé cohort provides a wealth of information with extensive brand-specific dietary data collected through validated repeated 24-h dietary records (24HDRs) since 2009. Therefore, we aimed to investigate, for the first time, associations between real-life chronic exposure to food coloring additives, either natural or artificial, and incidence of type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study Population

The NutriNet-Santé e-cohort is a prospective French study initiated in 2009 to investigate the association between nutrition and health (13). Participants aged ≥15 are recruited through extensive multimedia campaigns and invited to enroll in the study via a dedicated web-based platform (https://etudenutrinet-sante.fr/). Upon enrollment, participants are invited to provide detailed information by completing self-administered questionnaires covering sociodemographic and lifestyle information (14), health status, dietary intake (15–17), anthropometric data (18,19), and physical activity level (20). Participants are then invited to update these data regularly via follow-up questionnaires.

Eligible participants (n = 134,076) were those who had completed two or more 24HDRs during the first 2 years in the cohort. We excluded energy overreporters (n = 54) and underreporters (n = 23,098) (21,22), and all prevalent diabetes type 1 (n = 299) and type 2 cases (n = 1,902); therefore, the final study population included 108,723 participants (Supplementary Fig. 1).

Ethics Approval

The study is registered at https://clinicaltrials.gov/ct2/show/NCT03335644, conducted according to the Declaration of Helsinki guidelines, and approved by the French Institute for Health and Medical Research Institutional Review Board (IRB-INSERM) and the "Commission Nationale de l'Informatique et des Libertés" (CNIL no. 908450/no. 909216). Each participant provides an electronic informed consent form in the NutriNet-Santé cohort before enrollment.

Dietary Assessment

Upon registration and every 6 months thereafter, participants were invited to complete sequences of validated web-based 24HDRs (15–17). At each period, 24HDRs were randomly assigned to 3 nonconsecutive days over 2 weeks (2 weekdays and 1 weekend day). Dietary intakes in energy, fiber, and macro- and micronutrients were assessed by merging with the NutriNet-Santé food composition table. Details on dietary data collection and identification of under-/overenergy reports can be found in Supplementary Method 1.

Assessment of Food Coloring Additive Exposures

Assessment of food additive intakes in the NutriNet-Santé cohort through brand-specific data of the 24HDRs has been previously described (23). Details are provided in Supplementary Method 2. 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 across time. Each food item consumed and reported in a specific dietary record was matched against three databases to assess presence of any food additive: Observatoire de la qualité de l'alimentation (OQALI), Open Food Facts, and Mintel Global New Products Database (GNPD). Next, the dose of food additive ingested with each food item was estimated based on *1*) ad hoc laboratory assays quantifying additives in specific food items, *2*) doses in generic food categories provided by EFSA, or *3*) generic doses from Codex General Standard for Food Additives (GSFA). All coloring additives, defined as such by EFSA, GSFA or U.K. Food Standard Agency, with nonnull consumption, were accounted for in the calculation of total coloring additives and their classes Table 2.

Associations with type 2 diabetes incidence were investigated for coloring additives consumed by at least 10% of study population (to guarantee sufficient statistical power and avoid very low number of cases in exposure categories). These included individual coloring additives: curcumin (European [E] code E100), cochineal-carminic acid-carmines (E120), plain caramel (E150a), sulfite ammonia caramel (E150d), carotenoids without specification (E160), β-carotene (E160a), annatto-bixin-norbixin (E160b), paprika-capsanthin-capsorubin (E160c), lutein (E161b), and anthocyanins (E163). Coloring additives

categories included total caramel (E150 [caramel colors without specification], E150a, E150b [caustic sulfite caramel], E150c [ammonia caramel], and E150d), total carotenes (E160, E160a, E160b, E160c, E160d [lycopene], E160e [β-apo-8′-carotenal], and E161b), and total food coloring additives (E100, E101 [riboflavin], E102 [tartrazine], E104 [quinoline yellow], E110 [sunset yellow FCF], E120, E122 [carmoisine], E123 [amaranth], E124 [ponceau 4R], E127 [erythrosine], E129 [allura red AC], E132 [indigo carmine], E133 [brilliant blue FCF], E140 [chlorophylls], E141 [copper complexes of chlorophylls], E150, E150a, E150b, E150c, E150d, E151 [brilliant black BN], E155 [brown HT], E160, E160a, E160b, E160c, E160d, E160e, E161b, E162 [beetroot red], E163, E170 [calcium carbonate], E171 [titanium dioxide], E172 [iron oxides and hydroxides], E131 [patent blue V], E153 [vegetable carbon], and E175 [gold]).

Incident Type 2 Diabetes Ascertainment

Type 2 diabetes was evaluated using a multisource approach. During the follow-up period, participants could report health events, medical treatments, and examinations through biannual health questionnaires or at any time via the health interface of their personal account. Additionally, the NutriNet-Santé cohort is connected to the national health insurance database to gather further details on medical treatments and consultations. The cohort is also linked to the French national mortality registry (Centre d'épidémiologie sur les causes médicales de décès [CépiDC]) to track the occurrence and causes of death. Detailed information can be found in Supplementary Method 3.

Statistical Analyses

Baseline participants' characteristics are described as mean (SD) for quantitative variables and *n* (%) for qualitative variables overall and per sex-specific tertiles of total food coloring additive exposure. Intakes of coloring additives during first 2 years of follow-up were reported as mean (SD), 25th, 50th (median) and 75th percentiles, among the whole population and in consumers of each specific additive (mg/d and per kg of body wt). A correlation matrix was generated to visualize Spearman correlations between intakes of individual coloring additives. For each studied additive or group of additives, participants were categorized into low, medium, and high consumers, defined as sex-specific tertiles if the additive was consumed by at least two-thirds of participants, or else as nonconsumers, and lower or higher consumers separated by the sex-specific median (cutoffs provided in Supplementary Table 1).

The associations between exposure to coloring additives coded as cumulative time-dependent variables and type 2 diabetes incidence were investigated using multivariable Cox proportional hazard models with age as time scale. Hazard ratios (HR) and 95% CI were computed. Participants contributed person-time to the models from their age at enrollment in the cohort until their age at the date of diabetes diagnosis, death, last contact, or 31 December 2023, 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 a weighted average of the most recent 2-year period and prior periods, thereby using all available dietary data (details in Supplementary Method 4).

Proportional hazard assumption was tested using Schoenfeld residuals. Restricted cubic splines were computed with three knots at 27.5th, 72.5th, and 95th percentiles of food coloring additive distribution to explore potential dose-response relationships. The covariates were determined using a directed acyclic graph informed by prior studies on their potential association with exposure and/or outcome (Supplementary Fig. 2). The first model was adjusted for age (time-scale), sex, number of dietary records (continuous), BMI (continuous, kg/m^2), physical activity (categorical International Physical Activity Questionnaire [IPAQ] variable: low, moderate, or high), smoking status (never, former, or current smoker), number of cigarettes smoked in pack-years (continuous), educational level (less than high school, $\leq$3 years after high school, or >3 years after high school), family history of diabetes (yes or no), previous metabolic diseases (cardiovascular disease, dyslipidemia, or hypertension; yes or no), and mutually adjusted for total food coloring additive intake excluding the one studied.

The second model was additionally adjusted for time-dependent daily intakes of energy without alcohol (continuous, kcal/d), alcohol (continuous, g/d), saturated fats (continuous, g/d), sodium (continuous, mg/d), fiber (continuous, g/d), sugars (continuous, g/d), fruit and vegetables (continuous, g/day), dairy products (continuous, g/day), and processed meat (continuous, g/day). Specific coloring additives were further adjusted for nutrient intakes: total carotene, E160, E160a, E160b, and E161b were adjusted for dietary β-carotene; E160c was adjusted for dietary capsorubin, capsanthin, and β-carotene; and E100 was adjusted for curcumin.

The main model (model 3) was further adjusted for UPFs (continuous, percentage of weight of total food/day in g). *P* values with and without correction for multiple testing by the false discovery rate (FDR) were computed. Sensitivity analyses with additional adjustments based on model 3 are detailed in Supplementary Method 4. To test whether coloring additives and type 2 diabetes associations differed by sex, BMI, amount of UPFs, sugar-sweetened beverages, smoking, and physical activity, we used interaction terms and likelihood ratio tests. Additional sensitivity and exploratory analyses are detailed in Supplementary Method 4. Missing values for covariates were handled using multiple imputation via additive regression, bootstrapping, and predictive mean matching (n = 20) in the Harrell miscellaneous (Hmisc) R package (Supplementary Method 5).

All tests were two-sided, and $P < 0.05$ was considered statistically significant. All statistical analyses were conducted in R 4.5.1 software, except for restricted cubic spline, which was conducted in SAS 9.4 software.

Data and Resource 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.

RESULTS

Descriptive Characteristics

Over a median follow-up of 8.05 years (841,296.4 person-years), 1,131 incident type 2 diabetes cases were detected. Table 1 presents the baseline characteristics of the study participants, 79.2% of whom were women. The participants had a mean age at baseline of 42.5 years (SD 14.6). On average, they completed 18 (SD 17) 24HDRs during follow-up. The mean number of dietary records per 2-year study period is provided in Supplementary Table 2. Compared with low consumers, higher consumers of total food coloring additives were younger, had higher educational level, more likely to be current smokers, less physically active, more likely to have higher energy intake, and consume more UPFs but less alcohol.

A total of 87.0% of participants had a nonnull intake of coloring additives in the first 2 years of follow-up (Table 2). Among consumers, the mean (SD) intake of total food coloring additives were 213.5 (564.3) mg/day compared with 185.8 (531.3) mg/day in the total population (186.4 [524.5] mg/day in women and 183.6 [556.6] mg/day in men). Supplementary Table 3 shows the daily food coloring additive exposures among consumers by follow-up periods. Overall, participants did not exceed the EFSA Acceptable Daily Intakes (ADI) (Supplementary Table 4), except for lutein, for which three participants exceeded the ADI (i.e., 1 mg/kg body wt/day), with a mean intake of 0.02 (SD 0.05) mg/kg body wt/day (25th–75th

Table 1—Baseline characteristics of participants according to cumulative exposure to total food coloring additive, NutriNet-Santé cohort, 2009–2023 (*N*= 108,723)

Characteristic	Overall (*N* = 108,723)	Sex-specific tertiles of total food coloring additives			*P* value[a]
		Tertile 1 (*n* = 36,241)	Tertile 2 (*n* = 36,241)	Tertile 3 (*n* = 36,241)	
Age (years)	42.5 (14.6)	44.2 (14.8)	44.6 (14.5)	38.5 (13.6)	<0.001
Women, *n* (%)	86,085 (79.2)	28,695 (79.2)	28,695 (79.2)	28,695 (79.2)	NA
BMI (kg/m^2)[d]	23.6 (4.4)	23.3 (4.2)	23.6 (4.2)	23.8 (4.6)	<0.001
Family history of diabetes[b,d], *n* (%)	17,003.0 (15.7)	5,609.0 (15.5)	5,804.0 (16.1)	5,590.0 (15.5)	0.052
Educational level[d], *n* (%)					<0.001
Less than a high school degree	19,011.0 (17.7)	6,803.0 (19.0)	6,687.0 (18.6)	5,521.0 (15.3)	
≤3 years after high school	52,775.0 (49.0)	17,190.0 (48.0)	17,343.0 (48.4)	18,242.0 (50.7)	
>3 years after high school	35,894.0 (33.3)	11,835.0 (33.0)	11,838.0 (33.0)	12,221.0 (34.0)	
Smoking status[d], *n* (%)					<0.001
Never	54,660.0 (50.4)	17,751.0 (49.2)	18,614.0 (51.5)	18,295.0 (50.6)	
Former smoker	35,231.0 (32.5)	12,252.0 (34.0)	12,233.0 (33.8)	10,746.0 (29.7)	
Current smoker	18,509.0 (17.1)	6,057.0 (16.8)	5,302.0 (14.7)	7,150.0 (19.8)	
Smoking pack years[d]	4.82 (10.7)	5.26 (11.4)	4.85 (10.6)	4.35 (10.0)	<0.001
IPAQ physical activity level,[d] *n* (%)					<0.001
Low	22,544.0 (24.0)	7,044.0 (22.4)	7,316.0 (23.2)	8,184.0 (26.4)	
Moderate	40,448.0 (43.1)	13,366.0 (42.6)	13,544.0 (43.0)	13,538.0 (43.6)	
High	30,952.0 (32.9)	10,990.0 (35.0)	10,639.0 (33.8)	9,323.0 (30.0)	
Energy intake without alcohol (kcal/day)[c]	1,853.5 (456.5)	1,786.5 (454.8)	1,865.6 (433.6)	1,908.4 (471.8)	<0.001
Alcohol intake (g/day)[c]	7.7 (11.8)	7.6 (12.1)	8.3 (11.8)	7.3 (11.4)	<0.001
Saturated fat (g/day)[c]	33.2 (12.1)	31.2 (12.2)	33.9 (11.6)	34.6 (12.4)	<0.001
Sodium (mg/day)[c]	2,721.9 (890.6)	2,621.3 (913.6)	2,767.1 (854.1)	2,777.3 (894.6)	<0.001
Fiber (g/day)[c]	20.1 (10.0)	21.2 (11.6)	20.3 (9.3)	18.9 (8.8)	<0.001
Sugar (g/day)[c]	93.2 (33.8)	87.5 (33.8)	93.2 (31.3)	99.0 (35.0)	<0.001
Fruit and vegetables (g/day)[c]	465.8 (232.6)	491.4 (257.1)	475.2 (212.5)	431.0 (221.7)	<0.001
Dairy product (g/day)[c]	158.5 (147.6)	149.4 (149.9)	160.7 (143.1)	165.5 (149.1)	<0.001
Processed meat (g/day)[c]	34.5 (31.9)	30.1 (32.0)	35.9 (30.6)	37.6 (32.6)	<0.001
Ultra-processed food (% of weight intake)[c]	17.3 (9.9)	14.8 (8.6)	15.7 (8.0)	21.6 (11.3)	<0.001
Total food coloring additive intake (mg/day)	185.8 (531.3)	0.1 (0.2)	9.9 (9.0)	547.4 (806.6)	<0.001

Data are mean (SD), unless indicated otherwise as n (%). NA, not applicable. [a]Kruskal-Wallis rank sum test for continuous variables; Pearson χ^2 test for categorical variables.[b]Family history of diabetes in first-degree relatives. [c]All dietary intake data in this table were calculated as the mean daily intake across all records during the first 4 years of participation in the study (mean number of 24-h records per person during this period, 6 [SD 3]). [d]Missing values: BMI, *n* = 3,001 in tertiles 1, 2, and 3 (1,032; 922; 1,047); family history of diabetes, *n* = 333 (162; 109; 62); education level, *n* = 1,043 (413; 373; 257); socioprofessional categories, *n* = 410 (209; 129; 72); monthly household income per consumption unit, *n* = 13,183 (4,721, 4,155, 4,307); smoking status, *n* = 323 (181; 92; 50); smoking pack years, *n* = 329 (182, 92, 55); IPAQ physical activity level, *n* = 14,779 (4,841; 4,742; 5,196).

Table 2—Daily food coloring additive exposures among study participants from the NutriNet-Santé cohort, 2009–2023 (*N* = 108,723)[a,b]

	All participants, mg/day					Consumers, mg/day						Consumers, mg/day/kg of body weight				
Additive	Mean	SD	P25	P50	P75	Mean	SD	P25	P50	P75	Proportion of consumers (%)	Mean	SD	P25	P50	P75
Curcumin (E100)	0.61	2.28	0.00	0.00	0.00	2.43	4.05	0.03	0.69	3.35	25.05	0.04	0.06	0.00	0.01	0.05
Riboflavin (E101)	0.35	2.61	0.00	0.00	0.00	5.37	8.85	0.12	3.21	6.70	6.45	0.08	0.14	0.00	0.05	0.10
Tartrazine (E102)	0.03	0.35	0.00	0.00	0.00	0.90	1.69	0.10	0.28	1.05	3.35	0.01	0.03	0.00	0.00	0.02
Quinoline yellow (E104)	0.00	0.03	0.00	0.00	0.00	0.32	0.41	0.10	0.20	0.35	0.26	0.00	0.01	0.00	0.00	0.01
Sunset yellow FCF (E110)	0.00	0.06	0.00	0.00	0.00	0.13	0.46	0.02	0.04	0.09	1.57	0.00	0.01	0.00	0.00	0.00
Cochineal- carminic acid- carmines (E120)	0.13	0.65	0.00	0.00	0.02	0.49	1.17	0.08	0.21	0.49	27.19	0.01	0.02	0.00	0.00	0.01
Carmoisine (E122)	0.00	0.00	0.00	0.00	0.00	0.42	0.44	0.06	0.30	0.75	0.01	0.01	0.01	0.00	0.00	0.01
Amaranth (E123)	0.00	0.00	0.00	0.00	0.00	0.18	0.15	0.13	0.18	0.23	0.00	0.00	0.00	0.00	0.00	0.00
Ponceau 4R (E124)	0.00	0.01	0.00	0.00	0.00	0.15	0.13	0.07	0.11	0.22	0.36	0.00	0.00	0.00	0.00	0.00
Erythrosine (E127)	0.02	0.44	0.00	0.00	0.00	3.43	4.24	1.04	2.34	4.52	0.65	0.05	0.07	0.02	0.03	0.07
Allura red AC (E129)	0.00	0.02	0.00	0.00	0.00	1.00	0.86	0.23	0.96	1.42	0.02	0.02	0.02	0.00	0.01	0.02
Patent blue V (E131)	0.01	0.29	0.00	0.00	0.00	0.34	1.57	0.01	0.04	0.14	3.39	0.01	0.03	0.00	0.00	0.00
Indigotine (E132)	0.00	0.11	0.00	0.00	0.00	0.74	2.52	0.11	0.26	0.71	0.18	0.01	0.05	0.00	0.00	0.01
Brilliant blue FCF (E133)	0.01	0.22	0.00	0.00	0.00	0.19	0.91	0.01	0.06	0.15	5.61	0.00	0.02	0.00	0.00	0.00
Copper complexes of chlorophylls (E141)	0.13	1.55	0.00	0.00	0.00	2.48	6.32	0.14	0.34	1.43	5.27	0.04	0.10	0.00	0.01	0.02
Caramel colors without specification (E150)	2.37	29.24	0.00	0.00	0.00	118.67	170.48	32.44	69.16	144.68	1.99	1.84	2.60	0.49	1.07	2.27
Plain caramel (E150a)	5.20	22.37	0.00	0.00	0.00	22.39	42.06	1.53	6.58	26.79	23.24	0.35	0.66	0.02	0.10	0.41
Caustic sulfite caramel (E150b)	0.09	1.82	0.00	0.00	0.00	8.00	15.60	1.30	2.44	6.51	1.09	0.12	0.24	0.02	0.04	0.10
Ammonia caramel (E150c)	5.27	65.03	0.00	0.00	0.00	99.97	266.06	12.06	26.79	63.09	5.27	1.57	4.38	0.19	0.41	0.99
Sulfite ammonia caramel (E150d)	145.58	477.11	0.00	0.00	7.14	556.37	800.89	89.23	291.70	683.57	26.17	8.49	12.32	1.37	4.49	10.35
Brilliant Black BN (E151)	0.00	0.01	0.00	0.00	0.00	0.47	0.39	0.17	0.27	0.59	0.01	0.01	0.01	0.00	0.01	0.01
Brown HT (E155)	0.00	0.01	0.00	0.00	0.00	1.48	0.90	0.95	1.23	1.87	0.01	0.03	0.02	0.01	0.02	0.04
Carotenoids without specification (E160)	0.21	0.86	0.00	0.00	0.02	0.57	1.35	0.02	0.05	0.62	37.00	0.01	0.02	0.00	0.00	0.01
β-Carotene (E160a)	1.38	8.55	0.00	0.00	0.03	3.24	12.85	0.02	0.05	0.21	42.67	0.05	0.20	0.00	0.00	0.00
Annatto- bixin- norbixin (E160b)	0.03	0.12	0.00	0.00	0.00	0.19	0.24	0.04	0.11	0.25	17.00	0.00	0.00	0.00	0.00	0.00
Paprika extract- capsanthin- capsorubin (E160c)	0.21	0.49	0.00	0.00	0.20	0.44	0.64	0.08	0.21	0.54	47.94	0.01	0.01	0.00	0.00	0.01
Lycopene (E160d)	0.00	0.01	0.00	0.00	0.00	0.44	0.32	0.24	0.37	0.54	0.01	0.01	0.01	0.00	0.01	0.01

Continued on p. 1072

Table 2—Continued

Additive	All participants, mg/day					Consumers, mg/day					Proportion of consumers (%)	Consumers, mg/day/kg of body weight				
	Mean	SD	P25	P50	P75	Mean	SD	P25	P50	P75		Mean	SD	P25	P50	P75
β-apo-8′-carotenal (E160e)	0.05	0.71	0.00	0.00	0.00	2.35	4.38	0.31	0.89	2.51	2.05	0.04	0.07	0.01	0.02	0.04
Lutein (E161b)	0.35	1.88	0.00	0.00	0.00	1.21	3.36	0.00	0.00	0.60	28.50	0.02	0.05	0.00	0.00	0.01
Beetroot red (E162)	0.47	2.59	0.00	0.00	0.00	5.21	7.07	1.19	2.86	6.43	9.02	0.08	0.11	0.02	0.04	0.10
Anthocyanins (E163)	1.35	7.54	0.00	0.00	0.00	10.10	18.37	2.57	5.36	10.37	13.37	0.16	0.30	0.04	0.08	0.16
Calcium carbonate (E170)	21.29	207.84	0.00	0.00	0.00	590.24	928.52	50.00	266.67	750.00	3.61	9.47	15.02	0.85	4.25	11.97
Titanium dioxide (E171)	0.54	4.48	0.00	0.00	0.00	7.69	15.22	1.53	3.43	7.68	6.99	0.12	0.25	0.02	0.05	0.12
Iron oxides & hydroxides (E172)	0.14	2.54	0.00	0.00	0.00	8.16	17.74	1.18	3.73	9.26	1.70	0.12	0.28	0.02	0.06	0.14
Total azoic dyes	0.03	0.37	0.00	0.00	0.00	0.86	1.67	0.09	0.25	0.92	3.93	0.01	0.03	0.00	0.00	0.01
Total caramel	158.50	484.42	0.00	0.00	56.59	349.31	671.20	12.62	85.29	399.48	45.38	5.33	10.32	0.20	1.30	6.10
Total carotene	2.23	8.99	0.01	0.18	1.08	2.87	10.11	0.09	0.39	1.70	77.73	0.04	0.16	0.00	0.01	0.03
Total nanoparticle-based colors	0.68	5.55	0.00	0.00	0.00	8.27	17.72	1.61	3.84	8.38	8.18	0.13	0.29	0.03	0.06	0.13
Total food coloring additives	185.81	531.31	0.20	6.71	90.06	213.47	564.27	0.95	12.93	142.26	87.04	3.28	8.74	0.01	0.20	2.17

P25, 25th percentile; P50, 50th percentile; P75, 75th percentile. [a]Classes of food coloring additives included the following substances: total caramel (E150, E150a, E150b, E150c, and E150d), total carotene (E160, E160a, E160b, E160c, E160d, E160e, E161b), total azoic dyes (E102, E104, E110, E122, E123, E124, E129, and E155), total nanoparticle-based color additives (E171 and E172), and total food coloring additives (E100, E101, E102, E104, E110, E120, E122, E123, E124, E127, E129, E132, E133, E140, E141, E150, E150a, E150b, E150c, E150d, E151, E155, E160, E160a, E160b, E160c, E160d, E160e, E161b, E162, E163, E170, E171, E172, E131, E153, E175). [b]*Spirulina* extract (E134), copper complexes of chlorophylls (E140), fast green FCF(E143), vegetable carbon (E153), canthaxanthin (E161g), gold (E175), tannic acid (E181), jagua (E183), and calcium sulfate (E516) are allowed in the European Union but were not consumed by any participants.

percentiles 0.00002–0.10500). These participants had on average higher intake of milk, yogurt, milk-based desserts, biscuits/cookies, sweet products, and sauces, which could explain higher observed lutein exposure.

Of the total number of coloring additives detected in the study population, most were synthetic colors (20 of 34 colors; i.e., 58.8% vs. 20.6% each for natural colors and ambivalent). However, apart from caramel colors, synthetic colors were consumed only by a small or very small proportion of the population (Table 2), as opposed to colors of natural origin. By proportion of consumers, the main coloring additives were paprika, capsanthin, capsorubin (47.9%), β-carotene (42.7%), carotenoids without specification (37.0%), lutein (28.5%), cochineal-carminic acid-carmines (27.2%), sulfite ammonia caramel (26.2%), curcumin (25.1%), plain caramel (23.2%), annatto-bixin-norbixin (17.0%), and anthocyanins (13.4%). No strong correlation between intakes of coloring additives was identified (Supplementary Fig. 3). Coloring additives consumed by <10% of the study population are listed in a footnote to Fig. 2. Furthermore, nine coloring additives are allowed in the European market but were not consumed by participants in this study (seldom used in the French market). Their list is provided in footnote to Table 2.

The contribution of food groups to food coloring additive intakes is presented in Fig. 1 and Supplementary Table 5. Unsweetened (49.6%) and sweetened drinks (32.2%) were the main contributors to total food coloring exposure. Key sources varied, such as drinks for caramels, confectionery for carotenoids and anthocyanins, dairy for curcumin and lutein, and fish/seafood for paprika-derived colors. For compounds that also occur naturally in the diet, the relative contribution from food additives were 0.07% for β-carotene, 22.0% for capsanthin, 33.0% for curcumin, and 39.6% for capsorubin.

Associations Between Food Coloring Additive Intakes and Type 2 Diabetes Incidence

Schoenfeld residuals did not refute the proportional hazard assumption (Supplementary Fig. 4). Restricted cubic spline plots are presented in Supplementary Fig. 5. No departure from linearity was observed (*P* values for nonlinearity ≥0.05) for total

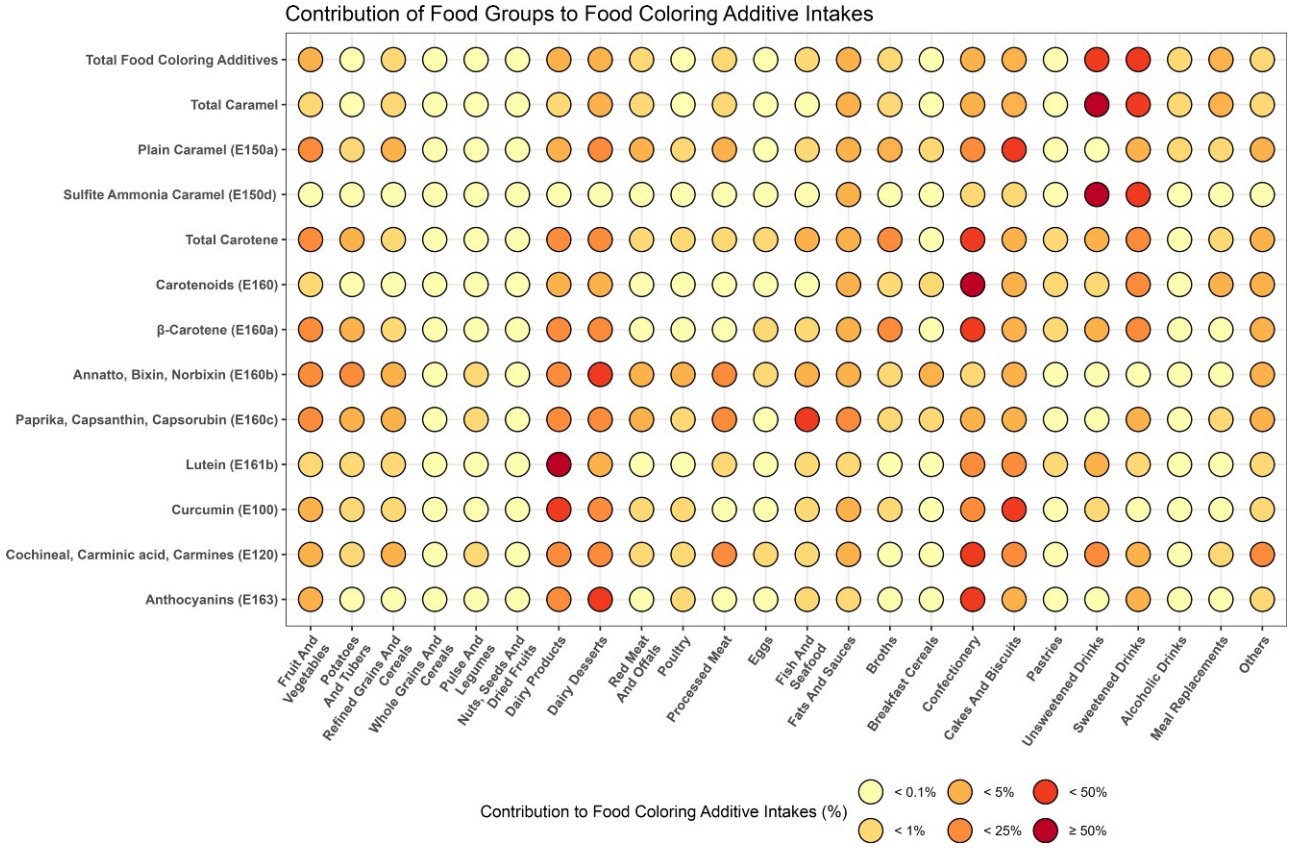

Figure 1—Dietary sources of food coloring additive intakes among study participants from the NutriNet-Santé cohort, 2009–2023 (N = 108,723).[a,b,c] [a]For food additives consumed by at least 10% of the study population. These included individual food colors curcumin (E100), cochineal-carminic acid-carmines (E120), plain caramel (E150a), sulfite ammonia caramel (E150d), carotenoids without specification (E160), β-carotene (E160a), annatto-bixin-norbixin (E160b), paprika-capsanthin-capsorubin (E160c), lutein (E161b), and anthocyanins (E163). Food color categories included total caramel (E150, E150a, E150b, E150c, and E150d), total carotene (E160, E160a, E160b, E160c, E161b, E160d, and E160e), and total food coloring additives (E100, E101, E102, E104, E110, E120, E122, E123, E124, E127, E129, E132, E133, E140, E141, E150, E150a, E150b, E150c, E150d, E155, E160, E160a, E160b, E160c, E160d, E160e, E161b, E162, E163, E170, E171, E172, E131, E153, and E175). Food coloring additives consumed by <10% of the study population were included in total and category-specific intakes but could not be evaluated individually. These included riboflavin (E101), tartrazine (E102), quinoline yellow (E104), sunset yellow FCF (E110), carmoisine (E122), amaranth (E123), ponceau 4R (E124), erythrosine (E127), allura red AC (E129), patent blue V (E131), indigotine (E132), brilliant blue FCF (E133), copper complexes of chlorophylls (E141), caramel subclasses (E150b, E150c), brilliant black BN (E151), brown HT (E155), lycopene (E160d), β-apo-8′-carotenal (E160e), beetroot red (E162), calcium carbonate (E170), titanium dioxide (E171), iron oxides and hydroxides (E172), azoic dyes (E102, E104, E110, E122, E123, E124, E129, E155), and total nanoparticle-based colors (E171, E172). [b]Detailed percentages are presented in Supplementary Table 5. [c]The "Others" food group includes food items such as herbs and spices, sugar-free sweets and chewing gums, unprepared powders (e.g., instant coffee) and condiments (e.g., mustard, hot pepper sauce, or wasabi).

caramel, sulfite ammonia caramel, carotenoids, β-carotene, annatto-bixin-norbixin, paprika-capsanthin-capsorubin, and curcumin, cochineal-carminic acid-carmines, and in this case, P values for trend are provided in Fig. 2. For some associations, the dose-response curve suggested a plateau effect (P values for nonlinearity <0.05), for total food coloring additives, plain caramel, total carotene, lutein, and anthocyanins. In these cases, overall likelihood ratio P values are presented. Both P trends and overall P values are provided for all tested additives in Supplementary Table 6.

Associations of food coloring additive exposure with type 2 diabetes incidence are presented in Fig. 2 and Supplementary Table 6. Following FDR correction, in the fully-adjusted model (model 3), intakes of following coloring additives were associated with higher type 2 diabetes incidence: total food coloring additives (hazard ratio $[HR]_{higher\ vs.\ non/lower\ consumers}$ 1.38 [(95% CI 1.17–1.63], P = 0.0002), total caramel (1.43 [1.21–1.67], P = 0.0002), plain caramel (1.46 [1.26–1.70], P = 0.0002), sulfite ammonia caramel (1.30 [1.07–1.59], P = 0.007), total carotene (1.27 [1.08–1.48], P = 0.007), carotenoids (1.39 [1.19–1.62], P = 0.0002), β-carotene (1.44 [1.23–1.68], P = 0.0002), paprika-capsanthin-capsorubin (1.26 [1.08–1.46], P = 0.004), lutein (1.20 [1.02–1.40], P = 0.0002), curcumin (1.49 [1.29–1.73], P = 0.0002), cochineal-carminic acid-carmines (1.27 [1.10–1.48], P = 0.003), and anthocyanins (1.40 [1.17–1.68], P = 0.0002). These results were similar across all sensitivity analyses testing further adjustments (Supplementary Table 6).

We found no evidence of interaction between food coloring additive intakes and sex, BMI, amount of UPFs, sugar-sweetened beverages, smoking, or physical activity for type 2 diabetes incidence (all interaction FDR P value > 0.05). Naturally occurring β-carotene ($HR_{higher\ vs.\ non/lower\ consumers}$ 1.02 [95% CI 0.85–1.22], P_{trend} = 0.85), curcumin (0.95 [0.79–1.15], P_{trend} = 0.60), capsanthin (0.99 [0.85–1.15], P_{trend} = 0.94), and capsorubin (0.99 [0.85–1.15], P_{trend} = 0.94) were not

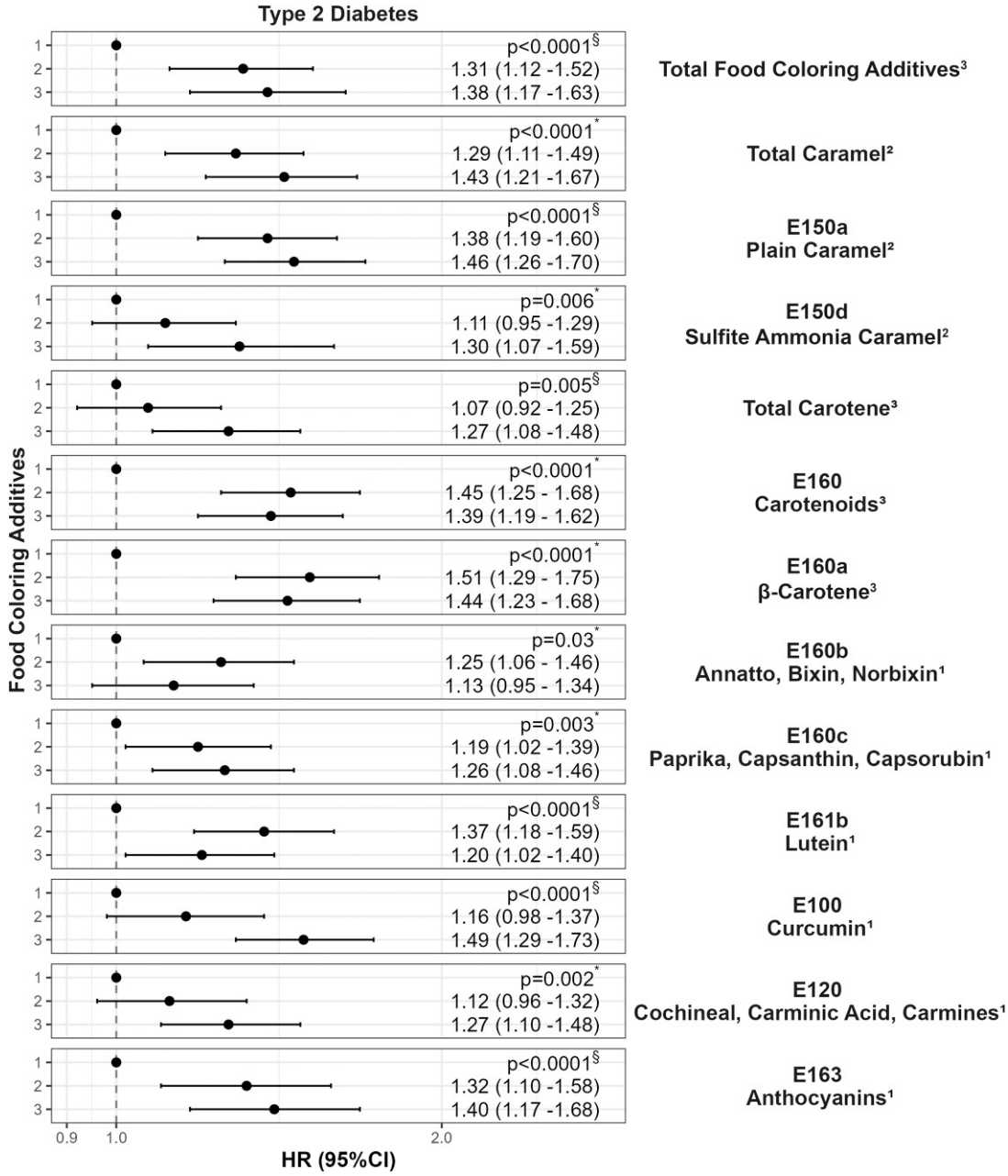

Figure 2—Associations between exposure to food coloring additives and type 2 diabetes incidence among study participants from the NutriNet-Santé cohort, 2009–2023 (n = 108,723).[a,b,c,d] [1]Natural; [2]Artificial; [3]Ambivalent (natural or artificial). [a]Multivariable Cox proportional hazard models (model 3) adjusted for age (time-scale), sex, number of dietary records, baseline BMI (continuous, kg/m^2), physical activity (categorical IPAQ variable: high, moderate, or low), smoking status (never, former, or current smoker), number of smoked cigarettes in pack-years (continuous), educational level (less than high school, ≤3 years after high school, or >3 years after high school), family history of diabetes (yes or no), previous metabolic diseases (yes or no), time-dependent daily intakes of energy without alcohol (continuous, kcal/d), alcohol (continuous, g/day), saturated fats (continuous, g/d), sodium (continuous, mg/d), fiber (continuous, g/d), sugars (continuous, g/d), fruit and vegetables (continuous, g/day), dairy products (continuous, g/day), processed meat (continuous, g/day), UPF (continuous, percentage weight of total food/day in g), and mutually adjusted for total food coloring additive intake excluding the one studied. Specific food coloring additive models were further adjusted for natural sources: total carotene, E160, E160a, E160b, and E161b were adjusted for dietary β-carotene; E160c was adjusted for dietary capsorubin, capsanthin, and β-carotene; and E100 was adjusted for curcumin. [b]The three food coloring additive categories were defined as follows: sex-specific tertiles for total food coloring additives and total carotene and otherwise (if less than two-thirds of consumers): 1/nonconsumers, 2/lower, and 3/higher consumers, the latter two being separated by the sex-specific median. Cutoffs were recalculated for each follow-up period and are available in Supplementary Table 1. [c]Associations with diabetes risk were investigated for food coloring additives consumed by at least 10% of the study population. [d]When the log-linearity assumption was not rejected (P for nonlinearity ≥0.05 assessed by restricted cubic splines models), the P for linear trend was retained (obtained by coding the exposure as an ordinal categorical variable 1, 2, 3). When the assumption of log-linearity was not met (P for nonlinearity <0.05), it was not adapted to calculate a P for linear trend; thus, the likelihood ratio overall P value was retained (obtained by coding the exposure as a nonordinal categorical variable and calculating likelihood ratio test between model with food additive exposure and model without food additive exposure). The P value displayed in the forest plot is *P for trend (when P for nonlinearity was ≥0.05) or the overall §P (when P for nonlinearity was <0.05). [e]Model 3 (main model): corresponding P values after FDR adjustment: total food coloring additives: 0.0002; total caramel: 0.0002; E150a: 0.0002; E150d: 0.007; total carotene: 0.007; E160: 0.0002; E160a: 0.0002; E160b: 0.03; E160c: 0.004; E161b: 0.0002; E100: 0.0002; E120: 0.003; and E163: 0.0002.

associated with increased type 2 diabetes incidence. In our study, UPF consumption was associated with a higher incidence of type 2 diabetes (HR 1.20 [95% CI 1.11–1.29], $P < 0.001$). Mediation analysis was conducted to assess the proportion of this association mediated by total food coloring additives. Indirect effect through total food coloring intake was statistically significant (pure natural indirect effect HR 1.02 [95% CI 1.00–1.03], $P = 0.03$). Overall, 8.6% (95% CI 1.6–18.5) of the association between UPF consumption and type 2 diabetes incidence was mediated by total food coloring additives ($P = 0.03$).

CONCLUSIONS

Our findings revealed associations between several food coloring additives and higher type 2 diabetes incidence for plain caramel, sulfite ammonia caramel, carotenoids, β-carotene, paprika-capsanthin-capsorubin, lutein, curcumin, cochineal extract-carminic acid-carmines, and anthocyanins, as well as total food coloring additives, total caramel, and total carotene, after adjustment for most known or potential risk factors or confounders.

To our knowledge, this is the first epidemiological study to investigate associations between coloring additives and incidence of type 2 diabetes in a large prospective setting. The qualitative and quantitative exposures to coloring additives were assessed for the first time in the NutriNet-Santé cohort by considering different commercial brands of products, which is necessary to identify specific colors consumed by participants at the individual level, given the huge variability of food additives content in commercial products. Thus, directly comparing our findings with previous epidemiological literature is not possible. For coloring additives with available EFSA data, lower mean intakes were observed in NutriNet-Santé versus EFSA estimates, reflecting differences in assessment dates, study populations, and methods—NutriNet-Santé used precise brand-specific repeated 24-h records versus generic items and limited data on which EFSA estimates are based.

Our findings for several coloring additives are supported by mechanistic evidence. In a recent in vitro study (24) from our consortium, cochineal-carminic acid-carmines—red colors used in confectionery, beverages, and processed meats—significantly increased DNA damage markers and reduced cell viability. Moreover, paprika-capsanthin-capsorubin—dark red color in sauces, snacks, and spice blends—caused decreased cell viability at higher levels. These findings suggest coloring additives may induce cellular stress in metabolically active tissues, providing biological plausibility for their role in chronic disease pathogenesis.

Total food coloring additives include azo dyes, synthetic compounds with diazotized amine combined with another amine or phenol characterized by azo linkages and aromatic amine precursors. Aromatic amines are biotransformed by azo reductases of intestinal microflora, with adverse health effects largely associated with this biotransformation (25). In rats, tartrazine—a yellow color used in bread, beverages, candies, snacks, dairy products, and sauces— increased serum glucose by 15.8% versus control individuals and elevated protein kinase C (9), which is linked to secondary insulin resistance via hyperinsulinemia and/or hyperglycemia (26).

Recent evidence shows that tartrazine induces mitochondrial dysfunction in zebrafish (27), notable given that type 2 diabetes has been linked to impaired mitochondrial genome integrity, mitochondrial RNA expression, and mitophagy in pancreatic β-cells (28). Evidence also links dysbiotic gut microbiota to metabolic disease, with certain food additives exacerbating this via increased intestinal permeability; sunset yellow, in particular, caused intestinal histopathological alterations in mice, compromising mucosal integrity (10).

Some coloring additives may have potential obesogenic effects by disrupting cellular redox balances critical for energy metabolism (29). Certain colors, notably erythrosine—red color used in candies, bakery products, popsicles, and beverages— and tartrazine, show endocrine-disrupting effects in in vivo studies (30). These effects may have potential to trigger insulin resistance and dysregulation of metabolic homeostasis, with implications in the pathogenesis of type 2 diabetes.

In our study, azo dyes—brilliant blue, tartrazine, sunset yellow, erythrosine, carmoisine, and allura red—counted toward total food coloring additives but could not be assessed individually due to low consumption reflecting limited use in the French market. Although numerous artificial food colors are permitted, many are rarely used as the food industry increasingly favors natural colors for functional and marketing purposes. Natural colors are often perceived by consumers as inherently safer, though this assumption is not consistently supported by toxicological evidence, and regulatory and public health attention (particularly in the U.S.) remains primarily focused on artificial colors. We observed significant associations between both natural and artificial food colors and incident type 2 diabetes, consistent with literature suggesting potential health risks across both classes (31).

Coloring additives may exert adverse metabolic effects via embedded chemical constituents. In vivo evidence shows 4-methylimidazole, a byproduct of caramel coloring (notably ammonia caramel and ammonia sulfite caramel) induces pancreatic β-cell hyperplasia and hyperinsulinemia, leading to enhanced glucose clearance and reduced fasting glucose and HbA_{1c} (32). This persistent overstimulation suggests potential for long-term β-cell exhaustion or insulin resistance, hallmarks of type 2 diabetes. Furthermore, chronic exposure to allura red AC—used in beverages, confectionery, breakfast cereals, and baked goods—in mice at doses present in diet produces colitis by promoting serotonin synthesis and inflammation via microbiota-dependent and -independent pathways (12). Nevertheless, many common coloring additives remain unexplored for metabolic effects, warranting further experimental and epidemiological research.

Isolating the effect of the studied food coloring additive from its food vector is challenging. Sensitivity analyses adjusting for UPF characteristics (overall UPF intake, other additives associated with diabetes, *trans* fats) and main food vectors (e.g., beverages for caramel colors) found attenuated (which may be due to overadjustment) but overall similar results, supporting a potential effect of the studied substance itself, that should be confirmed in future experimental studies. Extensive evidence shows substances exert different effects depending on the matrix in which they are ingested (33). Indeed, the food matrix properties—composition, structure, pH—affect absorption and metabolism by microbiota and host, and physical and

chemical interactions of substances with other elements of the environment play modulatory roles (34,35). For instance, while no association was detected for natural β-carotene in fruit and vegetables, high dose β-carotene isolated in dietary supplements, in interaction with tobacco/asbestos exposure, causally increases lung cancer risk (36). In vitro experiments showed that β-carotene upregulates inflammation-related genes under hyperglycemic conditions, with histone modifications suggesting epigenetic regulation (37). Similarly, while dietary fibers within complex natural fruit, vegetable, and legume matrices are protective, isolated purified fibers (e.g., inulin) exacerbated colitis in mice models (38). In recent studies, we observed associations of multiple food additive preservatives, but not natural food-born substances, with higher type 2 diabetes and cancer risks (39,40). Thus, experimental studies should explore differential health effects of chemicals by source and nature (additives vs. naturally occurring). Moreover, coloring additives–type 2 diabetes associations exhibited both linear and nonlinear patterns. Departures from linearity were observed for several colors, suggesting threshold or plateau effects. Further mechanistic and epidemiological investigations are needed to better understand these findings.

Our study's strengths include a large prospective population-based cohort with a long follow-up, regularly updated brand-specific 24HDRs linked to multiple food composition databases, ad hoc laboratory assays for the most frequently consumed additive-food pairs in food products, and dynamic matching accounting for reformulations.

There are also some limitations. Although we controlled for multiple confounding factors, unmeasured or residual confounding cannot be excluded. Measurement errors in dietary assessment and additive exposure might occur; however, records were validated against dietitian interviews and blood and urinary biomarkers for energy and nutrients. Nevertheless, specific exposure to coloring additives has not been validated against blood or urine assays because of absence of specific biomarkers for most additives. Coloring additives exposure was restricted to substances permitted in the European Union, and several coloring additives were not ingested by a sufficient number of participants for individual investigation. The cohort consists of a high proportion of women and health-conscious individuals; thus, caution is warranted when extrapolating findings. Last, although it may be inherently challenging to disentangle the independent effects of coloring additives from those of other food additives and food composition parameters, our results were stable when adjusting models for artificial sweeteners, nitrites, emulsifiers, preservatives, *trans* fats, energy, and nutrients.

In conclusion, our findings revealed positive associations between widely consumed food coloring additives and type 2 diabetes incidence. To our knowledge, this is the first study to provide insights into the role of coloring additives in the development of diabetes. Further long-term epidemiological and experimental research is needed to understand underlying mechanisms. If confirmed, these results call for a reevaluation of regulations governing the use of food coloring additives by the food and beverage industry to better protect public health.

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