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Ultraprocessed Food Consumption and Risk of Type 2 Diabetes Among Participants of the NutriNet-Santé Prospective Cohort

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IMPORTANCE Ultraprocessed foods (UPF) are widespread in Western diets. Their consumption has been associated in recent prospective studies with increased risks of all-cause mortality and chronic diseases such as cancer, cardiovascular diseases, hypertension, and dyslipidemia; however, data regarding diabetes are lacking.

OBJECTIVE To assess the associations between consumption of UPF and risk of type 2 diabetes (T2D).

DESIGN, SETTING, AND PARTICIPANTS In this population-based prospective cohort study, 104 707 participants aged 18 years or older from the French NutriNet-Santé cohort (2009-2019) were included. Dietary intake data were collected using repeated 24-hour dietary records (5.7 per participant on average), designed to register participants' usual consumption for more than 3500 different food items. These were categorized according to their degree of processing by the NOVA classification system.

MAIN OUTCOMES AND MEASURES Associations between UPF consumption and risk of T2D were assessed using cause-specific multivariable Cox proportional hazard models adjusted for known risk factors (sociodemographic, anthropometric, lifestyle, medical history, and nutritional factors).

RESULTS A total of 104 707 participants (21 800 [20.8%] men and 82 907 [79.2%] women) were included. Mean (SD) baseline age of participants was 42.7 (14.5) years. Absolute T2D rates in the lowest and highest UPF consumers were 113 and 166 per 100 000 person-years, respectively. Consumption of UPF was associated with a higher risk of T2D (multi-adjusted hazard ratio [HR] for an absolute increment of 10 in the percentage of UPF in the diet, 1.15; 95% CI, 1.06-1.25; median follow-up, 6.0 years; 582 252 person-years; 821 incident cases). These results remained statistically significant after adjustment for several markers of the nutritional quality of the diet, for other metabolic comorbidities (HR, 1.13; 95% CI, 1.03-1.23), and for weight change (HR, 1.13; 95% CI, 1.01-1.27). The absolute amount of UPF consumption (grams per day) was consistently associated with T2D risk, even when adjusting for unprocessed or minimally processed food intake (HR for a 100 g/d increase, 1.05; 95% CI, 1.02-1.08).

CONCLUSIONS AND RELEVANCE In this large observational prospective study, a higher proportion of UPF in the diet was associated with a higher risk of T2D. Even though these results need to be confirmed in other populations and settings, they provide evidence to support efforts by public health authorities to recommend limiting UPF consumption.

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Supplemental content

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Type 2 diabetes mellitus (T2D) is a major public health problem worldwide, affecting 425 million people in 2017, with an estimated projection of 629 million cases by 2045.[1] It is therefore urgent to control the disease by intervening on modifiable risk factors, including diet, physical activity, and weight. According to the 2018 Global Burden of Diseases, 34.9% of disability-adjusted life-years (DALYs) of diabetes are attributable to dietary factors,[2] such as high intakes of sugar and meat, and low intakes of vegetables, fruits, whole grains, legumes, nuts, and yogurt.[3,4]

Ultraprocessed foods (UPF) (ie, foods undergoing multiple physical, biological, and/or chemical processes, among which mostly of exclusive industrial use, and generally containing food additives[5]) are widespread worldwide and especially in Western diets,[6-11] representing between 25% and 60% of total daily energy.[12-24] During the past decade, scientists' interest in this topic has increased because several characteristics of these products, beyond a poorer nutritional quality,[12-20,25] are hypothesized to convey adverse health effects. Indeed, UPF usually go through several physical and chemical processes such as extruding, molding, prefrying, hydrogenation,[5] possibly leading to the production of new compounds with potential cardiometabolic disruption properties. They also typically contain food substances of no or rare culinary use (eg, some varieties of refined sugars, hydrogenated oils) and various types of cosmetic additives (eg, emulsifiers, sweeteners, thickening agents, colorants),[5] with cardiometabolic effects postulated for some.[26-28] Finally, UPF often have longer shelf-lives compared with non-UPF, particularly owing to the use of preservatives. Thus, they stay for long periods in their packaging, favoring potential migration of materials in contact with food, such as bisphenol A, associated with increased T2D risk in a recent meta-analysis of observational studies.[29]

Recently, our research group showed in the NutriNet-Santé cohort that UPF consumption (using the NOVA classification[30]) was associated with increased risks of cancer,[31] mortality,[32] depressive symptoms,[33] inflammatory bowel syndrome,[34] and cardiovascular diseases.[35] Other prospective studies also observed associations with mortality risk,[36] depression,[37] frailty,[38] dyslipidemia in children,[39] overweight/obesity,[40] and hypertension.[41] However, no such large-scale prospective study has been conducted regarding T2D. Our objective was to explore the associations between the consumption of UPF and the risk of T2D in a large cohort of French adults.

Key Points

Question Is consumption of ultraprocessed foods associated with the risk of developing type 2 diabetes (T2D)?

Findings This observational prospective study of 104 707 participants found that a higher proportion of ultraprocessed foods in the diet was associated with a higher risk of T2D.

Meaning Ultraprocessed food intake is a modifiable factor that may play a role in T2D etiology. Public health authorities in several countries recently started to recommend privileging unprocessed/minimally processed foods and limiting ultraprocessed food consumption.

Methods

Study Population and Data Collection

The NutriNet-Santé study is an ongoing web-based cohort launched in 2009 in France aiming to study the associations between nutrition and health.[42] It was approved by the relevant institutional review boards (Inserm and Cnil). Participants provided electronic informed consent. Adults aged 18 years or older are continuously recruited among the general population and followed using a dedicated web interface (etude-nutrinet-sante.fr). At baseline, participants completed a set of 5 questionnaires related to sociodemographic and lifestyle characteristics[43] (eg, sex, date of birth, educational level, smoking status), anthropometry[44,45] (eg, height, weight), physical activity (7-day International Physical Activity Questionnaire [IPAQ]),[46] health status, and dietary intake. In addition, fasting blood samples were collected for 19 772 participants.

Dietary Data and Food Processing Categorization

Participants were invited to complete a series of 3 nonconsecutive validated web-based 24-hour dietary records at baseline and every 6 months (to vary the season of completion), randomly assigned over a 2-week period (2 weekdays and 1 weekend day).[47-49] Corresponding nutrient intakes were calculated using the NutriNet-Santé food composition database, containing more than 3500 food items. Mean dietary intake from 24-hour dietary records available during the first 2 years of each participant's follow-up were averaged and considered as baseline usual dietary intakes in this prospective analysis. The NutriNet-Santé web-based self-administered 24-hour dietary records have been tested and validated against an interview by a trained dietitian,[47] and against blood and urinary biomarkers.[48,49] Details on dietary and biological data collection is provided in the eMethods in the Supplement.

All food and beverage items of the NutriNet-Santé composition table were categorized into 1 of the 4 NOVA categories (unprocessed/minimally processed foods, culinary ingredients, processed foods, ultraprocessed foods),[50] a food classification system based on the extent and purpose of food processing.[30,51,52] This study primarily focused on the "ultraprocessed foods" NOVA group. Definitions and examples are presented in the eMethods in the Supplement.

Case Ascertainment

Participants were asked to declare major health events though the yearly health questionnaire, through a specific health check-up questionnaire every 3 months, or at any time through a specific interface on the study website. They were also asked to declare all currently taken medications and treatments via the check-up and yearly questionnaires. In addition, data are linked to medico-administrative databases of the SNIIRAM, providing detailed information about the reimbursement of

medication and medical consultations. Details on T2D case ascertainment (*International Statistical Classification of Diseases and Related Health Problems, Tenth Revision [ICD-10]* code E11) are provided in the eMethods in the Supplement, including *Anatomical Therapeutic Chemical (ATC) Classification* codes considered for T2D medication. Mortality cases were identified using a linkage to CépiDC, the French national mortality registry.

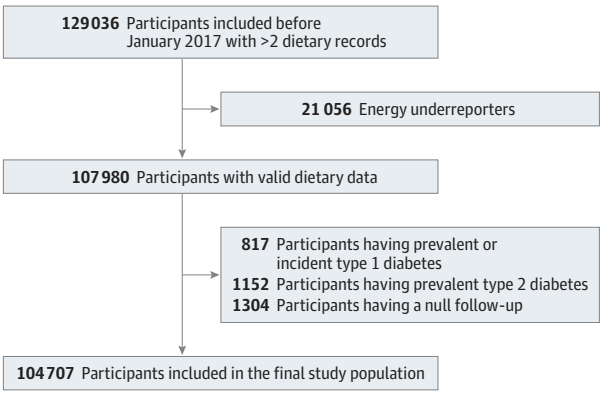
Statistical Analyses

The flowchart for participants' selection is presented in the **Figure**. The final population study included 104 707 individuals. For each participant, the proportion (percentage) of UPF in the total weight of food and/or beverages consumed (grams per day) was calculated. It was determined by making a weight ratio rather than an energy ratio to take into account UPF that do not provide energy (eg, artificially sweetened beverages). Multiple imputation for missing data was performed using the multivariate imputation by chained equations (MICE) method.[53] Unadjusted means of the proportion of UPF in the diet were calculated and presented across strata of the population using appropriate unpaired, 2-tailed *t* tests or analysis of variance for assessing the differences between groups. Regression analysis was performed to assess the association between nutrient and food group intakes, and UPF proportion, adjusted for sex, age, and total energy intake. The distribution of the ultraprocessed variable in the sample is described in eFigure 1 in the Supplement.

Cause-specific Cox models were performed, with a left-truncation to account for delayed entries, and age as timescale, to evaluate the association between the proportion of UPF in the diet (coded as a continuous variable for a 10-point increment) and incidence of T2D. For purposes of analysis, T2D and death during follow-up were handled as competing events. Cause-specific hazard ratios (HRs) and 95% CIs were computed. The Cox model assumptions were verified (eFigures 2 and 3 in the Supplement). Participants contributed person-time until the date of T2D diagnosis or death (competing events), the date of last completed questionnaire, or January 9, 2019, whichever occurred first. The Fine and Gray model for competing events[54] was additionally tested in sensitivity analyses.

Models were adjusted for age (time-scale), sex, educational level, body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), physical activity level, smoking status, alcohol intake, number of 24-hour dietary records, energy intake without alcohol, family history of diabetes, and overall nutritional quality of the diet as measured by the validated Food Standard Agency nutrient profiling system dietary index (FSAm-NPS DI) (Model 1). This index, based on the British FSA nutrient profiling system is the one underlying the official French, Belgian, Spanish and German front-of-package food labeling (the Nutri-Score). It was extensively described and validated elsewhere[55-57] and its computation is detailed in the eMethods in the Supplement. In secondary analyses, Model 2 was further adjusted for several nutrient intakes, whereas Model 3 was adjusted for various food groups associated with T2D risk with consistent evidence.[3] Model 4 was based on Model 1 and included further adjustments for baseline dyslipidemia and hypertension and treatments for these conditions, and Model 5 was adjusted for weight change during follow-up. The associations with T2D risk were also tested for the proportion of UPF among specific food groups, the absolute amount of UPF consumption (in grams per day) (adjusted for the absolute amount of unprocessed/minimally processed food), and the proportion of unprocessed/minimally processed foods in the diet. A series of sensitivity analyses was performed to assess the robustness of the findings (eMethods in the Supplement). All tests were 2-sided, and $P < .05$ was considered statistically significant. For analyses, SAS statistical software (version 9.4; SAS Institute, Inc) was used.

Figure. Flowchart for the Selection of the Study Population, NutriNet-Santé Cohort, 2009 to 2019



A total of 129 036 participants enrolled before January 2017 provided at least 2 valid 24-hour dietary records during their first 2 years of follow-up were eligible for the present study. After exclusion of energy underreporters, participants having prevalent or incident type 1 diabetes, those having prevalent type 2 diabetes, and those with a null follow-up, 104 707 participants were included in the final study population.

Results

A total of 104 707 participants (21 800 [20.8%] men and 82 907 [79.2%] women) were included. Mean (SD) baseline age of participants was 42.7 (14.5) years. The mean weight contribution of UPF to the diet was 17.3%. Overall, UPF proportions were higher in younger participants, obese individuals, those with lower physical activity levels, and current smokers (**Table 1**). Higher consumption of UPF was associated with higher FSAm-NPS DI scores (reflecting a poorer nutritional quality of the diet), higher intakes of energy, SFA, sodium and sugar, lower intakes of fiber and alcohol, higher consumptions of sugary drinks and red and processed meats, and lower consumptions of whole grains, yogurt, nuts, and fruits and vegetables (**Table 2**).

The contribution of main food groups to the ultraprocessed category, along with the proportions of the other NOVA categories are presented in the eResults in the Supplement.

Table 1. Proportion (in Weight) of Ultraprocessed Food in the Diet of 104 707 Participants, NutriNet-Santé Cohort (2009-2019)

Characteristic	No. (%)	Ultraprocessed Food in the Diet, %	
		Mean (SD)	*P* Value[a]
All	104 707 (100.0)	17.29 (9.81)	
Age at baseline, y (n = 104 707)			
18-44	59 247 (56.58)	19.42 (10.65)	<.001
45-59	28 930 (27.62)	14.77 (8.06)	
≥60	16 530 (15.79)	14.04 (7.20)	
Sex (n = 104 707)			
Men	21 800 (20.82)	17.58 (9.99)	<.001
Women	82 907 (79.18)	17.21 (9.77)	
Educational level (n = 98 024)			
<High school degree	17 952 (17.14)	17.25 (10.34)	<.001
<2 y after high school	17 882 (17.08)	18.96 (10.94)	
≥2 y after high school	62 190 (59.39)	16.97 (9.34)	
Smoking status (n = 104 633)			
Current	17 892 (17.09)	18.95 (11.39)	<.001
Former	34 217 (32.68)	16.00 (8.92)	
Never	52 524 (50.16)	17.56 (9.68)	
IPAQ physical activity level (n = 90 146)			
High	29 382 (28.06)	16.09 (9.30)	<.001
Moderate	38 788 (37.04)	17.06 (9.43)	
Low	21 976 (20.99)	18.69 (10.37)	
Body mass index[b] (n = 101 823)			
<25	72 357 (69.10)	17.14 (9.68)	<.001
25-29.9	21 209 (20.25)	17.02 (9.64)	
≥30	8257 (7.88)	18.86 (11.13)	

Abbreviation: IPAQ, International Physical Activity Questionnaire.

[a] *P* values were obtained with unpaired 2-tailed *t* tests (comparison between 2 categories) or analysis of variance (comparison between 3 categories).

[b] Calculated as weight in kilograms divided by height in meters squared.

Table 2. Associations Between the Proportion (in Weight) of Ultraprocessed Food in the Diet and Nutritional Factors (Nutrients and Food Group Intakes) of 104 707 Participations in the NutriNet-Santé Cohort (2009-2019)

Nutritional Factor	Mean (SD)	Proportion of Ultraprocessed Food in the Diet	
		Change in Nutritional Factor, β (SE)[a]	*P* Value[b]
FSAm-NPS dietary index	6.59 (2.46)	0.62 (0.01)	<.001
Energy intake without alcohol, Kcal/d	1847.14 (450.86)	29.95 (1.36)	<.001
Alcohol intake, g/1000 kcal/d	3.91 (5.53)	−0.50 (0.02)	<.001
Sodium intake, mg/1000 kcal/d	1479.10 (369.21)	6.97 (1.20)	<.001
Saturated fatty acids, g/1000 kcal/d	17.78 (4.02)	0.31 (0.01)	<.001
Fiber, g/1000 kcal/d	10.72 (3.57)	-0.78 (0.01)	<.001
Sugar, g/1000 kcal/d	50.39 (13.45)	1.32 (0.04)	<.001
Whole grains, g/1000 kcal/d	18.96 (24.36)	-3.14 (0.08)	<.001
Yogurt, g/1000 kcal/d	33.68 (42.75)	-2.58 (0.14)	<.001
Sugary drinks, g/1000 kcal/d	24.94 (53.64)	25.22 (0.15)	<.001
Red and processed meat, g/1000 kcal/d	40.01 (27.34)	1.68 (0.09)	<.001
Nuts, g/1000 kcal/d	2.52 (5.40)	-0.49 (0.02)	<.001
Fruits and vegetables, g/1000 kcal/d	228.93 (129.04)	-37.54 (0.37)	<.001

Abbreviation: FSAm-NPS DI, Food Standards Agency nutrient profiling system dietary index, described in eMethods in the Supplement.

[a] Change for an absolute increase of 0.1 in the proportion (in weight) of ultraprocessed food in the diet.

[b] *P* values were obtained from linear regression models adjusted for sex, age, and energy intake.

During follow-up (582 252 person-years; median follow-up time, 6.0 years; interquartile range [IQR], 2.8-8.4 years), 821 incident T2D cases were detected. Absolute incidence rates for T2D in the whole population were 132 per 100 000 person-years; age and sex corrected absolute rates were 113, 125, 143 and 166 per 100 000 person-years in the first quarter (lowest consumers), second, third, and fourth quarter (highest consumers) of the proportion of UPF intake in the diet, respectively.

Ultraprocessed food intake was associated with an increased T2D risk (Model 1: HR for a 10-point increment in the percentage of UPF in the diet, 1.15; 95% CI, 1.06-1.25; *P* = .001). The associations remained significant after further adjust-

ments for Model 2, 3, 4, and 5 covariates (**Table 3**). The findings also remained robust throughout all sensitivity models (eTable 1 in the Supplement). Although HRs were in the same direction, this association was significant in women only, but statistical power was reduced for men (eTable 1 in the Supplement). The absolute amount of UPF consumption in grams per day was consistently associated with T2D risk, even when adjusting for the absolute amount (in g/d) of unprocessed/minimally processed food intake (HR for a 100 g/d increase in UPF consumption, 1.05; 95% CI, 1.02-1.08; $P = .003$).

The proportions of UPF in beverages, sugary products, fats/sauces, and dairy products were more specifically associated with increased T2D risk (eTable 2 in the Supplement).

The proportion of unprocessed/minimally processed foods in the diet was inversely associated with T2D risk (HR for a 10-point increment, 0.91; 95% CI, 0.84-0.98; $P = .01$; [Model 1 covariates]).

Table 3. Associations Between the Proportion (in Weight) of UPF in the Diet and Risk of Type 2 Diabetes From Cause-Specific Multiadjusted Cox Proportional Hazard Models in 104 707 Patients in the NutriNet-Santé Cohort (2009-2019)[a]

Variable	Absolute Increment of 10% of UPF in the Diet, HR (95% CI)	*P* Value
No. of cases/total	821/104 707	
Model 1	1.15 (1.06-1.25)	.001
Model 2	1.19 (1.09-1.30)	<.001
Model 3	1.14 (1.04-1.25)	.005
Model 4	1.13 (1.03-1.23)	.006
Model 5[b]	1.13 (1.01-1.27)	.04

Abbreviations: UPF, ultraprocessed foods; FSAm-NPS DI, Food Standards Agency nutrient profiling system dietary index, described in eMethods in the Supplement.

[a] Median follow-up times 6.0 years, 582 252 person-years. Model 1 was a cause-specific Cox proportional hazard model adjusted for age (timescale), sex, educational level (<high school degree/<2 years after high school/≥2 years after high school), baseline body mass index (BMI, continuous, calculated as weight in kilograms divided by height in meters squared), physical activity level (high/moderate/low), smoking status (never/former/current), alcohol intake (g/d, continuous), number of 24-hour dietary records (continuous), energy intake (kcal/d, continuous), FSAm-NPS DI score (continuous), and family history of T2D (yes/no). Model 2 = Model 1 unadjusted for FSAm-NPS DI but adjusted instead for saturated fatty acid intake, sodium intake, sugar intake, dietary fiber intake (continuous variables). Model 3 was Model 1 unadjusted for FSAm-NPS DI but adjusted instead for intakes of red and processed meat, sugary drinks, fruits and vegetables, whole grains, nuts, and yogurt (continuous variables). Model 4 was Model 1 plus baseline prevalent dyslipidemia and hypertension (yes/no), and treatments for these conditions (yes/no). Model 5 was Model 1 plus percentage of weight change (weight in the last anthropometric questionnaire minus weight in the baseline questionnaire divided by weight in the baseline questionnaire multiplied by 100) among participants having available repeated anthropometric data. Overall, there were 340 competing cases of deaths detected during follow-up. Cause-specific hazard ratios for death in the 5 models were respectively: HR, 1.13; 95% CI, 1.00-1.28; $P = .049$; HR, 1.09; 95% CI, 0.97-1.24; $P = .15$; HR, 1.08; 95% CI, 0.94 to 1.23), $P = .26$, 1.13 (1.00 to 1.27), $P = .056$ and 1.03 (0.93 to 1.15), $P = .50$. Multiple imputation for missing data was performed using the MICE method[53] by fully conditional specification (20 imputed data sets) (62 to 97 additional T2D cases by imputed data set) for the following covariates: BMI, smoking status, educational level (≤5% of missing data), and physical activity (15% of missing data). Results were combined across imputation based on Rubin's combination rules[58,59] using the SAS PROC MIANALYZE procedure.[60]

[b] Number of cases, 461 of 79 752.

Discussion

In this large cohort, UPF consumption was associated with increased T2D risk. To our knowledge, although UPF consumption was previously found to be associated with increased risks of cancer,[31] cardiovascular diseases,[35] mortality,[32,36] depressive symptoms,[33,37] and metabolic disorders (obesity,[40] hypertension,[41] and dyslipidemia[39]), no prior prospective epidemiological study had evaluated their association with T2D risk.

Several mechanistic hypotheses can be postulated to explain these findings. Overall, UPF usually have a lower nutritional quality[35] because they are on average richer in sodium, energy, fat, sugar, and poorer in fiber[12-20,25] and often exhibit a higher glycemic index.[61] Several of these factors are associated with T2D with different levels of consensus.[3] Many food groups, mostly ultraprocessed (eg, processed meat, and sugary sweetened beverages) are recognized T2D risk factors.[3] Sugary sweetened beverages may impact metabolic health by several mechanistic pathways that are still currently debated.[62] Consistently, in a 1-month randomized clinical trial,[63] an ultraprocessed diet vs an unprocessed one led to an increased energy intake, which was highly correlated with weight gain. Of note, energy balance and overweight are both associated with T2D risk.[3] However, this could not have entirely explained the associations observed because our models were adjusted for BMI and weight change. Moreover, high consumers of UPF in our population had lower consumptions of whole grains, fruits, and vegetables, which are recommended in the prevention of T2D, consistent with our finding of lower T2D risk in higher consumers of minimally/unprocessed foods. However, our analyses showed that the UPF-T2D risk association was not entirely explained by the simultaneous lower consumption of unprocessed/minimally processed foods. Moreover, the UPF-T2D risk association was adjusted for overall diet quality and energy intake, and remained significant in our models after further adjustment for a wide range of dietary factors. Thus, these factors did not fully explain the observed associations.

Caution is needed in interpreting biological mechanisms underlying these associations because, so far, potentially involved compounds and modes of action are diverse and evidence is still limited. Beyond nutritional values, UPF are often characterized by the presence of food additives. Most of them are likely to be neutral for long-term health and some may even be beneficial (eg, antioxidants), but recent concerns emerged mainly from in vitro/in vivo models for several compounds commonly used in thousands of foods. For instance, carrageenan, a thickening and stabilizing agent, used in more than 5500 products in France and pertaining to the top-20 used additives in France, might contribute to the development of diabetes by impairing glucose tolerance, increasing insulin resistance, and inhibiting insulin signaling in human HepG2 cells.[64] However, as for most additives, human data on long-term health impacts are still lacking and potential cocktail effects remain largely unknown. These aspects will soon be in-

vestigated through a large-scale multidisciplinary research program, notably based on the NutriNet-Santé cohort,[65] combining epidemiological and experimental data. Moreover, 2 meta-analyses observed associations between T2D risk and the intakes of nonnutritive sweeteners and artificially sweetened beverages.[28,66]

In addition, UPF may be contaminated by the migration of contact materials, especially because they often stay in their packaging for long periods owing to extended expiration dates. In particular, the exposure to bisphenol-A (BPA), a hydrophobic substance of very high concern,[66] having endocrine disrupting properties, as well as high BPA serum concentrations, have been associated with increased T2D risk in recent meta-analyses.[29,67] Of note, BPA was forbidden for use in food packaging in 2015 in France, after the dietary data collection period in this study. However, BPA is being replaced by other components such as bisphenol-S, also presenting endocrine disruption properties, and suspected to be about 250 times more absorbed orally than BPA.[68] A recent study conducted in the United States showed that UPF consumption was associated with increased exposure to phthalates,[69] endocrine-disrupting chemicals[70] used in industrial plastic packaging.

Furthermore, UPF that went through processes such as high-temperature heating and extruding may contain neoformed contaminants. For instance, acrylamide[71] and acrolein[72] metabolites were associated with insulin resistance, and urinary biomarkers of polycyclic aromatic hydrocarbons were positively associated with diabetes.[73] Acrylamide is found mainly in fried potatoes, biscuits, cakes, bread, or coffee, but is not specific to industrial processes. On the other hand, high levels of furans were observed in industrial breakfast cereals, canned food, and coffee. Even though furans might be detected in cooked/baked home-made food (toasted bread for instance) especially in foods rich in carbohydrates, it is likely that industrial processes lead to substantially higher levels of furans.[74] Hepatotoxic and genotoxic properties for this substance were suspected by the European Food Safety Authority.[75] Finally, industrial partial oil hydrogenation may lead to the creation of transunsaturated fatty acids in products containing hydrogenated oils. Although still debated, trans fats were linked to increased risks of heart disease[76] and T2D.[77] Additional research is needed to understand the biological mechanisms underlying the present observations.

Limitations

This study has some limitations. Even though we used a multisource case ascertainment approach, exhaustiveness could not be guaranteed. About 20% of T2D cases are estimated to be underdiagnosed in France.[78] This probably resulted in a loss of statistical power. Only 1304 participants had a null follow-up and were excluded. Some of them may have had T2D that was not detected thereafter. However, this should represent a small number of missed cases (<20 cases considering T2D incidence in France[78]) and, owing to the prospective design, the resulting potential misclassification bias was most likely nondifferential and rather resulted in an underestimation of the associations. Second, causation could not be established from this single observational study and residual confounding cannot be entirely ruled out. Nevertheless, several mechanistic hypotheses support the biological plausibility of these findings, and the results remained unchanged after a series of sensitivity analyses adjusting for many lifestyle and dietary confounders. These findings are in line with previous observational studies showing associations between UPF and cardiometabolic outcomes.[32,35,36,39-41] To our knowledge, only 1 short-term randomized clinical trial published so far showed a strong effect of an ultraprocessed diet on weight gain and energy intake.[63] This kind of trial would not be ethically or logistically feasible to investigate longer-term associations with hard health end points (eg, cancer, cardiovascular diseases, T2D), but provides useful insights into potential mechanisms underlying associations observed in long-term epidemiological cohorts. Third, misclassification bias in the NOVA cannot be ruled out; however, this would have led to a nondifferential measurement error (in cases and noncases), and potentially biasing toward the null hypothesis. Fourth, the ultraprocessed category covers diverse products; this exploratory approach was not designed to focus on a specific food category or to isolate a particular process/additive. However, it allowed us to explore overall exposure to UPF and to observe associations with T2D resulting from cumulative intakes and potential cocktail effects of their ingredients. It would be interesting to explore the associations with chronic diseases of substituting UPF by less processed foods. Classic substitution models, initially designed for macronutrients, are less straightforward for complex food groups,[79] but adapted statistical methods should be developed to tackle these challenges. Finally, compared with the general French population, participants to this study were younger, more often women, with higher educational levels[80] and healthier dietary habits.[81] This might have underestimated the associations owing to a narrower range of UPF intake. Furthermore, T2D incidence was lower (186 cases per 100 000 person-years in our sample after standardization vs 289 per 100 000 in the French population[78]), thereby limiting statistical power, especially for some stratified analyses (eg, in men).

Conclusions

These results suggest an association between UPF consumption and T2D risk. They need to be confirmed in large prospective cohorts in other settings, and underlying mechanisms need to be explored in ad hoc epidemiological and experimental studies. Beyond nutritional factors, nonnutritional dimensions of the diet may play a role in these associations, such as some additives, neoformed contaminants, and contact materials. Even if a causal link between UPF and chronic diseases cannot be established so far, the accumulation of consistent data leads public health authorities in several countries such as France[82] or Brazil[83] to recommend privileging the consumption of unprocessed/minimally processed foods, and limiting the consumption of UPF in the name of the precautionary principle.

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