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Original article

Simple sugar intake and cancer incidence, cancer mortality and all-cause mortality: A cohort study from the PREDIMED trial

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SUMMARY

Objective: To examine associations between intake of simple sugars and cancer incidence, cancer mortality, and total mortality in a prospective cohort study based on the PREDIMED trial conducted from 2003 to 2010.
Methods: Participants were older individuals at high cardiovascular risk. Exposures were total sugar, glucose and fructose from solid or liquid sources, and fructose from fruit and 100% fruit juice. Cancer incidence was the primary outcome; cancer mortality and all-cause mortality were secondary outcomes. Multivariable-adjusted, time-dependent Cox proportional hazard models were used.
Results: Of 7447 individuals enrolled, 7056 (94.7%) were included (57.6% women, aged 67.0 ± 6.2 years). 534 incident cancers with 152 cancer deaths and 409 all-cause deaths were recorded after a median follow-up of 6 years. Intake of simple sugars in solid form was unrelated to outcomes. Higher cancer

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; CI, confidence interval; FFQ, food frequency questionnaire; HRs, hazard ratios; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids; PREDIMED, PREvención con DIeta MEDiterránea; SFAs, saturated fatty acids; SSB, sugar-sweetened beverages.

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incidence was found per 5 g/day increase in intake of liquid sugars, with multivariable-adjusted HR of 1.08 (95% CI, 1.03–1.13) for total liquid sugar, 1.19 (95% CI, 1.07–1.31) for liquid glucose, 1.14 (95% CI, 1.05–1.23) for liquid fructose, and 1.39 (95% CI, 1.10–1.74) for fructose from fruit juice. Cancer and all-cause mortality increased to a similar extent with intake of all sugars in liquid form. In categorical models, cancer risk was dose-related for all liquid sugars.

Conclusions: Simple sugar intake in drinks and fruit juice was associated with an increased risk of overall cancer incidence and mortality and all-cause mortality. This suggests that sugary beverages are a modifiable risk factor for cancer and all-cause mortality.

1. Introduction

The prevalence of obesity and type-2 diabetes are increasing globally [1,2], and there is accumulating evidence that these two conditions are associated with the incidence of some types of cancer. In 2012, 5.7% of incident cancers worldwide, amounting to nearly 800,000 new cases, were attributable to the combined effects of diabetes and a high body mass index (BMI) [3]. Cancer-related mortality is also increased in patients with diabetes compared to non-diabetics [4]. Independently of diabetes status, overweight and obesity are strongly associated with cancer risk [5,6].

Sugar-sweetened beverages (SSB) are an important contributor to the "diabesity" epidemic. SSB intake promotes weight gain, as energy compensation does not work equally well with liquid than solid foods [7]. Given the strong link of sugary drinks with obesity and diabetes [8,9], there has been an increasing interest in the putative cancer risk of SSB and fructose intake [10,11]. A recent systematic review of longitudinal studies [12] indicated that there was no clear association between total sugar intake and cancer risk. Similarly, the 2018 report of the World Cancer Research Fund/American Institute for Cancer Research on nutrition and cancer concluded that evidence was not sufficient to support a link between sugar intake and cancer risk [13]. Concerning sugars and cancer-related mortality, data from large prospective studies are inconclusive, as no association [14], a weak positive association [15], and a U-shaped relationship [16] have been reported.

We hypothesized that simple sugar intake would be associated with cancer incidence and mortality in individuals at high risk. Therefore, we assessed the association of intake of sugars by source with these outcomes, as well as cardiovascular disease (CVD) and all-cause mortality, in a population at high risk because of old age and high prevalence of obesity and diabetes, drawn from the PREvención con DIeta MEDiterránea (PREDIMED) study [17].

2. Material and methods

The PREDIMED study is a multicenter, randomized clinical trial testing the efficacy of Mediterranean diets enriched with extra-virgin olive oil or mixed nuts against a control diet for the primary prevention of CVD in older individuals at high cardiovascular risk [18,19]; results on the main outcome have been published [17].

2.1. Study subjects

We used data from the PREDIMED study [17] considered as a prospective cohort. PREDIMED enrolled 7447 participants, aged 55–80 years, with 57% women. The recruitment took place between October 2003 and June 2009. The trial was completed in December 2010; endpoints for the present analysis were based on an extended follow-up until June 2012. Data were analyzed from January 22 to September 3, 2020.

2.2. Measurements and assessment of confounders

Information about medical, socio-demographic, anthropometric, and lifestyle variables was obtained at baseline and updated yearly. The validated Spanish version of the Minnesota questionnaire was used to assess leisure-time physical activity [20,21]; time spent in several activities in minutes/d was multiplied by its typical energy expenditure, expressed in metabolic equivalent tasks (METs). Dietary habits were collected at baseline and yearly via a validated semi-quantitative food frequency questionnaire (FFQ) [22] administered in face-to-face interviews by trained dieticians. The FFQ included 137 food items, and frequencies of consumption were reported on an incremental scale with 9 levels (never or almost never; 1–3 times/month; 1, 2–4, and 5–6 times/week; and 1, 2–3, 4–6, and >6 times/day). The estimated daily energy and nutrient intake of each individual were calculated from intake frequencies, weighted for portion sizes, using Spanish food composition tables [23]. The reproducibility was assessed with repeated FFQs using four 3-d diet records as references to examine validity, as described [6]. The respective intraclass correlation coefficients for reproducibility and relative validity were 0.865 and 0.559 for glucose and 0.903 and 0.592 for fructose ($P < 0.001$).

Simple sugar intake was estimated for each participant based on total intake of sucrose and the monosaccharides glucose and fructose, derived from their content in each food item. Sucrose was the only disaccharide considered; as sucrose is split into fructose and glucose in the intestinal lumen, the sucrose amount in grams for each food item was divided by two and added to its content of fructose and glucose, as appropriate. Consequently, three types of sugar intake were considered: total sugar (fructose + glucose), fructose and glucose. Fructose in fruit juice was derived from reported intakes of 100% fruit juice, usually from citrus fruits. As table sugar, expressed as number of daily teaspoons, was a specific question in the food frequency questionnaire (FFQ) [22], its association with outcomes was assessed separately.

2.3. Ascertainment of outcomes

Cancer incidence was a secondary outcome in the original study protocol. All cancer sites, excluding non-melanoma skin cancer, were included as relevant outcomes in the yearly interim analyses prepared for the Data and Safety Monitoring Board of the PREDIMED trial. Confirmation of incident cancer cases was based on pathology or cytology reports (82%). Cases of cancer were otherwise accepted when strong clinical and radiological or laboratory marker evidence was available. All outcomes were reported to the endpoint adjudication committee, whose members were blinded to treatment allocation and sugar intake. The committee confirmed major events, determined the cause of death, and updated yearly information on these endpoints. The endpoints for the present study were total cancer incidence and cancer mortality, CVD mortality, and all-cause mortality. Outcomes were ascertained through

contact with families and general practitioners, review of medical records, and consultation of the National Death Index. The medical records of deceased participants were requested to determine the cause of death. This allowed the assessment of mortality regardless of attrition, thus mortality results were not affected by dropout rates.

2.4. Statistical analyses

Participants with prevalent cancer (n = 159), total energy intakes beyond predefined limits (500–3500 kcal/d for women and 800–4000 kcal/d for men) (n = 154), and those with incomplete dietary information in the FFQ (n = 78) were excluded from analyses (Fig. 1). To take advantage of the repeated measurements of food consumption, we used yearly updated measures of simple sugar intake with data from baseline to the last FFQ before the occurrence of pre-specified outcomes.

Follow-up time was calculated as the interval between the date of randomization and the date of cancer diagnosis, death, or end of follow-up (the date of the last visit or the last recorded clinical event of participants while still alive), whichever came first. Cancer incidence was the primary outcome for this prospective study. Cancer mortality, CVD mortality, and all-cause mortality were secondary outcomes. Cox regression models were used to assess the relationship between simple sugar intake and the subsequent incidence of any type of cancer, and cancer, CVD and all-cause mortality. Sugar intakes were modeled as continuous variables and hazard ratios (HRs) and their 95% confidence intervals (CIs) for each outcome were calculated per increases in total sugar, glucose, fructose and fructose in fruit juice of 5 g/d, which corresponds to ≈50 mL of an SSB for total liquid sugar and ≈100 mL for individual liquid sugars. Additionally, HRs was calculated per each increase in 1 teaspoon/d of table sugar (1 teaspoon = 5 g of sugar). Regression models were constructed for intake of total sugar, glucose and fructose in solid foods; and total sugar, glucose, and fructose in liquid foods, as well as fructose from fruit, fructose in 100% fruit juice, and teaspoons of table sugar. We categorized solid sugar intake into quartiles, assigning the reference category to the first quartile, and liquid sugar intake into tertiles of participants with any intake, as there were many with zero intakes (reference category). The median values of each category were modeled as continuous variables to examine linear trends. Multivariable regression models were stratified by recruitment center and adjusted for sex, age, history of diabetes (yes/no), history of hypertension (yes/no), history of dyslipidemia (yes/no), smoking habit (never, current and former), BMI, total energy intake, alcohol intake, physical activity (METs/min/d), aspirin intake (yes/no), vitamin supplementation (yes/no), family history of cancer (yes/no), salt intake (g/day), red meat consumption (g/day), processed meat consumption (g/day), adherence to Mediterranean diet score (0–14 points), intervention group, and yearly (time-dependent variable) change in simple sugar intake. In PREDIMED there were small departures from the individual randomization protocol, as 425 members of the same household of a previously randomized participant were directly allocated to the same intervention arm and 441 participants from one of the 11 recruiting centers (site D) were allocated by clusters (clinics) instead of using individual randomization [3]. To account for intra-cluster correlations, we additionally adjusted Cox models for robust variance estimators, considering as clusters the members of the same household and the participants in the same clinics of site D.

We further estimated cancer risk when liquid sugars were replaced by other nutrients in energy-density models that included total energy intake, saturated fatty acids (SFAs), trans fatty acids, monounsaturated fatty acids (MUFAs), polyunsaturated fatty acids (PUFAs), total protein, sugar from solid sources, complex carbohydrates, and alcohol. By leaving liquid sugars out of the model, regression coefficients for the alternate nutrients can be interpreted as the estimated effect of isocalorically substituting the nutrients of interest for liquid sugars while holding total energy and other nutrients constant. Because energy intake and BMI and their changes could be in the causal pathway between intake of liquid sugars and outcomes, we performed sensitivity analyses by leaving energy intake and baseline BMI out of the models and also by controlling for yearly-updated changes in energy intake and BMI.

All statistical tests were 2-sided, and $P < 0.05$ was considered statistically significant. Analyses were conducted using SAS software, version 9 (SAS Institute). Data were analyzed from January 22 to March 11, 2020.

3. Results

3.1. Patients and characteristics

Of the PREDIMED cohort of 7447 participants, 7056 (94.7%) were included in the study, 4063 women (57.6%) and 2993 men (42.4%), with a mean (SD) age of 67.0 (6.2) years. By study design, there was a high prevalence of obesity (53.1%) and diabetes (49%). Baseline characteristics of participants included in analyses were similar to those of participants excluded, except for slightly different intervention allocation rates (Table S1 in Supplementary data). After a median follow-up of 6 years, 534 new cancers with 152 cancer deaths, 102 CVD deaths, and 409 all-cause deaths were recorded. The site and frequency of documented cancers are described in Table S2 in Supplementary data. Prostate, breast and colorectal, in this order, were the most frequently diagnosed cancer sites. Baseline characteristics of the total cohort and of study subjects distributed in quartiles of total sugar intake are presented in Table 1. Those with higher sugar intake were more frequently women and had a higher prevalence of hypertension, dyslipidemia and smoking, with higher Mediterranean diet score, vitamin supplements, energy intake and physical activity levels, but a lower frequency of diabetes and lower alcohol intake. Baseline intake of simple sugars by source for the total population and of study subjects distributed in quartiles of sugar intake is depicted in Table 2. Intake of liquid sugars or fruit juice was low in this older Mediterranean cohort: 57.5% of participants reported any intake of total sugars in liquid form and 29.3% reported intake of 100% fruit juice.

3.2. Outcomes by sugar source

In multivariable-adjusted Cox models, total sugar intake (Table S3 in Supplementary data) and simple sugar intake in solid form, either as total solid sugar, solid glucose, solid fructose, or fructose present in fruits, were unrelated to outcomes (Fig. S1 in Supplementary data). In contrast, a 5 g/day increase in intake of total liquid sugar, liquid glucose, liquid fructose, or fructose in fruit juice was positively associated with cancer risk, cancer-related mortality, and all-cause mortality (Fig. 2). For every outcome, the highest risk was associated with intake of fructose from fruit juice.

Table sugar intake was also associated with risk of all-cause mortality (HR 1.07; 95% CI, 1.00–1.14 for each intake of 1 teaspoon/d) (Table S4 in Supplementary data).

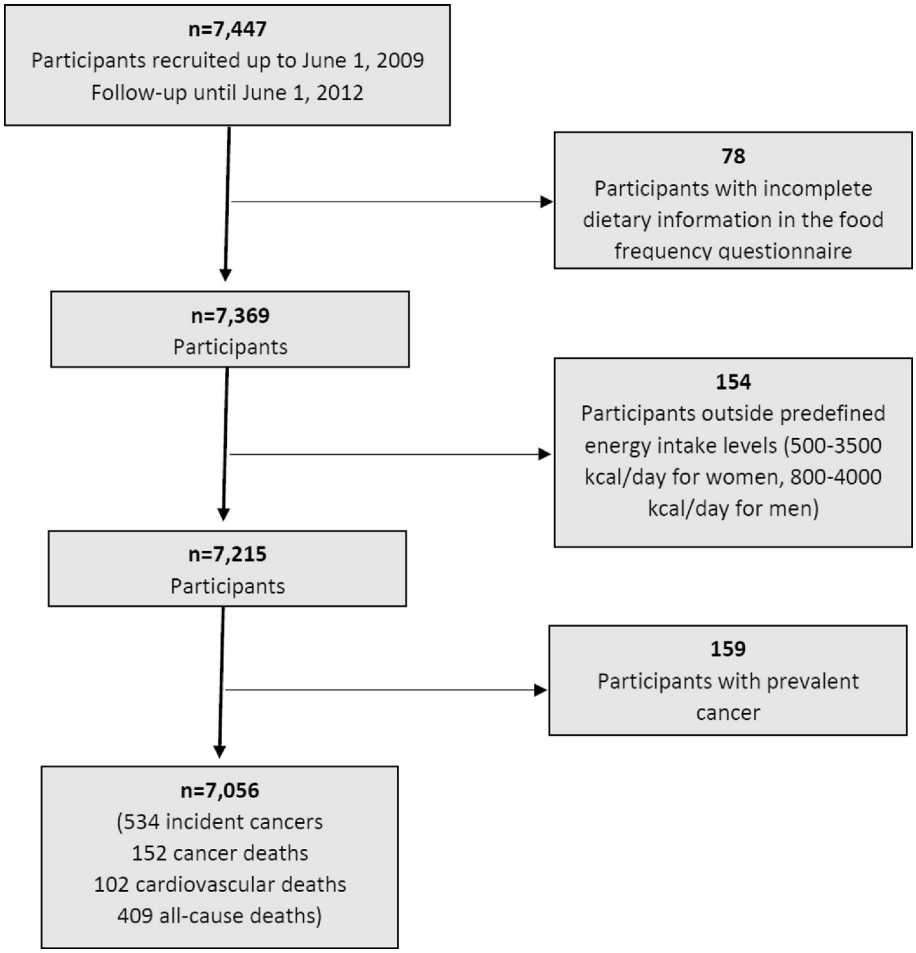

Fig. 1. Flowchart depicting the selection of participants in the PREDIMED study included in the present analysis.

Table 3 depicts HRs for the outcomes of interest by categories of liquid sugar intake. Cancer risk increased linearly with increasing doses of liquid sugars. Compared with non-consumers, individuals in the top category of intake of total liquid sugar, liquid glucose, liquid fructose and fructose in fruit juice had significant increases in cancer risk ranging from 30% to 51% in multivariable-adjusted models. For liquid sugars, cancer and all-cause mortality increased non-significantly in a dose-dependent manner, except for a significant increase in cancer mortality for liquid fructose. No associations were observed for CVD mortality. Categories of solid sugar intake were unrelated to outcomes (Table S5 in Supplementary data). Participants in the highest category of table sugar intake had higher cancer and all-cause mortality (Table S6 in Supplementary data).

3.3. Substitution and sensitivity analyses

Results for the main substitution analyses are presented in Table 4. Isocaloric replacement of liquid sugars by the other main nutrients was associated with a 28%–36% reduction in cancer risk, which was statistically significant for all nutrients except *trans* fatty acids. When liquid sugars were replaced for MUFAs, sugars from solid sources or complex carbohydrates, cancer mortality risk was significantly reduced from 36% to 41%. Replacement of liquid sugars by PUFAs reduced all-cause mortality by 34% (Table S7 in Supplementary data).

The findings for liquid sugars and cancer risk were not materially changed when baseline energy intake and BMI were left out of the models or when we adjusted for yearly-updated changes in energy intake and BMI (Table S8 in Supplementary data).

3.4. Subgroup analyses

In stratified analyses (Tables S9-S11 in Supplementary data), the associations persisted in all subgroups except for an interaction ($P = 0.016$) on all-cause mortality between total liquid sugars and dyslipidemia; the HRs per 5 g/day increase were 1.14 (95% CI, 1.07–1.21) among dyslipidemic participants vs. 0.96 (95% CI, 0.85–1.09) among those without dyslipidemia. Mutual adjustment of the models for sugars from solid and liquid sources had no effect on the observed associations (Tables S12 and S13 in Supplementary data).

4. Discussion

In this prospective study of individuals at high risk of CVD and cancer, we found a significant association of simple sugar intake in liquid form (total sugar, glucose and fructose, including fructose from fruit juice) with an increased risk of cancer incidence and mortality. The association remained significant after adjustment for the main recognized risk factors for cancer, as well as after adjustment for daily energy intake and annual change in simple sugar intake. The findings for cancer incidence were consistent when assessed by categories of liquid sugar intake, for which linear dose–response associations were observed. Cancer incidence and

Table 1
Baseline Characteristics of the 7056 Study Subjects by Total Sugar Intake quartiles.

Characteristic	Total n = 7056	≤47 g/day n = 1764	>47 to 62.2 g/day n = 1757	>62.2 to 81.8 g/day n = 1770	>81.8 g/day n = 1765	*P* value[a]
Men	2993 (42.4)	785 (44.5)	757 (43.1)	743 (42.0)	708 (40.1)	0.059
Age (years)	67.0 (6.2)	66.9 (6.2)	67.1 (6.3)	67.0 (6.2)	67.0 (6.2)	0.714
Body mass index (kg/m^2)	29.97 (3.9)	30.06 (3.97)	29.97 (3.89)	29.96 (3.76)	29.89 (3.83)	0.642
Diabetes, n (%)	3455 (49.0)	768 (43.5)	834 (47.5)	932 (52.7)	1067 (60.5)	<0.001
Hypertension, n (%)	5838 (82.7)	1444 (81.9)	1428 (81.3)	1460 (82.5)	1506 (85.3)	0.008
Dyslipidemia, n (%)	5098 (72.3)	1210 (68.6)	1239 (70.5)	1287 (72.7)	1362 (77.2)	<0.001
Family history of cancer, n (%)	3466 (49.1)	806 (45.7)	869 (48.5)	873 (49.3)	918 (52)	0.003
Smoking habit, n (%)						0.002
Never	4341 (61.5)	1018 (57.7)	1077 (61.3)	1107 (62.5)	1139 (64.5)	
Current	985 (14.0)	287 (16.3)	244 (13.9)	228 (12.9)	226 (12.8)	
Former	1730 (24.5)	459 (26.0)	436 (24.8)	435 (24.6)	400 (22.7)	
Total energy intake (kcal/day)	2238 (544)	1960 (490)	2129 (491)	2302 (488)	2559 (518)	<0.001
Alcohol Intake (g/day)	8.3 (14.1)	9.7 (16.2)	8.7 (15.4)	7.7 (12.4)	7.3 (11.8)	<0.001
Na (mg/day)	2361 (846)	2145 (830)	2280 (817)	2423 (822)	2593 (849)	<0.001
Red meat (gr/day)	48.5 (35.9)	48.2 (38.5)	47.8 (33.4)	50.9 (36.3)	47.1 (35.3)	0.010
Processed meat (gr/day)	26.1 (19.4)	24.5 (19.8)	25.6 (17.3)	27.2 (20.5)	27.1 (21.4)	<0.001
Total physical activity (METs/min/day)	230.1 (237.9)	201.3 (223.9)	227.4 (229.1)	243.6 (245.5)	248.2 (249.4)	<0.001
Intervention group, n (%)						0.103
Mediterranean diet + EVOO	2427 (34.4)	588 (33.3)	616 (35.1)	582 (32.9)	641 (36.3)	
Mediterranean diet + Nuts	2301 (32.6)	562 (31.9)	556 (31.6)	599 (33.8)	584 (33.1)	
Control diet	2328 (33.0)	614 (34.8)	585 (33.3)	589 (33.3)	540 (30.6)	
Aspirin intake, n (%)	1577 (22.3)	1375 (77.9)	1382 (78.7)	1374 (77.6)	1348 (76.4)	0.428
Vitamin supplements, n (%)	761 (10.8)	166 (9.4)	174 (9.9)	185 (10.5)	236 (13.4)	0.001
Hormone replacement therapy, n (%)	112 (1.6)	27 (1.5)	31 (1.8)	31 (1.8)	23 (1.3)	0.658
Mediterranean diet score	8.7 (1.9)	8.3 (1.8)	8.6 (1.9)	8.8 (1.9)	9.0 (1.9)	<0.001

Continuous variables are expressed as means (SD) and categorical variables as number (percent).
Abbreviations: MET, metabolic equivalent tasks; EVOO, extra-virgin olive oil.
[a] Differences for participants of total sugar intake quartiles by ANOVA or chi-square as appropriate.

Table 2
Simple Sugars by Source at Baseline According to the Median of Sugar Intake quartiles.

Grams/day	Total	≤47 g/day	>47 to 62.2 g/day	>62.2 to 81.8 g/day	>81.8 g/day
No. of participants	7056	1764	1757	1770	1765
Liquid Glucose	0.3 (0.0–4.2)	0.1 (0.0–1.4)	0.3 (0.0–2.1)	0.6 (0.0–4.2)	0.8 (0.0–4.9)
Solid Fructose	33.5 (25.4–44.3)	20.4 (16.6–23.0)	29.7 (27.4–31.5)	38.2 (35.5–41.3)	52.4 (47.5–60.5)
Liquid Fructose	0.3 (0.0–4.3)	0.1 (0.0–2.0)	0.3 (0.0–2.4)	0.7 (0.0–4.3)	0.9 (0.0–6.1)
Fructose in Fruit Juice	0.0 (0.0–0.4)	0.0 (0.0–0.0)	0.0 (0.0–0.4)	0.0 (0.0–0.4)	0.0 (0.0–0.9)
Fructose in Fruits	14.1 (9.2–19.2)	7.5 (4.9–10.3)	12.8 (9.7–15.3)	16.4 (12.9–19.8)	22.7 (17.9–30.7)
Total Solid Sugar	62.2 (47.0–81.7)	38.0 (31.5–42.3)	54.8 (51.0–58.4)	71.3 (66.2–76.2)	97.2 (88.3–112.2)
Total Liquid Sugar	0.6 (0.0–8.6)	0.3 (0.0–3.4)	0.6 (0.0–4.7)	1.3 (0.0–8.6)	1.8 (0.0–10.5)
Total Sugar	67.0 (50.6–88.5)	40.3 (33.4–45.9)	57.5 (52.8–62.0)	74.8 (68.7–81.5)	104.6 (92.7–122.5)

Sugar intake is expressed as medians (interquartile ranges).

mortality were lower when liquid sugars were isocalorically replaced by MUFAs, solid sugars, or complex carbohydrates. Simple sugars consumed in solid form, including fructose from fruit, were unrelated to outcomes.

Epidemiological data supporting a relationship between increased simple sugar intake and risk of cancer are scarce [12,13], although an association with certain specific cancer sites has been suggested. Thus, in the large European Prospective Investigation into Cancer and Nutrition cohort [24], a positive association was found between increased total sugar intake and risk of liver cancer. Results from other large prospective studies, such as the NIH-AARP Diet and Health Study, have suggested that free fructose consumption significantly increased the risk of cancer of the small intestine [25] and pancreas [26]. An association of fructose intake with pancreatic cancer risk was also suggested in a meta-analysis of 10 cohort studies [27]. The large prospective NutriNet-Santé French cohort provides suggestive evidence of the cancer-promoting properties of SSBs [28], as sugary drink consumption was associated with total cancer risk (HR for a 100 mL/d increase of 1.18–95% CI, 1.10–1.27), and with breast cancer risk (HR of 1.22–95% CI, 1.07–1.39). Of note, a similar association of fruit juice consumption with total cancer risk was observed per an increase of 100 mL/d (HR of 1.12–95% CI, 1.03–1.23). With HRs between 1.08 and 1.19 per 5 g/d increments, the strength of the associations between total sugar, glucose and fructose in liquid form and overall cancer found in our study is similar to that of the NutriNet-Santé study for equivalent 100 mL/d increases in SSBs. Concerning fructose from 100% fruit juice, our cancer risk estimate for a 5 g/d increase (HR, 1.39) nearly tripled the effect size for a 100 mL/d increment reported in the NutriNet-Santé study. However, a note of caution is necessary, since there were few consumers of fruit juice in our cohort. In fact, a marginal consumption of natural fruit juice has also been observed in an older Spanish population with characteristics similar to those of PREDIMED participants [29]. At any rate, a recent comprehensive review concluded that there is no conclusive evidence that consumption of 100% fruit juice has adverse health effects [30]. A recent report from the same French study suggests an increased overall cancer risk from total sugar intake, but the association was driven exclusively by breast cancer [31].

Epidemiological evidence of increased cancer mortality from sugar intake is inconclusive [14–16]. Our risk estimates for the association between 5 g/day increases in intake of total liquid

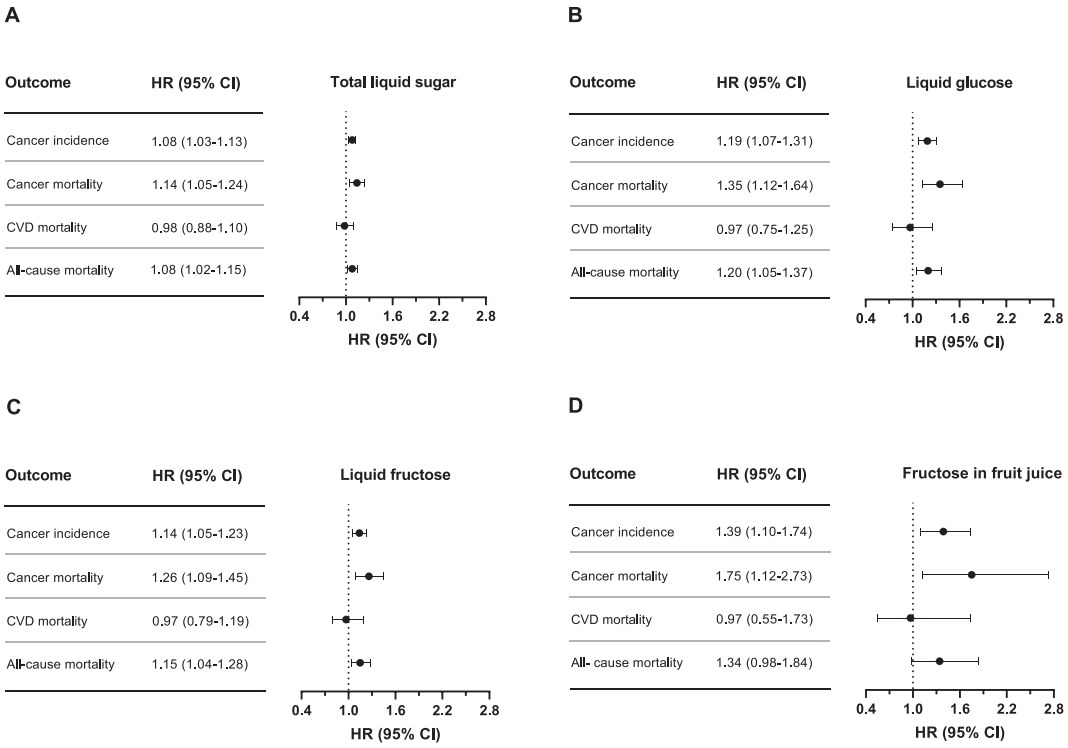

Fig. 2. Association of intake of liquid sugars with cancer incidence and mortality, cardiovascular disease mortality, and all-cause mortality.
Multivariable Cox regression models stratified by recruiting center and adjusted for age, sex, history of diabetes (yes/no), history of hypertension (yes/no), history of dyslipidemia (yes/no), smoking habit (never, current, and former), body mass index, total energy intake, physical activity (METs/min/day), aspirin intake (yes/no), vitamin supplementation (yes/no), hormone replacement therapy (yes/no), family history of cancer (yes/no), salt intake (g/day), red meat consumption (g/day), processed meat consumption (g/day), adherence to Mediterranean diet score (0–14), intervention group, and annual (time dependent variable) change in total sugar intake in g/day. The models were further adjusted for robust variance estimators to account for small deviations from individual randomization.

sugars, liquid glucose and liquid fructose with cancer mortality provided HRs ranging from 1.14 to 1.35, similar to those reported from the large cohorts of Nurses' Health Study and Health Professionals Follow-up Study for SSBs [15]. The HR of fructose from fruit juice for cancer mortality risk (1.75) was higher than that of other liquid sugars, but again the data are based on low numbers of consumers of fruit juice. In any case, these figures must be taken with caution because cancer mortality is a less robust outcome than cancer incidence, as many patients with a cancer diagnosis die from causes unrelated to cancer, particularly CVD [32].

Our results suggesting a modest increase in all-cause mortality risk from liquid sugar intake concur with prior data on exposure to sugary beverages from large US [14,15,33] and European [34] cohorts. Of note, in the REGARDS study [33] the reported mortality risk for fruit juice duplicated that ascribed to conventional SSBs, which agrees with our data on fructose from fruit juice. Of interest, consumption of table sugar, customarily used to sweeten beverages or semiliquid foods, was also associated with all-cause mortality in our study. SSB consumption has been associated with an increased risk for CVD mortality among US adults [15,33,35], but we observed no such associations in the PREDIMED cohort. Reflecting the adherence of our older participants to a Mediterranean-style diet [17], the intake of simple sugars in liquid form among them was rather low, a reason why our study may not have had a wide enough range to asses effects on relatively low numbers of fatal CVD.

There is still discussion on the role of simple sugars in human health, specifically whether they have a distinct deleterious effect or are simply the vehicles for excess energy [36]. Our results showing a significant association of simple sugar intake with cancer incidence and mortality, independently of energy intake and BMI, point to a specific harmful effect beyond the energy provided and its consequences on adiposity. Another point of debate is whether the physical form in which simple sugars are consumed influences their clinical effects. Concerning weight gain, the prevailing evidence suggests that intake of liquid calories in SSBs results in low satiety indices and an incomplete compensatory reduction in energy intake at subsequent meals, which leads to passive energy hyperconsumption [7]. Postprandial hyperglycemia induced by intake of readily absorbable sugars in liquid form also leads to hyperinsulinemia and related metabolic disturbances [37]. The positive associations between liquid but not solid sugars and clinical outcomes in our study concur with a harmful effect of liquid sugars, which is further supported by the results of substitution analyses of liquid sugars for other nutrients.

4.1. Strengths and limitations

Our study has several strengths, such as its prospective design, large sample size, and relative long duration of follow-up. Furthermore, we used yearly updated measures of simple sugar intake from baseline to the last FFQ, a better approach than using a single baseline FFQ because the participant's diet may have changed during follow-up. Additionally, the availability of adjudicated clinical events and the fact that most incident cancer diagnoses were based on histological or cytological data minimized the risk of outcome misclassification. Finally, the data on cancer incidence for most liquid sugars was consistent in both continuous and dose–response models.

There are also limitations to our study. First, our results were obtained in an older Mediterranean cohort at high cardiovascular risk, thus may not be generalized to other populations. Second,

Table 3
HRs (95% CIs)[a] for cancer incidence and mortality and CVD and all-cause mortality by categories of intake of liquid sugars in the PREDIMED cohort.

Intake in grams/day					
	Non-consumers	Tertile 1	Tertile 2	Tertile 3	*P*-linear trend[b]
Total liquid sugars	0	>0 to ≤1.9	>1.9 to ≤10.3	>10.3	
No. of participants	3002	1375	1383	1296	
Cancer incidence					
Crude model	1.0 (ref)	0.97 (0.76–1.23)	1.08 (0.85–1.36)	1.31 (1.04–1.66)	0.011
Fully adjusted model	1.0 (ref)	1.03 (0.81–1.32)	1.19 (0.94–1.51)	1.46 (1.12–1.90)	0.004
Cancer mortality					
Crude model	1.0 (ref)	0.79 (0.50–1.24)	1.10 (0.72–1.68)	1.07 (0.69–1.67)	0.575
Fully adjusted model	1.0 (ref)	0.89 (0.56–1.40)	1.33 (0.86–2.07)	1.38 (0.84–2.27)	0.152
CVD mortality					
Crude model	1.0 (ref)	0.91 (0.54–1.55)	0.69 (0.39–1.21)	0.87 (0.50–1.51)	0.690
Fully adjusted model	1.0 (ref)	0.98 (0.58–1.67)	0.75 (0.43–1.33)	0.96 (0.54–1.74)	0.939
All-Cause mortality					
Crude model	1.0 (ref)	0.83 (0.64–1.08)	0.82 (0.63–1.07)	0.87 (0.66–1.14)	0.478
Fully adjusted model	1.0 (ref)	0.96 (0.74–1.25)	0.99 (0.76–1.30)	1.15 (0.85–1.56)	0.311
Liquid glucose	0	>0 to ≤0.9	>0.9 to ≤4.49	>4.49	
No. of participants	3002	1375	1344	1335	
Cancer incidence					
Crude model	1.0 (ref)	0.97 (0.76–1.24)	1.06 (0.84–1.33)	1.34 (1.07–1.69)	0.005
Fully adjusted model	1.0 (ref)	1.03 (0.81–1.32)	1.15 (0.91–1.47)	1.51 (1.17–1.96)	0.001
Cancer mortality					
Crude model	1.0 (ref)	0.79 (0.50–1.24)	1.05 (0.68–1.63)	1.12 (0.72–1.73)	0.432
Fully adjusted model	1.0 (ref)	0.89 (0.56–1.40)	1.27 (0.81–1.99)	1.46 (0.90–2.39)	0.093
CVD mortality					
Crude model	1.0 (ref)	0.91 (0.54–1.55)	0.67 (0.37–1.19)	0.89 (0.52–1.53)	0.770
Fully adjusted model	1.0 (ref)	0.97 (0.57–1.66)	0.72 (0.40–1.28)	1.04 (0.59–1.84)	0.841
All-Cause mortality					
Crude model	1.0 (ref)	0.83 (0.64–1.07)	0.80 (0.61–1.05)	0.88 (0.67–1.16)	0.569
Fully adjusted model	1.0 (ref)	0.96 (0.74–1.25)	0.96 (0.73–1.26)	1.19 (0.89–1.60)	0.206
Liquid fructose	0	>0 to ≤1.0	>1.0 to ≤6.0	>6.0	
No. of participants	3002	1325	1337	1392	
Cancer incidence					
Crude model	1.0 (ref)	0.93 (0.72–1.19)	1.18 (0.94–1.48)	1.25 (0.99–1.57)	0.033
Fully adjusted model	1.0 (ref)	0.98 (0.77–1.27)	1.29 (1.02–1.63)	1.37 (1.06–1.78)	0.013
Cancer mortality					
Crude model	1.0 (ref)	0.78 (0.49–1.25)	0.98 (0.63–1.53)	1.19 (0.78–1.81)	0.273
Fully adjusted model	1.0 (ref)	0.88 (0.56–1.40)	1.20 (0.76–1.90)	1.58 (0.99–2.51)	0.035
CVD mortality					
Crude model	1.0 (ref)	0.94 (0.56–1.60)	0.76 (0.43–1.32)	0.76 (0.43–1.34)	0.383
Fully adjusted model	1.0 (ref)	1.02 (0.60–1.73)	0.81 (0.46–1.42)	0.82 (0.45–1.48)	0.512
All-Cause mortality					
Crude model	1.0 (ref)	0.80 (0.61–1.05)	0.78 (0.59–1.02)	0.93 (0.71–1.21)	0.919
Fully adjusted model	1.0 (ref)	0.93 (0.71–1.22)	0.96 (0.73–1.27)	1.22 (0.92–1.63)	0.126
Fructose in fruit juice	0	0> to ≤0.88	>0.88 to ≤2.8	>2.82	
No. of participants	4988	601	816	651	
Cancer incidence					
Crude model	1.0 (ref)	0.75 (0.54–1.05)	1.16 (0.89–1.50)	1.11 (0.83–1.48)	0.253
Fully adjusted model	1.0 (ref)	0.79 (0.56–1.11)	1.26 (0.96–1.65)	1.30 (0.94–1.81)	0.035
Cancer mortality					
Crude model	1.0 (ref)	0.56 (0.28–1.16)	1.11 (0.67–1.84)	1.22 (0.71–2.08)	0.356
Fully adjusted model	1.0 (ref)	0.62 (0.30–1.27)	1.29 (0.76–2.21)	1.36 (0.72–2.59)	0.221
CVD mortality					
Crude model	1.0 (ref)	0.71 (0.34–1.49)	0.67 (0.34–1.34)	0.69 (0.31–1.53)	0.264
Fully adjusted model	1.0 (ref)	0.83 (0.39–1.76)	0.79 (0.39–1.62)	0.84 (0.38–1.86)	0.657
All-Cause mortality					
Crude model	1.0 (ref)	0.72 (0.50–1.06)	0.86 (0.62–1.20)	0.89 (0.62–1.28)	0.490
Fully adjusted model	1.0 (ref)	0.83 (0.57–1.22)	1.05 (0.74–1.48)	1.02 (0.67–1.55)	0.825

Tertiles are for the subgroups of consumers of any liquid sugar.

[a] Multivariable Cox regression models stratified by recruiting center and adjusted for age, sex, history of diabetes (yes/no), history of hypertension (yes/no), history of dyslipidemia (yes/no), smoking habit (never, current, and former), body mass index, total energy intake, physical activity (METs/min/day), aspirin intake (yes/no), vitamin supplementation (yes/no), hormone replacement therapy (yes/no), family history of cancer (yes/no), salt intake (g/day), red meat consumption (g/day), processed meat consumption (g/day), adherence to Mediterranean diet score (0–14), intervention group, and annual (time dependent variable) change in total sugar intake in g/day. The models were further adjusted for robust variance estimators to account for small deviations from individual randomization.

[b] Tests for linear trend across quantiles were conducted by modeling the median value within each quantile.

although we controlled for a wide range of CVD and cancer risk factors, we cannot rule out the existence of unknown confounders. Third, as reported for the general Spanish population, particularly in older populations [38], there was a low range of exposures to liquid sugars in our cohort, which might have compromised finding associations for some outcomes. Fourth, we examined the effect of 9 dietary exposures in relation to 4 outcomes, which increases the probability that some findings might have occurred by chance. Finally, data were derived from FFQs, which rely on self-reported dietary intake that is susceptible to exposure misclassification. However, our FFQ was validated, with good correlation coefficients for reproducibility and relative validity, similar to those of FFQs used in other prospective studies.

Table 4
Risk of cancer incidence and mortality associated with Isocaloric replacement of liquid sugars with other nutrients.

	HR (95% CI)	*P* value[a]
Cancer incidence		
Saturated fatty acids	0.67 (0.48–0.96)	0.028
Trans fatty acids	1.16 (0.55–2.45)	0.695
Monounsaturated fatty acids	0.71 (0.56–0.90)	0.004
Polyunsaturated fatty acids	0.65 (0.48–0.86)	0.003
Total solid sugars	0.65 (0.51–0.81)	<0.001
Complex carbohydrate	0.71 (0.57–0.87)	0.001
Alcohol	0.72 (0.58–0.90)	0.004
Cancer mortality		
Saturated fatty acids	0.66 (0.35–1.22)	0.185
Trans fatty acids	0.90 (0.21–3.91)	0.883
Monounsaturated fatty acids	0.52 (0.33–0.82)	0.005
Polyunsaturated fatty acids	0.65 (0.41–1.05)	0.078
Total solid sugars	0.59 (0.38–0.91)	0.018
Complex carbohydrate	0.66 (0.45–0.96)	0.032
Alcohol	0.70 (0.48–1.04)	0.081

All nutrient replacements at 5% of energy, except *trans* fatty acids (1% of energy).
[a] Multivariable Cox regression models stratified by recruitment centre and adjusted for sex, age, history of diabetes (yes/no), history of hypertension (yes/no), history of dyslipidemia (yes/no), smoking habit (never, current and former), physical activity (METs/min/d), aspirin intake (yes/no), vitamin supplementation (yes/no), BMI, family history of cancer (yes/no), salt intake (g/day), red meat consumption (g/day), processed meat consumption (g/day), total energy intake, energy from protein, adherence to Mediterranean diet score (0–14 points), and intervention group. The models were further adjusted for intake of the substituted nutrients and additionally adjusted for robust variance estimators to account for small deviations from individual randomization.

5. Conclusions

In this study, higher intake of simple sugars in liquid form, specifically total sugar, glucose and fructose, was associated with increased cancer incidence and mortality and all-cause mortality among older Mediterranean adults. Significantly lower cancer incidence and mortality were observed when liquid sugars were replaced by MUFAs, solid sugars, or complex carbohydrate. While further studies of large cohorts with long-term follow-up are needed, our findings suggest that reduction in consumption of sugary drinks could be an effective preventive measure to reduce overall cancer incidence and mortality and all-cause mortality.

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Author's contributions

Juan C. Laguna: Conceptualization, Formal Analysis, Writing –review & editing **Marta Alegret**: Conceptualization, Formal Analysis, Writing –review & editing **Montserrat Cofán**: Investigation **Ana Sánchez-Tainta**: Investigation, **Andrés Díaz-López**: Investigation, Formal Analysis, Data Curation **Miguel A. Martínez-González**: Investigation, **José V. Sorlí**: Investigation, **Jordi Salas-Salvadó**: Investigation, Formal Analysis, Data Curation **Montserrat Fitó**: Investigation **Ángel M. Alonso-Gómez**: Investigation **Lluís Serra-Majem**: Investigation **José Lapetra**: Investigation **Miquel Fiol**: Investigation **Enrique Gómez-Gracia**: Investigation **Xavier Pintó**: Investigation, **Miguel A. Muñoz**: Investigation **Olga Castañer**: Investigation **Judith B. Ramírez-Sabio**: Investigation **José J. Portu**: Investigation **Ramón Estruch**: Investigation **Emilio Ros**: Investigation, Data Curation, Writing –original draft.

Data sharing

The datasets generated and analyzed during the current study are not expected to be made available outside the core research group, as neither participants' consent forms nor ethics approval included permission for open access. However, the researchers will follow a controlled data sharing collaboration model, as in the informed consent participants agreed with a controlled collaboration with other investigators for research related to the project's aims. Therefore, investigators who are interested in this study can contact the PREDIMED Steering Committee by sending a request letter to predimed-steering-committe@googlegroups.com. A data sharing agreement indicating the characteristics of the collaboration and data management will be completed for the proposals that are approved by the Steering Committee.

Conflict of interest

Jordi Salas-Salvadó reports serving on the board of and receiving grant support through his institution from the International Nut and Dried Fruit Council, and Eroski Foundation; serving in the Executive Committee of Instituto Danone Spain; has received research support from the Instituto de Salud Carlos III, Spain; Ministerio de Economía y Competitividad, Spain; Departament de Salut Pública de la Generalitat de Catalunya, Catalonia, Spain; European Commission. He has received research support from the California Walnut Commission, Folsom, CA, USA; Patrimonio Comunal Olivarero, Spain; La Morella Nuts, Spain; and Borges S.A., Spain. Reports receiving consulting fees and travel expenses from Danone; California Walnut Commission, Eroski Foundation, Instituto Danone - Spain, Nestle and Abbot Laboratories.

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Appendix A. Supplementary data

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