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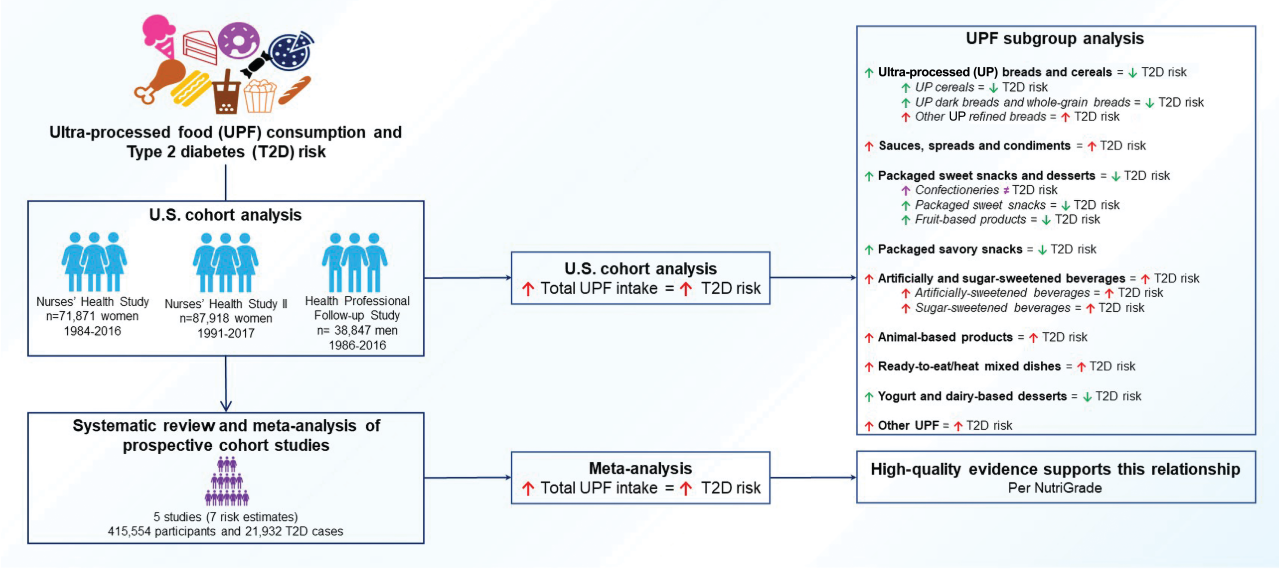

ARTICLE HIGHLIGHTS

- The association between ultra-processed food (UPF) consumption and risk of type 2 diabetes (T2D) has been a topic of much interest, but prospective cohort data on this association remain restricted to a few European cohorts.
- We used data from 3 large U.S. cohorts with diet repeatedly measured every 2–4 years over 30 years of follow-up and report a positive association between total UPF and T2D risk.
- This analysis was subsequently included in a broader meta-analysis that included all prospective cohort studies on this relationship to further strengthen the evidence.
- Per the NutriGrade scoring system, the quality of the meta-evidence is high.

Ultra-Processed Food Consumption and Risk of Type 2 Diabetes: Three Large Prospective U.S. Cohort Studies

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See accompanying article, p. 1327.

OBJECTIVE

We examined the relationship between ultra-processed food (UPF) intake and type 2 diabetes (T2D) risk among 3 large U.S. cohorts, conducted a meta-analysis of prospective cohort studies, and assessed meta-evidence quality.

RESEARCH DESIGN AND METHODS

We included 71,871 women from the Nurses' Health Study, 87,918 women from the Nurses' Health Study II, and 38,847 men from the Health Professional Follow-Up Study. Diet was assessed using food frequency questionnaires and UPF was categorized per the NOVA classification. Associations of total and subgroups of UPF with T2D were assessed using Cox proportional hazards models. We subsequently conducted a meta-analysis of prospective cohort studies on total UPF and T2D risk, and assessed meta-evidence quality using the NutriGrade scoring system.

RESULTS

Among the U.S. cohorts (5,187,678 person-years; *n* = 19,503 T2D cases), the hazard ratio for T2D comparing extreme quintiles of total UPF intake (percentage of grams per day) was 1.46 (95% CI 1.39–1.54). Among subgroups, refined breads; sauces, spreads, and condiments; artificially and sugar-sweetened beverages; animal-based products; and ready-to-eat mixed dishes were associated with higher T2D risk. Cereals; dark and whole-grain breads; packaged sweet and savory snacks; fruit-based products; and yogurt and dairy-based desserts were associated with lower T2D risk. In the meta-analysis (*n* = 415,554 participants; *n* = 21,932 T2D cases), each 10% increment in total UPF was associated with a 12% (95% CI 10%–13%) higher risk. Per NutriGrade, high-quality evidence supports this relationship.

CONCLUSIONS

High-quality meta-evidence shows that total UPF consumption is associated with higher T2D risk. However, some UPF subgroups were associated with lower risk in the U.S. cohorts.

As defined in the NOVA food classification system (1), ultra-processed foods (UPFs) are industrial formulations made mostly or entirely with substances extracted from foods, often chemically modified, with additives and with little, if any, whole foods

added (1). UPFs and their components have been shown to negatively affect gut microbiota, systemic inflammation, insulin resistance, and body weight, raising concerns about their long-term effects on cardiometabolic health (2–5). Still, prospective cohort data on the relationship between total UPF consumption and type 2 diabetes (T2D) remain restricted to a few investigations conducted among European cohorts (6–9). Albeit limited, these studies have been consistent in reporting a positive association, with T2D risk being 15% to 53% higher depending on the cohort and the level of total UPF intake (2–4,6–9). In the U.S., total UPF intake is much higher than in Europe and comprises higher intakes of specific UPF subgroups such as ultra-processed breads and cereals and artificially or sugar-sweetened beverages. These differences warrant U.S.-based studies to better understand the burden associated with overall and subgroup-specific UPF consumption (7). Additionally, building on such data to assess the relationship between UPF consumption and T2D risk globally using meta-analysis as well as assessing the quality of such meta-evidence would strengthen the case in support of public health policies targeting these food products.

In this study, we first evaluated the associations of total and subgroup intakes of UPFs and the risk of T2D among U.S. men and women from three large U.S. prospective cohorts. We subsequently conducted a systematic review and meta-analysis of total UPF consumption and T2D risk that included the results from these three U.S. cohorts and other previously published studies. Finally, we assessed the quality of these meta-evidence using the NutriGrade scoring system (10).

RESEARCH DESIGN AND METHODS

Cohort Analyses

Study Population

The Nurses' Health Study (NHS) was established in 1976 and included 121,701 U.S. registered female nurses aged 30–55 years at inception (11). The NHSII was initiated in 1989 and included 116,340 U.S. women aged 25–42 years (11). The Health Professionals' Follow-up Study (HPFS) was established in 1986 and recruited 51,529 U.S. male health professionals aged 40–75 years (12). In all cohorts, questionnaires were administered every 2 years to collect lifestyle and medical information. Diet was assessed using a validated food frequency questionnaire (FFQ) every 2–4 years. For the present study, baseline was set as 1984 for the NHS, 1986 for the HPFS, and 1991 for the NHSII. Among participants who completed the baseline FFQ, we excluded those who reported cardiovascular disease, cancer, or diabetes at baseline; those whose last returned questionnaire was at baseline; or who reported implausible daily energy intake ($<$500 or $>$3,500 kcal for women; $<$800 or $>$4,200 kcal for men). After exclusions, 198,636 participants were included in the analyses (NHS, $n = 71,871$; NHSII, $n = 87,918$; HPFS; $n = 38,847$) (Supplementary Fig. 1). The study protocol was approved by review boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health.

Assessment of UPF Consumption

We used the NOVA classification to categorize foods items included in the validated FFQ (13–15) into four groups: (1) unprocessed or minimally processed foods, (2) processed culinary ingredients, (3) processed foods, and (4) UPFs (15). NOVA classifies foods on the basis of the extent and purpose of the industrial processing they undergo and accounts for the physical, biological, and chemical methods used in their manufacture, including the use of additives (1,15). The approach used to classify the FFQ food items into the four NOVA groups is described in the Supplementary Methods. This strategy, along with the full classification of the food items, have also been published (15). We used servings per day to quantify UPF intake. In sensitivity analyses, we used four alternative metrics: calories (kcal) from UPF/day, percentage of kcal from UPF/day, percentage of grams from UPF/day, and energy-adjusted servings of UPF/day. Owing to limited information for nine items from the FFQ (namely, popcorn; soy milk; cream; pancakes or waffles; pie, home-baked or ready-made; chicken sandwich; beef, pork, or lamb sandwich; tomato sauce; potato or corn chips), these were assigned to a non-UPF group as their primary categorization. We conducted a sensitivity analysis while categorizing them as UPFs (15). We further divided UPFs into nine mutually exclusive subgroups (Supplementary Table 1). We did not include distilled alcohol in UPFs to avoid mixing the relationship with T2D risk (16).

Assessment of T2D

T2D cases were first identified by self-reporting of the main biennial questionnaire from the participants and subsequently were confirmed by the completion of a supplementary validated questionnaire on the symptoms, diagnostic tests, and treatment of diabetes (17,18). Before 1998, cases were confirmed in accordance with National Diabetes Data Group criteria (19). After, cases were confirmed using the American Diabetes Association criteria (20). Only diabetes cases confirmed with the supplementary questionnaire were considered for the present study.

Assessment of Covariables

Using the biennial follow-up questionnaires, updated information on height, body weight, cigarette smoking, physical activity, family history of diabetes, and history of hypertension and hypercholesterolemia was collected. Among women, information on menopausal status, postmenopausal hormone use, and oral contraceptive use (NHSII only) was assessed.

Statistical Analyses

We used SAS statistical package (version 9.4) to perform analyses. A two-sided P value <0.05 was considered statistically significant unless otherwise specified. We calculated each participant's person-years from the date of return of the baseline questionnaire to the date of diabetes diagnosis, death, or the end of the follow-up (June 30, 2016, in the NHS; June 30, 2017, in the NHSII; and January 31, 2016, in the HPFS), whichever came first.

Cox proportional hazards regression models were used to calculate hazard ratios (HRs) and 95% CIs for incident T2D. To represent long-term diet and reduce within-person variation, a cumulative average update method was used for dietary variables. The regression models included age in months as the time scale and were stratified by calendar year (in 2-year intervals) and by cohort (which allowed concomitant stratification for sex). In multivariable model 1, we further adjusted for race/ethnicity, family history of T2D, baseline history of hypertension and/or hypercholesterolemia, smoking status, physical activity level, alcohol consumption, postmenopausal status and postmenopausal hormone use, oral contraceptive use, history of physical examination in the last 2 years, and total energy intake. In multivariable model 2, we additionally adjusted

for baseline BMI. All covariables (except ethnicity, family history of diabetes, baseline hypercholesterolemia, baseline hypertension, and baseline BMI) were updated every 2 years. Covariables were selected on the basis of their confounding potential.

We conducted several sensitivity analyses. First, we explored potential effect modifications by several factors, including age, sex, BMI, physical activity, diet quality (assessed using the 2010 Alternative Healthy Eating Index [AHEI-2010]), smoking, and family history of diabetes. We calculated *P* values for interaction from the likelihood ratio tests comparing the full model with the reduced model. Second, we repeated the main analysis by using the alternative metrics of total UPF intake and by recategorizing the nine aforementioned items with unclear processing level into the UPF category. Third, we repeated the main analyses by adjusting for BMI updated every 2 years instead of baseline BMI. We estimated the percentage of the association between total UPF intake and T2D risk that was mediated by updated BMI (21). Fourth, we repeated the main analyses by additionally adjusting for diabetes screening frequency. Fifth, because individuals at higher risk are likely to be screened for diabetes and diagnosed more rapidly, leading to surveillance bias, we evaluated the association of total UPF intake and symptomatic diabetes risk, ascertained by the report of at least one diabetes symptom in the supplementary questionnaire. Sixth, we repeated the main analyses by adjusting for intakes of non-UPF foods (i.e., non–ultra-processed vegetables, fruits, whole grains, nuts, legumes, red meat, fish, poultry, tea, and coffee) instead of total energy. Seventh, we examined the associations of the nine UPF subcategories with T2D risk. The subgroups were simultaneously included in the models as distinct covariables. To examine whether the associations with T2D risk were heterogeneous among UPF subgroups, we fitted a set of fully adjusted models: the first one included total UPF consumption as the exposure of interest, whereas the others included total UPF consumption plus consumption of all but one UPF subgroup. Then we used the likelihood ratio test (CHISQ.DIST.RT function in Microsoft Excel) to examine whether the model including UPF subgroups had better fit than the one including total UPF intake only (22). Finally, we estimated the percentage of the associations between UPF intakes and T2D risk mediated by dietary fiber (g/day), refined starch (g/day), added sugar (g/day), sodium (mg/day), minerals (i.e., sum of calcium, zinc, magnesium, phosphorus, iron, all measured in mg/day), and partially hydrogenated oils (percentage of daily energy), individually, and collectively.

Systematic Review and Meta-analysis of UPF Consumption and T2D

Descriptions of the systematic review, meta-analysis, sensitivity meta-analyses, and quality of evidence assessment protocols are provided in the Supplementary Methods. Briefly, the report was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (23). The protocol was registered on the international prospective register of systematic reviews (PROSPERO CRD42022337267). Supplementary Table 2 presents the strategy used to search Medline (via PubMed), Embase, and Web of Science up to June 6, 2022. In most previously published studies on UPF intake and T2D, the percentage of grams of total UPF intake relative to total diet weight was used to quantify UPF intake. We thus used this metric to harmonize UPF intake between studies. We first conducted a meta-analysis of high versus low total UPF intake by pooling risk estimates from the highest category of intake compared with the lowest category in each study, using random-effects models. Second, we performed a linear dose-response meta-analysis to assess T2D risk associated with a 10% increment of total UPF intake by using the two-stage generalized least squares trend estimation method (24). Third, a two-stage, random-effects, dose-response meta-analysis was conducted to assess potential nonlinearity of the association between total UPF intake and T2D risk. Restricted cubic splines with three knots (ie, the 10th, 50th, and 90th percentiles of UPF intake) were used to model the association (25). Finally, we assessed the meta-evidence quality using NutriGrade (10).

Data and Resource Availability

The data that support the findings of this study will not be made publicly available. Additional information, including the procedures for obtaining and accessing data from the Nurses' Health Studies and HPFS, is described at https://www.nurseshealthstudy.org/researchers (email: nhsaccess@channing.harvard.edu) and https://sites.sph.harvard.edu/hpfs/for-collaborators.

RESULTS

Cohort Analyses

During 5,187,678 person-years of follow-up, we documented 19,503 T2D cases in the three cohorts. Higher total UPF intake was associated with higher total energy, BMI, prevalence of hypercholesterolemia and/or hypertension, and lower AHEI-2010 scores and physical activity (Table 1). UPF subgroups contributing to the largest share of UPF were ultra-processed breads and cereals, sauces, spreads, and condiments, packaged sweet snacks and desserts, and artificially- and sugar-sweetened beverages (Supplementary Table 3).

Table 2 presents HRs of incident T2D according to the quintiles of total UPF intake. In multivariable model 1, the pooled HR for T2D comparing extreme quintiles on intake was 1.56 (95% CI 1.47–1.65; $P_{trend} < 0.0001$). Each 1 serving increment/day was associated with a 5% (95% CI 5–6%) higher risk of T2D. Further adjustment for baseline BMI (multivariable model 2) attenuated the associations (HR for extreme quintiles, 1.28, 95%CI 1.21–1.36; HR for 1 serving increment, 1.03, 95% CI 1.02–1.03).

In sensitivity analyses, the association between UPF intake and T2D risk persisted when we stratified the cohorts by BMI, physical activity, smoking, diet quality, and family history of diabetes. None of the interactions of these factors were statistically significant, except for age ($P_{interaction} < 0.0001$), but this did not alter the interpretation of the results (Supplementary Table 4). We observed similar results when categorizing the nine food items with uncertain processing level as UPFs or when assessing UPF intake using kcal/day, percentage of kcal/day, percentage of g/day, and energy-adjusted servings per day (Supplementary Table 5). Similarly, when adjusting for updated BMI instead of baseline BMI, additionally adjusting for T2D screening frequency, restricting the cases to symptomatic diabetes at diagnosis only, or adjusting for intakes of non–ultra-processed foods instead of total energy intakes, total UPF consumption remained associated with higher T2D risk (Supplementary Table 6). We estimated that updated BMI statistically accounted for 67.4% (57.2–76.1%)

Table 1—Age and age-standardized characteristics of participants in the NHS (1998), the NHSII (1999), and the HPFS (1998) according to total UPF consumption*

Characteristics	Quintiles of total UPF consumption (servings/day)				
	1	2	3	4	5
NHS (1998)					
Participants, *n*	12,534	12,520	12,526	12,520	12,530
Age, years	64.3 (6.9)	63.9 (7.1)	63.7 (7.1)	63.4 (7.1)	63.1 (7.2)
BMI, kg/m^2	25.6 (4.7)	26.1 (4.8)	26.3 (4.9)	26.7 (5.2)	27.3 (5.7)
Physical activity, MET-hours/week	18.7 (23.2)	18 (22.4)	17.6 (21.5)	17.2 (20.1)	16.3 (21.1)
Current smoker, %	11.1	10.0	10.1	10.0	11.1
Family history of diabetes, %	25.9	27.1	27.4	28.7	28.2
History of hypertension, %	46.3	47.5	49.2	50.5	52.2
History of hypercholesterolemia, %	52.2	54.5	56.0	58.1	58.4
Fasting blood glucose screening†, %	48.1	52.4	54.1	54.5	54.1
Dietary intakes					
UPFs, servings/day	3.3 (0.7)	4.9 (0.4)	6.1 (0.4)	7.6 (0.5)	10.5 (1.9)
Whole fruits, servings/day‡	1.6 (1)	1.6 (0.9)	1.7 (0.9)	1.7 (0.9)	1.7 (0.9)
Whole vegetables, servings/day‡	3 (1.5)	3.1 (1.5)	3.2 (1.5)	3.2 (1.5)	3.3 (1.5)
Tea and coffee, servings/day‡	2.7 (1.9)	2.9 (1.8)	3 (1.9)	3.1 (1.9)	3.4 (2)
Nuts and legumes, servings/day‡	0.4 (0.3)	0.5 (0.3)	0.5 (0.3)	0.5 (0.3)	0.5 (0.3)
Non–ultra-processed whole grains, servings/day§	0.4 (0.4)	0.4 (0.4)	0.4 (0.4)	0.4 (0.4)	0.4 (0.4)
Non–ultra-processed red meat/fish/poultry, servings/day	1.2 (0.5)	1.4 (0.5)	1.4 (0.5)	1.5 (0.5)	1.6 (0.6)
Total energy, kcal/day	1369 (312)	1590 (319)	1737 (341)	1894 (364)	2154 (417)
Total alcohol, g/day	6.4 (9.6)	5.7 (8.6)	5.7 (8.9)	5.2 (8.2)	4.8 (8)
Alternative healthy eating index	51 (9.1)	48.9 (8.5)	47.4 (8.4)	46 (8.3)	43.8 (8.2)
NHSII (1999)					
Participants, *n*	16,812	16,822	16,801	16,842	16,819
Age, years	44.8 (4.6)	44.3 (4.6)	44.2 (4.6)	44.0 (4.7)	44.0 (4.6)
BMI, kg/m^2	25.2 (5.2)	25.7 (5.6)	26.2 (5.9)	26.8 (6.2)	28.1 (6.9)
Physical activity, MET-hours/week	20.3 (24.9)	19.1 (23.6)	18.7 (22.9)	17.8 (21.7)	17.4 (22.5)
Current smoker, %	9.2	8.5	8.3	9.3	10.9
Family history of diabetes, %	31.7	32.5	33.5	33.4	35.3
History of hypertension, %	12.4	13.4	14.6	15.8	19.1
History of hypercholesterolemia, %	21.4	22.1	24.1	25.6	27.8
Fasting blood glucose screening†, %	40.6	42.8	43.4	43.7	45.0
Dietary intakes					
UPFs, servings/day	3.6 (0.8)	5.2 (0.4)	6.5 (0.4)	8.1 (0.5)	11.2 (2)
Whole fruits, servings/day‡	1.2 (0.9)	1.2 (0.8)	1.2 (0.8)	1.3 (0.8)	1.3 (0.8)
Whole vegetables, servings/day‡	2.8 (1.6)	3.0 (1.6)	3.1 (1.6)	3.2 (1.7)	3.3 (1.8)
Tea and coffee, servings/day‡	1.6 (1.3)	1.7 (1.3)	1.8 (1.3)	1.8 (1.4)	2.0 (1.5)
Nuts and legumes, servings/day‡	0.5 (0.4)	0.5 (0.4)	0.6 (0.4)	0.6 (0.4)	0.6 (0.4)
Non–ultra-processed whole grains, servings/day§	0.3 (0.3)	0.3 (0.3)	0.3 (0.3)	0.3 (0.3)	0.3 (0.3)
Non–ultra-processed red meat/fish/poultry, servings/day	1.2 (0.5)	1.4 (0.5)	1.5 (0.6)	1.6 (0.6)	1.8 (0.6)
Total energy, kcal/day	1,400 (336)	1,640 (348)	1,800 (379)	1,964 (413)	2,232 (469)
Total alcohol, g/day	3.8 (6.4)	3.6 (6.1)	3.4 (5.7)	3.4 (5.7)	3.2 (5.5)
Alternative healthy eating index	48.6 (9.2)	45.8 (8.9)	44.3 (8.8)	42.9 (8.7)	41.1 (8.8)
HPFS (1998)					
Participants, *n*	6,461	6,457	6,463	6,458	6,464
Age, years	64.8 (8.9)	64.3 (9)	64.1 (9)	63.9 (8.9)	63.7 (9)
BMI, kg/m^2	25.7 (3.6)	25.9 (3.5)	26 (3.5)	26.2 (3.6)	26.5 (4)
Physical activity, MET-hours/week	38.2 (42.8)	36.6 (37.6)	34.6 (38.4)	34.0 (39.1)	31.5 (37.6)
Current smoker, %	5	5	5	6	8
Family history of diabetes, %	12	13	14	14	15
History of hypertension, %	38	40	41	44	44
History of hypercholesterolemia, %	44	46	48	49	50
Fasting blood glucose screening†, %	44	46	48	49	50
Dietary intake					
UPFs, servings/day	3.2 (0.7)	4.9 (0.4)	6.3 (0.4)	7.8 (0.5)	11.2 (2.1)
Whole fruits, servings/day‡	1.7 (1.3)	1.7 (1.2)	1.7 (1.1)	1.7 (1.1)	1.7 (1.1)
Whole vegetables, servings/day‡	2.9 (1.7)	3 (1.6)	3.1 (1.6)	3.2 (1.7)	3.3 (1.8)
Tea and coffee, servings/day‡	1.6 (1.3)	1.7 (1.3)	1.8 (1.3)	1.8 (1.4)	2 (1.5)
Nuts and legumes, servings/day‡	0.7 (0.5)	0.8 (0.5)	0.9 (0.6)	0.9 (0.6)	1.1 (0.7)
Non–ultra-processed whole grains, servings/day§	0.6 (0.7)	0.6 (0.6)	0.5 (0.6)	0.5 (0.6)	0.5 (0.6)
Non–ultra-processed red meat/fish/poultry, servings/day	1.1 (0.5)	1.2 (0.4)	1.3 (0.5)	1.4 (0.5)	1.5 (0.6)

Continued on p. 1339

Table 1—Continued

Characteristics	Quintiles of total UPF consumption (servings/day)				
	1	2	3	4	5
Total energy, kcal/day	1,522 (351)	1,752 (361)	1,946 (393)	2,151 (430)	2,493 (514)
Total alcohol, g/day	12.5 (15.0)	11.7 (13.1)	10.8 (12.6)	10.4 (12.8)	9.5 (12.2)
Alternative healthy eating index	52.9 (9.6)	49.8 (9.0)	47.9 (9.1)	46.2 (9.1)	43.9 (8.8)

*Data are reported as mean (SD) or percentages and are standardized to the age distribution of the study population in 1998–1999 (i.e., approximately the midpoint of follow-up), except age. †Information on whether participants have had a fasting blood glucose screening in the past year was queried in the biennial health questionnaire (self-reported). This information was first collected in 1998 for the NHS, 2001 for the NHSII, and 2000 for the HPFS. ‡These specific food items did not include UPFs. §Non–ultra-processed whole grains excludes cereals and dark bread.

of the association between total UPF intake and T2D risk.

Among UPF subgroups (Fig. 1), intakes of sauces, spreads, and condiments; artificially- and sugar-sweetened beverages; animal-based products; ready-to-eat or -heat mixed dishes; and other UPFs were associated with higher T2D risk. Intakes of ultra-processed breads and cereals. packaged sweet snacks and desserts. packaged savory snacks. and yogurt and dairy-based desserts were associated with lower T2D risk. Among the ultra-processed breads and cereals subgroup, further subdivision allowed us to identify that intakes of ultra-processed cereals and ultra-processed dark breads and whole-grain breads were associated with lower T2D risk, whereas intakes of other ultra-processed refined breads were associated with higher risk. The inverse association between intakes of packaged sweet snacks and desserts and T2D risk appeared to be driven by intakes of packaged sweet snacks and fruit-based products, because no evidence of an association was found for confectioneries. The goodness of fit of the model that included total UPF consumption and all but one UPF subgroups plus other covariables was significantly higher than the one including total UPF intake and the covariables ($P < 0.0001$ for all likelihood ratio tests). This indicated that heterogeneity in the associations with risk of T2D among UPF subgroups was significant.

We estimated that intakes of dietary fibers, refined starch, added sugar, sodium, minerals, and partially hydrogenated oils collectively mediated 11.9% (4.6–27.7%) of the association between total UPF intake and T2D risk (Supplementary Table 7). However, when assessed individually, only dietary fibers and sodium were identified as significant mediators. For ultra-processed cereals, dark and whole-grain breads, and refined breads, dietary fibers and minerals mediated between 2.6% and 18.5% of the relationships with T2D. For confectioneries, packaged sweet snacks, and fruit-based products, added sugar mediated 29.4% (8.0–66.6%), 6.6% (4.3–10.1%), and 8.5% (5.3–13.4%) the association with T2D risk, respectively. Also, dietary fibers were found to mediate the relationship between T2D and fruit-based products, but not other packaged sweet UPFs. For packaged savory snacks, dietary fibers and partially hydrogenated oils both mediated approximately 4% of the relationship with T2D. Added sugar mediated the relationship between T2D risk and artificially sweetened beverages, but not sugar-sweetened beverages. Finally, minerals mediated 3.5–9.4% the relationships between animal-based products, ready-to-eat or -heat mixed dishes, and yogurt and dairy-based desserts with T2D, and dietary fibers also contributed to mediate 3.1–4.6% of the associations between animal-based products or ready-to-eat or -heat mixed dishes with T2D.

Systematic Review and Meta-analysis

After screening 1,017 studies, four (5, including the present analysis in the NHS, NHSII, and HPFS) (6–9) met inclusion criteria (Supplementary Fig. 2). Supplementary Table 8 presents characteristics of the included studies, which comprised seven risk estimates, 415,554 participants, and 21,932 events, with follow-up ranging from 3.4 to 32 years. Only the present study was conducted in the U.S. The four others were from Europe. Two of the five studies controlled for all primary and secondary confounders (Supplementary Table 9). Three studies obtained a Newcastle-Ottawa Scale score ≥ 7 and were at low risk of bias (Supplementary Table 10). All five studies were included in both the high versus low total UPF intake and the dose-response meta-analysis.

The pooled relative risk for T2D for the highest versus the lowest level of total UPF consumption (percentage of grams from UPF/day) was 1.40 (95% CI 1.23–1.59; $I^2 = 88.1\%$; $P_{\text{heterogeneity}} < 0.0001$) (Fig. 2*A*). The pooled relative risk for each 10% increment of total UPF intake was 1.12 (95% CI 1.10–1.13; $I^2 = 1.5\%$; $P_{\text{heterogeneity}} = 0.41$) (Fig. 2*B*). We found no evidence of a curvilinear association between UPF consumption and T2D risk ($P_{\text{nonlinearity}} = 0.84$) (Fig. 2*C*). This suggested a linear dose-response association and corroborated results from the dose-response meta-analysis. Visual examination of the funnel plot (Supplementary Fig. 3) and Egger's ($P = 0.69$) and Begg's ($P = 0.88$) tests showed no evidence of publication bias. The influence analysis suggested that no single study appeared to cause the heterogeneity (Supplementary Fig. 4). Last, we observed no significant interaction in prespecified subgroup meta-regressions (Supplementary Table 11).

Per the NutriGrade, the quality of meta-evidence for the positive association between total UPF consumption and T2D risk was considered high, with a score of 8 of 10 (Supplementary Table 12).

CONCLUSIONS

In three U.S. cohorts, total UPF consumption was associated with higher T2D risk. In subgroup analyses, intakes of refined breads; sauces, spreads, and condiments; artificially and sugar-sweetened beverages; animal-based products; and ready-to-eat mixed dishes were associated with higher T2D risk. Conversely, intakes of ultra-processed cereals; dark and whole-grain breads; packaged sweet and savory

Table 2—HRs (95% CIs) for incident T2D according to total UPF consumption in the NHS, the NHSII, and the HPFS follow-up study

	Quintiles of total UPF consumption (servings/day)						HR (95% CI) for 1 serving/day increment
	1 (Low)	2	3	4	5 (High)	P_{trend}*	
NHS (n = 71,871)							
Median, servings/day	3.3	4.7	6.0	7.4	10.0		
Cases/person-years	1,314/402,974	1,504/402,600	1,681/402,597	1,872/402,559	2,220/402,238		
Age-adjusted model†	1.00 (reference)	1.15 (1.07, 1.24)	1.30 (1.21, 1.40)	1.45 (1.35, 1.56)	1.73 (1.61, 1.85)	<0.0001	1.07 (1.06, 1.08)
Multivariable model 1‡	1.00 (reference)	1.12 (1.04, 1.21)	1.21 (1.12, 1.31)	1.28 (1.18, 1.38)	1.39 (1.28, 1.51)	<0.0001	1.04 (1.03, 1.05)
Multivariable model 2§	1.00 (reference)	1.07 (0.99, 1.16)	1.13 (1.05, 1.22)	1.15 (1.06, 1.25)	1.19 (1.09, 1.30)	<0.0001	1.02 (1.01, 1.03)
NHSII (n = 87,918)							
Median, servings/day	3.9	5.7	7.0	8.8	14.0		
Cases/person-years	962/447,031	1,176/447,521	1,441/447,057	1,547/447,745	2,051/446,303		
Age-adjusted model‡	1.00 (reference)	1.27 (1.17, 1.38)	1.57 (1.44, 1.70)	1.70 (1.57, 1.84)	2.27 (2.10, 2.45)	<0.0001	1.10 (1.09, 1.11)
Multivariable model 1‡	1.00 (reference)	1.25 (1.15, 1.37)	1.49 (1.37, 1.63)	1.55 (1.42, 1.70)	1.83 (1.67, 2.01)	<0.0001	1.07 (1.06, 1.08)
Multivariable model 2§	1.00 (reference)	1.18 (1.08, 1.29)	1.35 (1.23, 1.47)	1.32 (1.21, 1.45)	1.46 (1.33, 1.60)	<0.0001	1.04 (1.03, 1.05)
HPFS (n = 38,847)							
Median, servings/day	3.2	4.7	6.1	7.6	10.5		
Cases/person-years	651/188,064	664/187,561	720/188,078	787/187,910	913/187,440		
Age-adjusted model†	1.00 (reference)	1.04 (0.93, 1.16)	1.15 (1.03, 1.27)	1.24 (1.12, 1.38)	1.45 (1.31, 1.60)	<0.0001	1.05 (1.03, 1.06)
Multivariable model 1‡	1.00 (reference)	1.09 (0.97, 1.22)	1.21 (1.07, 1.35)	1.31 (1.16, 1.48)	1.51 (1.33, 1.72)	<0.0001	1.05 (1.03, 1.06)
Multivariable model 2§	1.00 (reference)	1.01 (0.90, 1.13)	1.05 (0.94, 1.18)	1.14 (1.01, 1.29)	1.22 (1.07, 1.39)	0.0004	1.02 (1.01, 1.04)
Pooled results							
Cases/person-years	2,916/1,038,069	3,346/1,037,682	3,744/1,037,732	4,081/1,038,214	4,599/1,035,981		
Age-adjusted model†	1.00 (reference)	1.17 (1.11, 1.23)	1.35 (1.29, 1.42)	1.49 (1.42, 1.56)	1.84 (1.76, 1.93)	<0.0001	1.08 (1.07, 1.08)
Multivariable model 1‡	1.00 (reference)	1.16 (1.10, 1.22)	1.30 (1.23, 1.37)	1.37 (1.30, 1.44)	1.56 (1.47, 1.65)	<0.0001	1.05 (1.05, 1.06)
Multivariable model 2§	1.00 (reference)	1.09 (1.04, 1.15)	1.19 (1.12, 1.25)	1.20 (1.14, 1.27)	1.28 (1.21, 1.36)	<0.0001	1.03 (1.02, 1.03)

*P values for trend based on continuous total UPF variable derived from the median UPF intake (servings/day) in each category of consumption. †Age-adjusted model: stratified by calendar year in 2-year intervals and by cohort (in pooled analysis only) and adjusted for age (months). ‡Multivariable model 1: Age-adjusted model plus race/ethnicity (White/other), family history of diabetes (yes/no), history of hypercholesterolemia at baseline (yes/no), history of hypertension at baseline (yes/no), smoking status (never, past, current), physical activity (MET-hours/week: <3.0, 3.0–8.9, 9.0–17.9, 18.0–26.9, ≥27.0), oral contraceptive use (in NHSII only: never, former, current), postmenopausal hormone use (in NHS and NHSII only: premenopausal, never, former, current), physical examination in the past 2 years (yes/no), neighborhood income (quintiles), total energy (kcal/day, quintiles), and total alcohol consumption (g/day, quintiles). All covariables (except race/ethnicity, family history of diabetes, baseline hypercholesterolemia, hypertension, and BMI) were updated every 2 years. §Multivariable model 2: Multivariable model 1 plus baseline BMI (kg/m^2: <21.0, 21.0–22.9, 23.0–24.9, 25.0–26.9, 27.0–29.9, 30.0–34.9, ≥35.0). All covariables (except race/ethnicity, family history of diabetes, baseline hypercholesterolemia, hypertension, and BMI) were updated every 2 years.

snacks; fruit-based products; and yogurt and dairy-based desserts were associated with lower risk. In the meta-analysis, a positive linear dose-response relationship for total UPFs and T2D lend further support to the findings among the U.S. cohorts. According to NutriGrade, the meta-evidence was of high quality. Overall, these findings support public health policies aiming to limit the total consumption of UPFs as well as the intake of UPFs associated with a higher T2D risk.

In the NHS, NHSII, and HPFS, over the past 30 years, UPF intake represented 36.1% of total weight of foods and beverages consumed (15). In comparison, UPFs constituted 15.4% of total foods in the NutriNet Santé cohort (France) (6) and 22.1% in the UK Biobank in the past two decades (7). These different levels of intake may explain, to some extent, the between-study heterogeneity we observed in the meta-analysis of high versus low UPF intake. Still, in the dose-response meta-analysis, there was negligible between-study heterogeneity related to the higher risk associated

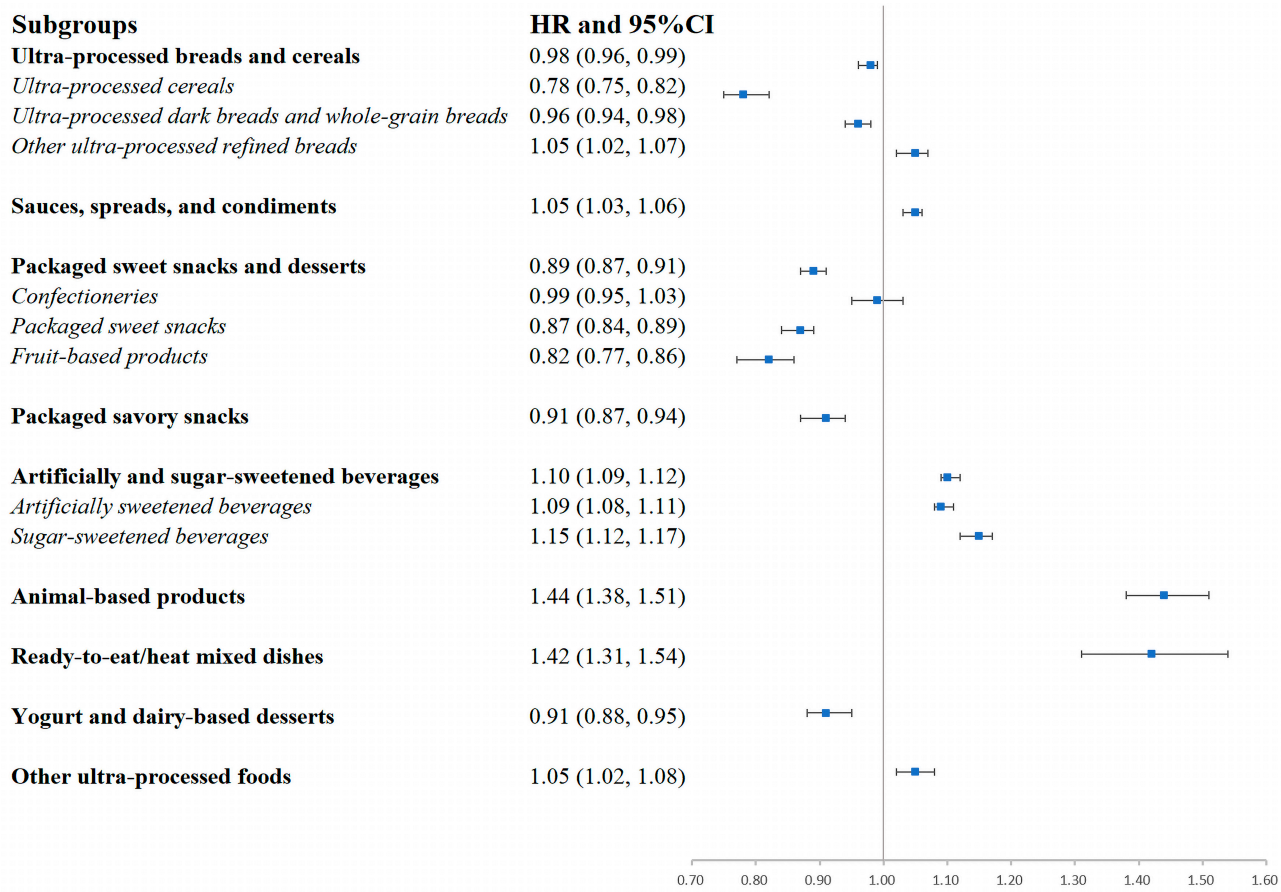

Figure 1—Associations of subgroups of UPFs and risk of T2D. Results were obtained from the pooled multivariable model 2 (final multivariable model) stratified by calendar time (in 2-year intervals) and cohort (sex), and adjusted for age, race/ethnicity (White/other), family history of diabetes (yes/no), history of hypercholesterolemia at baseline (yes/no), history of hypertension at baseline (yes/no), baseline BMI (kg/m^2: <21.0, 21.0–22.9, 23.0–24.9, 25.0–26.9, 27.0–29.9, 30.0–34.9, ≥35.0), smoking status (never, past, current), physical activity (MET-hours/week: <3.0, 3.0–8.9, 9.0–17.9, 18.0–26.9, ≥27.0), oral contraceptive use (in NHSII only: never, former, current), postmenopausal hormone use (in NHS and NHSII only: premenopausal, never, former, current), physical examination in the past 2 years (yes/no), neighborhood income (quintiles), total energy (kcal/day; quintiles), and total alcohol consumption (g/day; quintiles). All covariables (except race/ethnicity, family history of diabetes, baseline hypercholesterolemia, hypertension, and BMI) were updated every 2 years. The UPF groups (or subgroups) were included simultaneously in the models as distinct covariables. The CHISQ.DIST.RT function was used to calculate *P* value for likelihood ratio test. All *P* values were <0.0001 for likelihood ratio tests and indicated that heterogeneity in the associations with risk of T2D among subgroups of UPFs was significant.

with UPF intake, suggesting a consistent and robust detrimental relationship between total UPF consumption and T2D risk.

The NOVA UPF category is composed of a variety of animal- and plant-based foods. Given the known favorable relationship of plant-rich diets compared with animal-rich diets with T2D (26), this raises questions about whether all types of UPFs increase T2D risk. In the U.S. cohorts, the consumption of ultra-processed refined grains; animal-based products; artificially and sugar-sweetened beverages; ready-to-eat or -heat mixed dishes; and sauces, spreads, and condiments was positively associated with T2D risk. Conversely, intakes of cereals, dark and whole-grain breads, packaged sweet and savory snacks, fruit-based products, and yogurt and dairy-based desserts were associated with lower risk. Notably, the inverse association between T2D risk and intakes of ultra-processed cereals was stronger than for ultra-processed dark and whole-grains breads, which could be due to differences in their contents of fibers, minerals, vitamins, and phytochemicals (27). This was somewhat reflected in the mediation analyses, where the relationship was more attributable to dietary fibers and minerals for dark and whole-grain breads compared with cereals. The inverse relationship between intakes of yogurt and dairy-based desserts and T2D risk is also consistent with the literature (28,29). Yogurt consumption, the most consumed food from this UPF subgroup, has repeatedly been associated with lower risk of T2D (28). Ice cream consumption has also been previously associated with a lower risk of T2D (29). Exact reasons underlying this association remain unclear but could be caused by its high content of dairy fat constituents (e.g., odd-chain fatty acids, milk fat globule membrane) (30) or reverse causation (i.e., healthier individuals may be more prone to consume ice cream than are individuals with known cardiometabolic risk factors) (29). The inverse associations between consumption of packaged savory and sweet snacks, including fruit-based desserts, and T2D risk could be explained by the content of these foods in terms of dietary fibers, especially because no evidence of an association was found for confectioneries. Indeed, albeit minor (<5%), dietary fibers had a mediation effect on the relationships between fruit-based products and packaged savory snacks and T2D. Thus, we cannot exclude

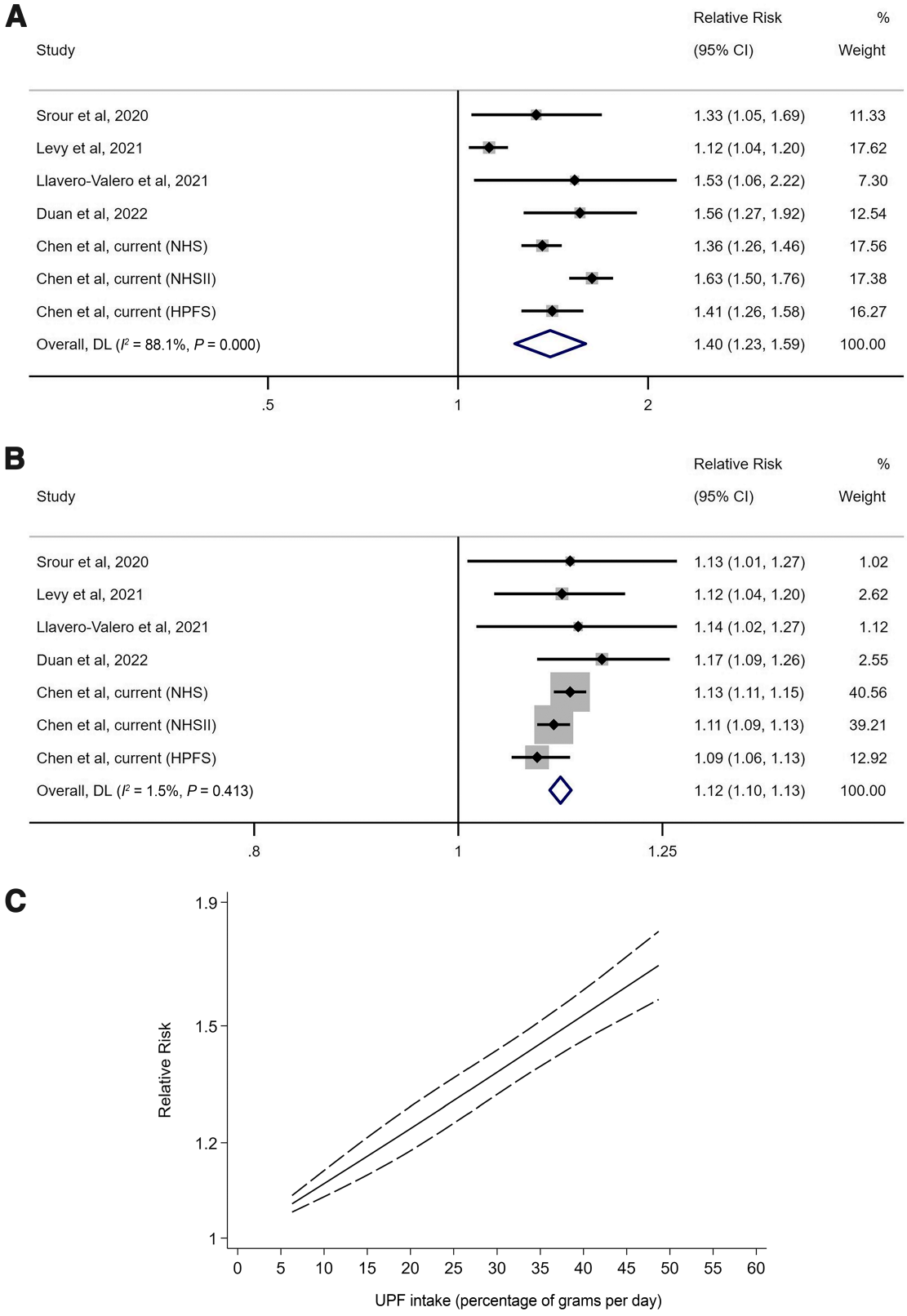

Figure 2—Meta-analyses of the association of total UPF consumption (in percentage of grams of UPF per day) with risk of T2D. *A*: Meta-analysis of high versus low total UPF intakes, using random effects meta-analyses. *B*: Meta-analysis for 10% increment in total UPF intake, using random-effects meta-analyses. *C*: Dose-response meta-analysis for UPFs and risk of T2D using restricted cubic splines ($P_{\text{nonlinearity}} = 0.90$). *A* and *B*: Weights of each of the studies are represented by the size of the square. Black diamonds represent the individual study effects, and black lines represent the 95% CIs. The overall effect estimates and 95% CIs are represented by the hollow diamond. DL, DerSimonian and Laird method.

that this association could also be driven by residual confounding associated with greater health consciousness of individuals consuming these foods. Still, other UPF subgroup–specific analyses and the related mediation analyses are consistent with findings reported in the literature and reflect adverse health effects of foods rich in added sugar, refined starch, sodium, and partially hydrogenated oils, with high glycemic index and low dietary fiber content (2,31). However, overall, the individual or combined mediation effects of the aforementioned nutrients accounted for <30% of the associations of total or subgroups of UPF. Beyond these traditional characteristics of nutritional quality, the variety of chemical compounds that are either added to UPF (e.g., emulsifiers, artificial sweeteners), formed during their manufacturing processes (e.g., acrylamide, acrolein metabolites), or released from their packaging materials (e.g., bisphenol A) have also been involved in T2D pathophysiology, such as weight gain, insulin resistance, and gut microbiota dysbiosis (2,4,32,33). Accordingly, we observed a significant mediating effect of BMI on the relationship between UPFs and T2D risk. More studies are needed to specifically assess the relative importance of emerging (i.e., ultra-processing–induced components) determinants of nutritional quality on the detrimental effects of UPF consumption on cardiometabolic health. Still, until then, our results have important implications for policy, because they allowed us to identify specific UPF categories that are particularly detrimental for cardiometabolic health. Work aiming at harmonizing UPF subgroup categorization and exploring the health effect of UPF subgroups is also needed to adequately translate these data into informed and consistent policies.

Another important question raised by the NOVA classification is whether the detrimental association between total UPF consumption and T2D risk is independent of overall diet quality (34). This question is analytically complex to evaluate because most diet-quality indices position specific UPFs as negative correlates of diet quality. For instance, in the AHEI-2010, intakes of sugar-sweetened beverages and processed meats negatively contribute to the score (35). To assess whether the association was attributable to diet quality, we conducted a sensitivity analysis in which non-UPF components of the diet quality were adjusted instead of total energy. Second, we conducted an analysis with stratification for diet quality. Overall, we found the positive association was not substantially attenuated by adjustment for non-UPF foods of diet quality, and the results were also consistent across the subgroups by overall diet quality.

The strengths of our analyses of the NHS, NHSII, and HPFS data include the long-term follow-up, the repeated assessments of diet and lifestyle, the low rates of loss to follow-up, and the large number cases. Furthermore, we conducted an extensive analysis of subgroups of UPF, and a series of sensitivity analyses, which provide extensive robustness of our findings. For the meta-analysis, the addition of the U.S. cohorts provides a more global perspective, because previous studies were limited to Europe. There are several limitations that are worth discussing. First, in the NHS, NHSII, and HPFS, dietary assessment was conducted using FFQs, which inevitably include measurement errors. However, the use of the cumulative average of repeated measured dietary data reduced random measurement errors caused by within-person variation. Furthermore, because FFQs do not cover the full spectrum of foods consumed, including UPFs, potential misclassification of some food items as ultra-processed may have introduced confounding, especially in UPF subgroup analyses (15). Indeed, given the lack of an assessment of validity of the FFQs used for assessing UPF intake in the three U.S. cohorts, it is acknowledged that the NOVA classification relies, at least partly, on assumptions and generalizations about food categories. A thorough validation study remains needed. Still, previous studies suggested that it was acceptable to use FFQs to identify and rank intake of UPFs (36,37). Also, the cohorts included primarily health professionals of Caucasian origin, which limits generalizability of our findings to other ethnic or socioeconomic groups. The latter also applies to results from the meta-analysis, because participants from all included cohorts had such profiles. Finally, although all cohorts in the meta-analyses had been controlled for a series of potential confounders, we cannot rule out the possibility of residual confounding due to nature of observational studies.

The results from both our cohort study and our meta-analysis show that total UPF consumption is associated with a higher risk of T2D. According to the NutriGrade scoring system, the meta-evidence we generated, supporting the positive association between total UPF consumption and T2D risk, are of high quality. However, some UPF subgroups were associated with lower risk in the U.S. cohorts. Overall, our study provides support for the current recommendations of limiting total UPF consumption, especially UPF subgroups associated with a higher risk of T2D.

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Author Contributions. J.-P.D.-C., Z.C., N.K., and F.B.H. conceived the study. Q.S., E.B.R., and J.E.M. were involved in data collection. Z.C. and C.D. screened the literature. Z.C. analyzed the data. J.-P.D.-C., N.K., and S.L.R. provided statistical expertise. Z.C. wrote the first draft of the article. All authors contributed to the interpretation of the results and revision of the manuscript for important intellectual content and approved the final version of the manuscript. Z.C. and J.-P.D.-C. are the guarantors of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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References

1. Monteiro CA, Cannon G, Levy RB, et al. Ultra-processed foods: what they are and how to identify them. Public Health Nutr 2019;22:936–941

2. Hall KD, Ayuketah A, Brychta R, et al. Ultra-processed diets cause excess calorie intake and weight gain: an inpatient randomized controlled trial of ad libitum food intake. Cell Metab 2019;30:67–77.e3

3. Rauber F, Chang K, Vamos EP, et al. Ultra-processed food consumption and risk of obesity: a prospective cohort study of UK Biobank. Eur J Nutr 2021;60:2169–2180

4. Chassaing B, Koren O, Goodrich JK, et al. Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome. Nature 2015;519:92–96

5. Srour B, Kordahi MC, Bonazzi E, Deschasaux-Tanguy M, Touvier M, Chassaing B. Ultra-

processed foods and human health: from epidemiological evidence to mechanistic insights. Lancet Gastroenterol Hepatol 2022;7:1128–1140
6. Srour B, Fezeu LK, Kesse-Guyot E, et al. Ultraprocessed food consumption and risk of type 2 diabetes among participants of the NutriNet-Santé prospective cohort. JAMA Intern Med 2020;180:283–291
7. Levy RB, Rauber F, Chang K, et al. Ultra-processed food consumption and type 2 diabetes incidence: A prospective cohort study. Clin Nutri 2021;40:3608–3614
8. Duan M-J, Vinke PC, Navis G, Corpeleijn E, Dekker LH. Ultra-processed food and incident type 2 diabetes: studying the underlying consumption patterns to unravel the health effects of this heterogeneous food category in the prospective Lifelines cohort. BMC Med 2022;20:7
9. Llavero-Valero M, Escalada-San Martín J, Martínez-González MA, Basterra-Gortari FJ, de la Fuente-Arrillaga C, Bes-Rastrollo M. Ultra-processed foods and type-2 diabetes risk in the SUN project: a prospective cohort study. Clin Nutri 2021;40:2817–2824
10. Schwingshackl L, Knüppel S, Schwedhelm C, et al. Perspective: NutriGrade: a scoring system to assess and judge the meta-evidence of randomized controlled trials and cohort studies in nutrition research. Adv Nutr 2016;7:994–1004
11. Bao Y, Bertoia ML, Lenart EB, et al. Origin, methods, and evolution of the three Nurses' Health Studies. Am J Public Health 2016;106: 1573–1581
12. Rimm EB, Giovannucci EL, Willett WC, et al. Prospective study of alcohol consumption and risk of coronary disease in men. Lancet 1991; 338:464–468
13. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. Am J Epidemiol 1992;135:1114–1126; discussion 1127–1136
14. Hu FB, Rimm E, Smith-Warner SA, et al. Reproducibility and validity of dietary patterns assessed with a food-frequency questionnaire. Am J Clin Nutr 1999;69:243–249
15. Khandpur N, Rossato S, Drouin-Chartier JP, et al. Categorising ultra-processed foods in large-scale cohort studies: evidence from the Nurses' Health Studies, the Health Professionals Follow-up Study, and the Growing Up Today Study. J Nutr Sci 2021;10:e77
16. Knott C, Bell S, Britton A. Alcohol consumption and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis of more than 1.9 million individuals from 38 observational studies. Diabetes Care 2015;38:1804–1812
17. Manson JE, Rimm EB, Stampfer MJ, et al. Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. Lancet 1991;338:774–778
18. Hu FB, Leitzmann MF, Stampfer MJ, Colditz GA, Willett WC, Rimm EB. Physical activity and television watching in relation to risk for type 2 diabetes mellitus in men. Arch Intern Med 2001; 161:1542–1548
19. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 1979; 28:1039–1057
20. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997; 20:1183–1197
21. Lin DY, Fleming TR, De Gruttola V. Estimating the proportion of treatment effect explained by a surrogate marker. Stat Med 1997;16:1515–1527
22. Rayat CS. Applications of Microsoft Excel in statistical methods. In Statistical Methods in Medical Research. Berlin, Germany, Springer, 2018, p. 139–146
23. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71
24. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol 1992;135:1301–1309
25. Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose–response data. Stata J 2006;6:40–57
26. Chen Z, Drouin-Chartier J-P, Li Y, et al. Changes in plant-based diet indices and subsequent risk of type 2 diabetes in women and men: three U.S. prospective cohorts. Diabetes Care 2021;44: 663–671
27. Hu Y, Ding M, Sampson L, et al. Intake of whole grain foods and risk of type 2 diabetes: results from three prospective cohort studies. BMJ 2020;370:m2206
28. Alvarez-Bueno C, Cavero-Redondo I, Martinez-Vizcaino V, Sotos-Prieto M, Ruiz JR, Gil A. Effects of milk and dairy product consumption on type 2 diabetes: overview of systematic reviews and meta-analyses. Adv Nutr 2019;10(suppl. 2):S154–S163
29. Chen M, Sun Q, Giovannucci E, et al. Dairy consumption and risk of type 2 diabetes: 3 cohorts of US adults and an updated meta-analysis. BMC Med 2014;12:215
30. Salas-Salvadó J, Guasch-Ferré M, Díaz-López A, Babio N. Yogurt and diabetes: overview of recent observational studies. J Nutr 2017;147: 1452S–1461S
31. Ley SH, Hamdy O, Mohan V, Hu FB. Prevention and management of type 2 diabetes: dietary components and nutritional strategies. Lancet 2014;383:1999–2007
32. Rancière F, Botton J, Slama R, et al.; D.E.S.I.R. Study Group. Exposure to bisphenol A and bisphenol S and incident type 2 diabetes: a case–cohort study in the French cohort D.E.S.I.R. Environ Health Perspect 2019;127:107013
33. Suez J, Cohen Y, Valdés-Mas R, et al. Personalized microbiome-driven effects of non-nutritive sweeteners on human glucose tolerance. Cell 2022;185:3307–3328.e19
34. Liu J, Steele EM, Li Y, et al. Consumption of ultraprocessed foods and diet quality among U.S. children and adults. Am J Prev Med 2022;62: 252–264
35. Chiuve SE, Fung TT, Rimm EB, et al. Alternative dietary indices both strongly predict risk of chronic disease. J Nutr 2012;142:1009–1018
36. Oviedo-Solís CI, Monterrubio-Flores EA, Cediel G, Denova-Gutiérrez E, Barquera S. Relative validity of a semi-quantitative food frequency questionnaire to estimate dietary intake according to the NOVA classification in Mexican children and adolescents. J Acad Nutr Diet 2022;122:1129–1140
37. Oviedo-Solís CI, Monterrubio-Flores EA, Rodríguez-Ramírez S, Cediel G, Denova-Gutiérrez E, Barquera S. A semi-quantitative food frequency questionnaire has relative validity to identify groups of NOVA food classification system among Mexican adults. Front Nutr 2022;9:737432