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Original article

Ultra-processed foods and type-2 diabetes risk in the SUN project: A prospective cohort study

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SUMMARY

Background & aim: The association between ultra-processed foods (UPF) consumption and the risk of type 2 diabetes (T2D) has not been much explored. We aimed to evaluate the association between consumption of UPF and the incidence of T2D.

Methods: We assessed 20,060 participants (61.5% women) from the SUN project (Seguimiento Universidad de Navarra) followed-up every two years (median follow-up 12 years). Food and drink consumption were evaluated through a validated 136-item food frequency questionnaire and grouped according to their degree of processing by the NOVA classification. Participants were categorized into tertiles of UPF consumption adjusted for total energy intake. We fitted Cox proportional hazard models with repeated dietary measurements at baseline and updating information on food consumption after 10 years of follow-up to minimise the potential effect of diet variation.

Results: During 215,149 person-years of follow-up, 175 new-onset T2D cases were confirmed. Participants in the highest baseline tertile (high consumption) of UPF consumption had a higher risk of T2D as compared to those in the lowest tertile (multivariable adjusted hazard ratio [HR] 1.53, 95% confidence interval [CI]: 1.06 to 2.22) with a significant dose–response relationship (p for linear trend = 0.024). The multivariable adjusted HR using repeated measurements of UPF intake was 1.65 (95% CI 1.14–2.38) when comparing extreme tertiles.

Conclusions: In a highly-educated Mediterranean cohort with a low absolute risk, a higher intake of UPF was independently associated with a higher risk for T2D. These results provide more evidence to encourage the limitation of UPF consumption to reduce the population burden of T2D.

1. Introduction

According to the last International Diabetes Federation (IDF) report, in 2019, approximately 463 million adults between 20 to 79 years had diabetes and 374 million people were at increased risk of developing type 2 diabetes (T2D). Furthermore, the proportion of people with T2D is increasing in most countries [1].

Dietary nutritional imbalances can drive to several cardiometabolic diseases [2]. T2D has always been linked to poor quality diet habits and overweight. In this context, several studies show that the displacement of non-ultra-processed by ultra-

Abbreviations: ADA, American Diabetes Association; BMI, Body mass index; FFQ, Food frequency questionnaire; HR, Hazard ratio; IDF, International Diabetes Federation; MUFAs, Monounsaturated fatty acids; PUFAs, Polyunsaturated fatty acids; SFAs, Saturated fatty acids; SUN, Seguimiento Universidad de Navarra; T2D, Type 2 diabetes; UPF, Ultra-processed foods.

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processed foods (UPF) is consistently associated with an overall deterioration of the nutritional quality of diets [3]. In fact, UPF are the main source (nearly 58%) of calories eaten in the US, and contribute almost 90% of the energy obtained from added sugars [4].

The NOVA Food Classification System defines UPF as industrial formulations made mostly or entirely from substances derived from foods and additives, with little or any intact unprocessed food. UPF are characterized by its low nutritional quality and high energy density products, with higher free sugar and sodium and lower content in fiber and protein compared to non-ultra-processed foods. Manufacturing techniques of UPF include extrusion, moulding, and preprocessing by means of frying [5]. Usually, these products are highly palatable, ready to consume and durable. They also tend to be low-cost products. These characteristics make UPF very attractive products often displacing the consumption of more nutritionally balanced foods.

Because of its nutritional profile, a high intake of UPF has been associated with several chronic diseases. In particular, our cohort has found a detrimental association between UPF and hypertension, obesity, depression and even all-cause mortality [6–9]. Specifically, the association between UPF consumption and the risk of T2D have not been much explored [10]. To our knowledge, no prior longitudinal epidemiological study had been published until recently, when Srour et al. [11] observed a higher risk of T2D associated with a higher proportion of UPF from the diet within the French NutriNet-Santé cohort after a median follow-up of six years. However, the NutriNet-Santé cohort only used measurements of UPF at baseline (with web-based 24 h dietary records repeated during the first 2 years) but they did not repeat the dietary assessment during follow-up. To our knowledge, when we sent our manuscript for the first time, no other previous cohort had assessed this association. For this reason, our objective was to assess the association between UPF consumption and the risk of T2D development in a large Mediterranean cohort (SUN cohort), a different population and setting from the previous results, and with a longer follow-up period.

2. Materials and methods

2.1. Study population

The SUN project (Seguimiento Universidad de Navarra) is a prospective, multipurpose, and dynamic cohort started in 1999. Details regarding the SUN Project design have been already published [12]. Briefly, the major aim of this cohort is to assess lifestyle determinants in the development of cardiovascular disease, diabetes, obesity, or depression, among other conditions. Graduate status is necessary as previous studies with university graduate samples have exhibited greater reliability and validity, and higher retention rates, particularly in studies requiring self-completion of extensive questionnaires. Participants are recruited through collaborations with alumni and professional associations throughout the country (e.g. Universidad de Navarra Alumni Association, regional associations of Physicians, Nurses, Pharmacists, Dentists, and Engineers). More than 50% of participants are health professionals (17.6% doctors, 13.2% pharmacists, 3.2% biologists, 14.1% nurses, 3.8% dietitians or nutritionists, 5.1% with other bio-sanitary university degree). Participants are invited to participate by means of a letter which briefly explains the SUN cohort objective, what their participation entails, and the collaboration that they will be asked over time. Currently, it is also possible to answer the questionnaire online through the study website. Information is collected from participants every 2 years, through validated questionnaires received by postal and/or e-mail, which included information about socio-demographic, lifestyle or dietary variables, as well as the prevalence or incidence of different diseases during the follow-up.

Up to December 2018, 22,790 participants completed their baseline questionnaire. To ensure a minimum follow-up of 2 years and 9 months to allow participants to complete and return the first follow-up questionnaire (an additional 9 months were provided to account for the lag time in returning the questionnaire), 323 participants who completed the baseline questionnaire after March 2016 were excluded. For the present analysis, we excluded 448 participants with total daily energy intake below or above percentiles 1 and 99, respectively. We also excluded 475 participants because of their lack of susceptibility to developing T2D (prevalent T2D, type 1 diabetes and other type of diabetes, pancreatectomy), and 1484 who were lost to follow-up (retention rate 93%). Finally, 20,060 participants were included in the analyses (Fig. 1).

The study was approved by the institutional review committee of the University of Navarra. Voluntary completion of the first questionnaire was considered to imply informed consent.

2.2. Dietary assessment

Dietary intake was assessed at baseline and again, after 10 years of follow-up, using a self-administered 136-item semiquantitative food frequency questionnaire (FFQ) previously validated in Spain [13–15]. We measured frequencies of consumption in nine categories (ranging from never or almost never to more than six servings daily), and the food frequency questionnaire included a typical portion size for each item. We multiplied the portion size by the frequency of consumption in order to estimate daily consumption for each food item. Adherence to a Mediterranean diet was evaluated using the score proposed by Trichopoulou et al. [16]. After excluding participants with implausible values for total energy intake, those participants with missing data in some items of the FFQ were considered as no consumption of the missing items. To minimise the potential effect of a variation in diet during follow-up, we fitted Cox proportional hazard models with repeated dietary measurements using the updated data on food consumption after 10 years of follow-up for those participants with available data ($n = 7265$), for those without dietary data at 10 years of follow-up we considered only baseline UPF consumption.

All food and beverages items included in the food frequency questionnaires were categorized into one of the four NOVA food groups [5]. The first group comprises unprocessed or minimally processed foods, which are natural foods that have been submitted to cleaning, removal of inedible or unwanted parts, fractioning, grinding, drying, fermentation, pasteurization, cooling, freezing, or other processes that may subtract part of the food, but which do not add oils, fats, sugar, salt or other substances to the original food. Examples in this groups are vegetables and fruits, seeds without salt or sugar added, eggs, legumes, fresh or pasteurized milk, yoghurt without sugar, coffee or herbal infusions. The second group refers to processed culinary ingredients that includes products extracted from natural foods or from nature by processes such as pressing, grinding, crushing, pulverizing, and refining. Items in this group may contain additives used to preserve the product's original properties. Examples for this group are vegetable oils, cooking salt or vinegar. The third group includes processed foods, which are relatively simple products made by adding sugar, oil, salt or other group 2 substances to group 1 foods, with the main purpose of increasing the durability of group 1 foods, or to modify or enhance their sensory qualities. Processes methods includes smoking, curing, or fermentation among others. Examples include canned or bottled vegetables, fruits and legumes, smoked meats, canned fish, cheeses and unpackaged freshly made breads. The fourth group

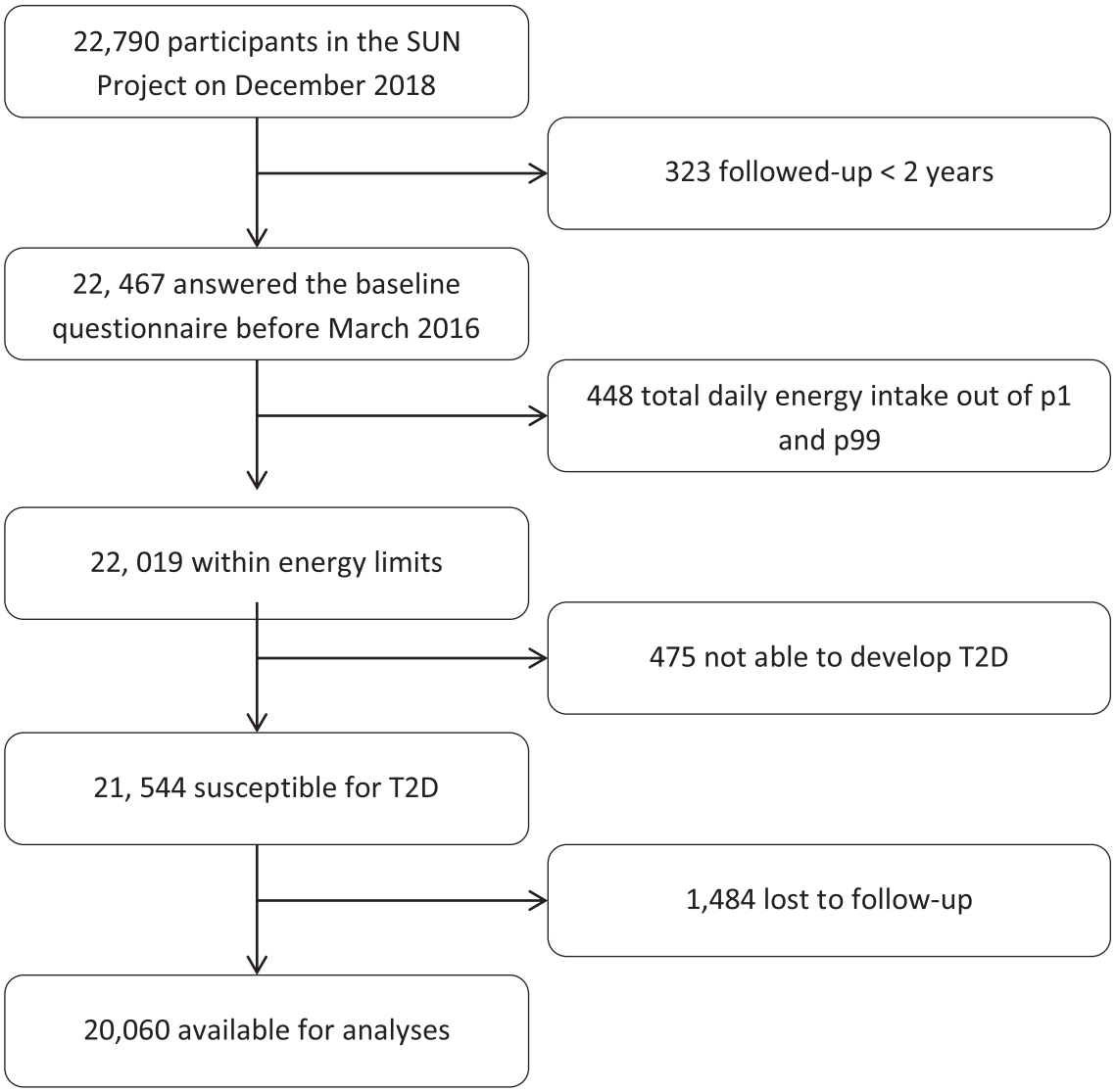

Fig. 1. Flow-chart of participants.

comprises ultra-processed foods and drink products that are industrial formulations made entirely or mostly from substances extracted from foods (oils, fats, sugar, starch, and proteins), derived from food constituents (hydrogenated fats and modified starch), or synthesized in laboratories from food substrates or other organic sources. Group 1 foods are a small proportion of, or are even absent from, ultra-processed products. Examples of this group include carbonated soft drinks, sweet or savoury packaged snacks, pastries, cakes and cake mixes, margarine, 'instant' sauces, fruit yogurts and fruit drinks, pre-prepared meat, pasta and pizza dishes, or meat and chicken extracts. In our study, we focused on this last group.

To estimate the frequency of consumption of UPF, we summed the amount consumed (grams per day) of each food item classified in the fourth category of the NOVA system (a total of 34 items). We adjusted UPF consumption for total energy intake through the residuals method [17]. After that, we divided the sample into tertiles according to total consumption of UPF.

2.3. Outcome assessment

The primary outcome was to assess the incidence of T2D among participants initially free of T2D. Those participants who reported T2D or were under insulin or oral antidiabetic drugs at baseline, were excluded. In each of the follow-up questionnaires repeated after every 2 years up to 18 year follow-up, participants were repeatedly inquired about medical diagnoses of T2D. If the participant reported a medical diagnosis of T2D during any of these 9 follow-up questionnaires, an additional questionnaire was sent, requesting further information. Participants were also asked to send their medical reports with all the specific details relevant to the diagnosis of T2D. Using the retrieved medical records and questionnaires, a blinded endocrinologist to UPF consumption classified the diagnosis as incident T2D diabetes or not, according to American Diabetes Association (ADA) criteria [18].

2.4. Other covariates

We also gathered information on sex, age, anthropometrics, using a questionnaire validated in a subsample of the cohort [19], sociodemographic characteristics, medical history, lifestyle and health-related habits including physical activity [20], television viewing time, smoking, following of any special diet at baseline (yes/no), and the habit of between-meal snacking (yes/no). We also built a 0-to-8-point active+sedentary lifestyle score, previously

developed in our cohort by Alvarez–Alvarez et al. [21], taking advantage of the extensive and previously validated information on physical activity and sedentary lifestyles collected at baseline [20]. The score was built based on the following 8 items: 1) Do you exercise? (No/Yes); 2) Exercise intensity (Light to moderate/Vigorous); 3) Energy expenditure (expending at least 16.1 METs-h/week, the cohort median); 4) Walking speed (Brisk or very brisk pace versus low or normal pace); 5) Walking time (min/d) (≥0.5 h/day versus < 0.5 h/day); 6) Climbing upstairs (≥3 floors/day versus ≤2 floors/day); 7) Television viewing time (h/d) (<1.5 h/day versus ≥1.5 h/day); 8) Sitting time (h/d) (<5 h/day versus ≥5 h/day).

2.5. Statistics

Firstly, we used inverse probability weighting to adjust participants' baseline characteristics for age and sex according to tertiles of UPF consumption in order to describe baseline characteristics of participants.

We conducted Cox regression models stratified by decades of age and year of recruitment at the cohort. We assessed the association between tertiles of UPF consumption and the risk of T2D using the lowest tertile as the reference category. To minimise the potential effect of a variation in diet during follow-up, we fitted Cox proportional hazard models with repeated dietary measurements using the updated data on food consumption after 10 years of follow-up.

Cox regression models were adjusted for several confounders: age, sex, tertiles of body mass index (BMI), educational level, family history of diabetes, smoking status, snacking, 8-item active + sedentary lifestyle score and following a special diet at baseline.

We also represented Nelson-Aalen survival curves (adjusted for potential confounding variables by means of inverse probability weighting methods) to describe the incidence of T2D over time across tertiles of UPF consumption.

Sensitivity analyses were also conducted by rerunning the models under different a priori assumptions: excluding prevalent cases of hypertension, cancer and cardiovascular disease to reduce the chance of reverse causality, among other scenarios, were carried out. Analyses further adjusting for Mediterranean diet, total energy intake or sugar difference intake during follow-up and saccharin intake were also performed to discard a healthy dietary pattern as a potential confounder or mediator of the studied association.

We also calculated Pearson correlation coefficient between Mediterranean diet and UPF consumption.

We considered p values of less than 0.05 to be statistically significant. Analyses were performed using STATA version 12.0 (StataCorp, College Station, TX).

3. Results

A total of 20,060 participants (61.5% women) were included in this analysis (Fig. 1). Mean age at baseline was 37.4 (SD 12.2) years and the median follow-up was 12 years. Overall, 175 new onset diabetes cases occurred during 215, 149 person-years of follow-up. Table 1 shows the baseline characteristics of participants according to tertiles of total UPF consumption adjusted for sex and age. Participants at the highest tertile of UPF consumption had a higher average BMI. Compared with participants in the first tertile, they were also more likely to be current smokers, to have higher level of university education, and more hypertension, depression, cancer and cardiovascular disease at baseline. They tended to snack more, consume more soft drinks and watch more TV. On average, they reached the lowest score at the Trichopoulou's 9-point score and did less physical activity. They also had the highest fat intake and the lowest protein consumption.

Participants at the highest tertile of UPF consumption had a 53% relatively higher hazard of new onset type 2 diabetes compared with those participants at the lowest tertile (HR 1.53; 95% CI 1.06 to 2.22; Table 2), with a significant dose–response relationship (p for trend 0.024).

Cox proportional hazard models were also fitted with repeated measurements using the updated data on food consumption after 10 years of follow-up. The hazard ratio for the third versus the first tertile was 1.65 (95% CI 1.14 to 2.38), with a p for trend of 0.023 (Table 2).

Figure 2 shows the cumulative hazard for type 2 diabetes development over time across tertiles of UPF consumption (adjusted for the same confounders that the multivariate model by inverse probability weighting). The highest tertile of UPF consumption (UPF_3) was associated with a higher incidence of type 2 diabetes.

Sensitivity analyses did not substantially change the results in any of the alternative scenarios (Table 3).

Pearson correlation coefficient between Mediterranean diet and UPF consumption showed only a weak negative relationship ($r = -0.16$, $p = <0.001$). Even after adjusting for adherence to Mediterranean diet the results remained very similar.

4. Discussion

A high intake of UPF has been associated with several cardiometabolic diseases but paradoxically, there is a lack of evidence about its effect on T2D, one of the major challenges to human health nowadays.

In this highly-educated Mediterranean cohort with a low initial absolute risk of T2D, a higher consumption of UPF was associated with an increased hazard for new onset type 2 diabetes, even after adjustment for a wide array of potential confounding factors. In addition, daily UPF consumption was adjusted for total energy intake. Our findings are in line with the results published by the NutriNet-Santé Prospective Cohort and consistently showed the higher risk of developing T2D associated with higher consumption of UPF [11]. In addition, our cohort supports this effect after a much longer follow-up and using repeated measurements of UPF intake. Furthermore, in order to be able to compare the amount of UPF consumed between our cohort and the NutriNet-Santé cohort, we have calculated the proportion of UPF in the diet in grams/per in the SUN cohort. We have found a mean of 9.5% (SD: 6.6) while the French cohort achieves a mean % of 17.29 (SD 9.81). So, despite that our mean % consumption of UPF is much lower, we found a significant direct association between UPF consumption and T2D. In addition, our results of consumption in percentage of weight are in agreement with results obtained in a subsample of the PREDIMED-PLUS study, Spanish men and women aged 55–75 years with overweight/obesity and metabolic syndrome (% of UPF consumption: 8.11, SD:7.41) [22]. Differences in percentages of UPF consumption between French and Spanish populations might be explained because of different methods to gather information on UPF consumption as well as different dietary habits.

Our results are also in line with the results of the UK Biobank published meanwhile our paper was under review by Renata B.Levy et al. [23], which showed a gradient of elevated risk of T2D associated with increasing quartiles of UPF intake after a mean follow-up of 5.4 years. Once again, the SUN cohort supports these results after a longer follow-up and using repeated measurements of UPF intake. Furthermore, as with the NutriNet-Santé Prospective Cohort, the mean UPF intake of the UK BioBank was much higher than ours (22.1% vs 9.5%).

Table 1
Age and sex-adjusted[a] characteristics of the SUN participants according to tertiles of ultra-processed consumption.

	TERTILES OF UPF			
	UPF1 <214.6 g/d	UPF 2 214.6 g/d – 323.3 g/d	UPF 3 >323.3 g/d	p value[b]
N	6687	6687	6686	
Age[c] (years) (SD)	37.3 (11.8)	37.3 (12.2)	38.2 (13.5)	0.024
Women[c] (%)	59.9	61.0	60.6	0.52
BMI (kg/m^2) (SD)	23.2 (3.3)	23.4 (3.4)	23.7 (3.8)	<0.001
Smoking status (%)				<0.001
Never	50.5	48.2	48.0	
Current	19.1	22.9	24.5	
Former	30.5	28.9	27.5	
Education level (%)				<0.001
Graduate	74.3	73.0	70.5	
Postgraduate	6.6	7.5	8.0	
Doctorate	8.8	10.2	11.3	
Family History of T2D (%)	14.3	14.3	14.5	0.63
Prevalent Hypertension (%)	17.9	19.0	20.8	<0.001
Prevalent cancer (%)	3.2	3.2	3.6	0.61
CVD at baseline (%)	1.4	1.2	1.9	0.004
Hypercholesterolemia (%)	16.6	16.3	16.7	0.09
Prevalent depression (%)	10.3	10.9	12.9	<0.001
Trichopoulou's 9-point score (SD)	4.9 (1.7)	4.0 (1.7)	3.7 (1.7)	<0.001
Energy intake (kcal/day)	2711.0 (756.3)	2309.5 (722.6)	2540.3 (818.2)	<0.001
Physical activity (METs-h/wk) (SD)	26.1 (25.1)	21.8 (20.7)	21.5 (21.4)	<0.001
Snacking (%)	31.1	34.4	38.9	<0.001
Soft drinks (portions/day) (SD)	0.1 (0.1)	0.1 (0.2)	0.4 (0.7)	<0.001
TV hours/day (SD)	1.6 (1.2)	1.6 (1.1)	1.7 (1.2)	<0.001
Protein intake (% of E) (SD)	18.1 (3.3)	18.3 (3.2)	17.5 (3.2)	<0.001
Carbohydrate intake (% of E) (SD)	44.3 (7.8)	42.8 (7.1)	43.5 (7.1)	<0.001
Fat intake (% of E) (SD)	35.7 (7.1)	37.0 (6.2)	37.1 (6.2)	<0.001
SFAs (% of E) (SD)	11.7 (3.3)	12.7 (3.0)	13.1 (3.2)	<0.001
PUFAs (% of E) (SD)	4.9 (1.5)	5.3 (1.5)	5.4 (1.6)	<0.001
MUFAs (% of E) (SD)	15.7 (4.0)	15.8 (3.5)	15.6 (3.4)	0.035

Continuous variables are expressed as means and (standard deviation) and categorical variables as percentages.
E: energy, MUFAs: Monounsaturated fatty acids, PUFAs: Polyunsaturated fatty acids, SFAs: Saturated fatty acids.
[a] Adjusted through inverse probability weighting.
[b] Through ANOVA and Chi-squared test weighted by the inverse probability weighting method.
[c] Not adjusted.

Table 2
Cox proportional HRs and 95% CI for incident T2D according to baseline consumption of ultra-processed foods.

	TERTILES			
	1	2	3	P trend
Incident TD2	66	53	56	
Person-years	72 121	72 078	70 950	
Age and sex adjusted	1.00 (reference)	1.09 (0.76–1.57)	1.66 (1.15–2.41)	0.007
Multivariable adjusted[a]	1.00 (reference)	0.99 (0.69–1.43)	1.53 (1.06–2.22)	0.024
Repeated dietary measurements¶				
Age and sex-adjusted	1.00 (reference)	1.14 (0.79–1.64)	1.70 (1.18–2.47)	0.005
Multivariable adjusted[b]	1.00 (reference)	1.07 (0.74–1.54)	1.65 (1.14–2.38)	0.023

[a] Adjusted for sex, age, tertiles of body mass index, educational status, family history of diabetes, smoking status, snacking between meals, 8-item active + sedentary lifestyle score, and following a special diet at baseline. Stratified by decades of age and recruitment period.
[b] Model with repeated measures (updated data at 10 years of follow-up).

In terms of grams/day of daily UPF consumption, the mean consumption in our cohort is 295.8 gr/day (SD: 217.4). The ENRICA study [24], a population-based cohort study of a representative sample of the noninstitutionalized Spanish population, describes an average consumption of UPF of 384.70 g/day, which is higher than ours. This was to be expected, given that participants of the SUN cohort are university graduates, they have higher educational level and greater health consciousness than the general population and probably their consumption is lower.

Different mechanisms might be involved in the observed association between a high consumption of UPF and increased T2D risk. First of all, UPF usually has a high energy density and a low nutrient density; UPF often contain high amount of added sugars, which can lead to energy disbalance and overweight, both of them recognized risk factors for the development of T2D [25–27]. Nonetheless, our multivariate analysis has been adjusted for baseline BMI. Added sugar could also dysregulate hepatic metabolism of fructose and by this way, may promote hepatic and whole-body insulin resistance. In fact, the high prevalence of non-alcoholic fatty liver disease observed in T2D may also represent the effects of endogenous fructose accumulation [28]. Added fructose is associated with a higher likelihood of low-grade inflammation and oxidative stress which can cause β-cell damage and reduce insulin secretion [29].

Another mechanism underlying the association between UPF and T2D is the low fiber content characteristic of UPF. High-fiber foods take longer to digest so their satiating power is higher than those foods with low fiber content like UPF. In addition, high-fiber diets reduce absolute values of glycated hemoglobin and fasting

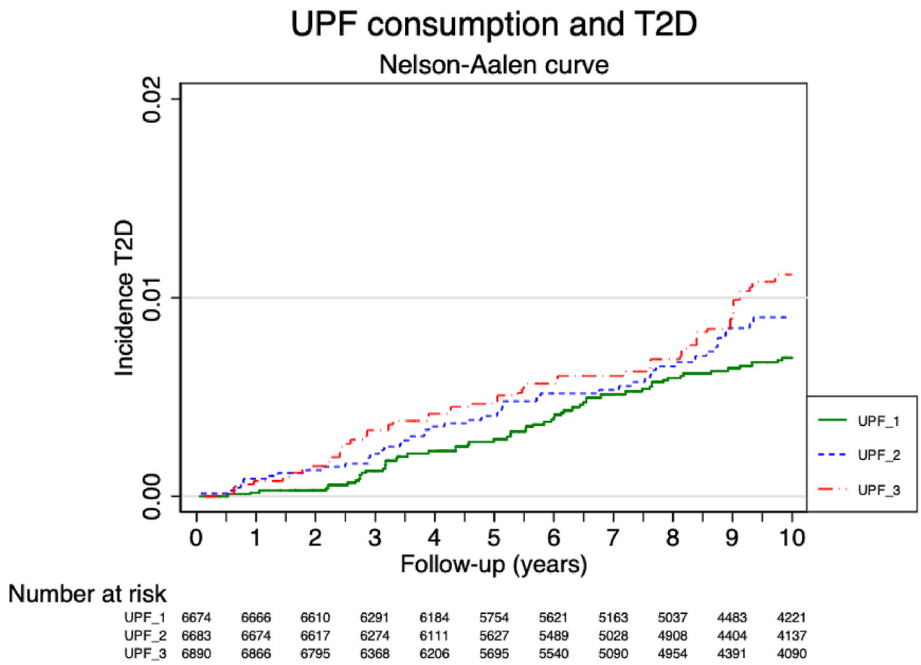

Fig. 2. Nelson-Aalen estimate of the incidence of type 2 diabetes according to tertiles of ultra-processed consumption.

Table 3
Sensitivity analysis for incident T2D according to baseline consumption of ultraprocessed food (third tertile versus first tertile).

VARIABLE	N	Incident T2D	HR (95% CI)
Overall[a]	20 060	175	1.53 (1.06–2.22)
Including only women	12 344	43	1.32 (0.59–2.94)
Including only men	7716	132	1.59 (1.03–2.43)
Excluding participants with family history of T2D	17 029	107	1.32 (0.82–2.13)
Willett's energy limits (<800 kcal/d or >4000 kcal/d in men and <500 kcal/d or >3500 kcal/d in women)	18 382	166	1.59 (1.08–2.33)
Energy limits: percentiles 5–95	18 039	159	1.64 (1.11–2.43)
Excluding participants with prevalent hypertension	16 286	66	1.60 (0.88–2.90)
Excluding participants with prevalent cancer	19 414	164	1.67 (1.13–2.46)
Excluding participants with prevalent cardiovascular disease	19 776	163	1.57 (1.06–2.31)
Additionally adjusting for Mediterranean diet	20 060	175	1.50 (1.02–2.21)
Additionally adjusting for difference sugar added intake during the follow-up and daily saccharin intake	2060	175	1.52 (1.05–2.21)
Additionally adjusted for total energy intake	2060	175	1.52 (1.05–2.22)

[a] Adjusted for sex, age, tertiles of body mass index, educational status, family history of diabetes, smoking status, snacking between meals, 8-item active + sedentary lifestyle score, and following a special diet at baseline. Stratified by decades of age and recruitment period.

plasma glucose in patients with type 2 diabetes [30], probably, by decreasing the rate of glucose absorption and consequently reducing the postprandial plasma glucose [31,32].

Finally, UPF have plenty of chemical additives, synthetic antioxidants and preservatives, present in both food itself and in the packaging [33]. It is known that food additives can release several chemicals that behave as endocrine-disruptors. At the same time, emerging evidence indicates an association between exposure to endocrine-disruptors and diabetes [34,35], like organophosphates present in oil additives or bisphenol A, used in plastic products. The use of non-caloric artificial sweeteners also present in UPF such us aspartame, sucralose or saccharin, known as an alternative safe option for diabetic patients, is currently controversial because they might produce deleterious metabolic effects [36].

4.1. Strengths and limitations

There are several strengths of our study including its long follow-up period with repeated dietary measurements, a high retention rate (93%), the use of validated methods and the adjustment for a wide range of potential confounders. In addition, the selection of only highly-educated participants, with more than fifty percent of them working as health professionals themselves, contributes to a higher quality and reliability of their self-reported information.

Middle-aged, highly educated adults, with an initial low BMI and with relatively high levels of physical activity are expected to present at baseline a very low absolute risk of T2D and this feature of the cohort design can contribute to prevent reverse causality. The results were confirmed in sensitivity analysis after excluding prevalent cases of hypertension, cancer and CVD, further supporting the chances of reverse causality.

The present study has also some limitations. Firstly, it is an observational study, therefore we cannot rule out the existence of residual confounding because unmeasured confounders may exist. However, the multivariate analysis has been adjusted for a wide number of potential confounders. Secondly, the cohort is made up of university graduates, of which more than 50% are health

professionals. This fact reduces the representativeness of the sample but, on the other hand, it increases the quality of their self-reported data. Thirdly, possibly due to the young mean age of our population, we found a low incidence of new onset diabetes and some analyses can be underpowered. Last, the food frequency questionnaire was not specifically designed to collect data about the new NOVA classification of UPF consumption. The study did not include cereal and energy bars, energy drinks, health and slimming products, and meat or vegetable nuggets, because we did not have information on the consumption of these items. This could lead to an underestimation of UPF consumption, potentially biasing results towards the null.

In conclusion, our study suggests that a high consumption of UPF was associated with a higher risk of T2D. The increasing T2D prevalence in our society demands an active prevention. Promoting the adherence to a minimally processed food, such as the traditional Mediterranean diet, could protect against T2D [37–40]. Due to the fact that T2D is increasing rapidly worldwide, the adoption of high-quality dietary patterns should be considered as a major priority to confront this huge public health problem.

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Authors' contributions

Conception and design: M.LL-V and M.B.-R. Acquisition, analysis and interpretation of data: M.LL-V and M.B.-R. Statistical analysis: M.LL.-V under the supervision of M.B.-R. Funding: M.A.M-G and M.B-R. Drafting of the manuscript: M.LL.-V. Critical revision of the manuscript for important intellectual content: M.B-R, J.E-S.M, M.A.M.-G, F.J.B.-G, C. F-A. All authors read and approved the final version.

Conflict of interest

No financial disclosures were reported by the authors of this paper.

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