

## **Sweet beverage consumption and risk of pancreatic cancer in the European Prospective Investigation into Cancer and Nutrition**

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**Running title:** Sweet beverage consumption and pancreatic cancer risk

**Abbreviations:** BMI: Body mass index; EPIC: European Prospective Investigation into Nutrition and Cancer; CI: Confidence Interval; HR: Hazard Ratio; ICD: International Classification of Diseases for Oncology; RR: relative risk

## Abstract

**Background:** Sweet beverage consumption has been associated with greater risk of type 2 diabetes and obesity, which may be involved in the development of pancreatic cancer. Therefore, it has been hypothesized that sweet beverages may increase pancreatic cancer risk as well.

**Objective:** The aim of this study was to examine the association between sweet beverage consumption (including total, sugar and artificially sweetened soft drink and juice & nectar consumption) and pancreatic cancer risk.

**Design:** This study was conducted within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. A total of 477,199 participants (70.2% women) with a mean age of 51.22 years at baseline were included, and 865 exocrine pancreatic cancers were diagnosed after a median follow-up of 11.6 years (interquartile range: 10.1; 12.6 years). Sweet beverage consumption was assessed using validated dietary questionnaires at baseline. Hazard ratios (HRs) and 95% confidence intervals (CIs) were obtained using multivariable Cox regression models stratified by age, sex and center and adjusted for educational level, physical activity, smoking status and alcohol consumption. Associations with total soft drink were adjusted for juice & nectar consumption, and vice versa.

**Results:** Total soft drink (HR per 100g/day=1.03; 95% CI: 0.99, 1.07), sugar sweetened soft drink (HR per 100g/day=1.02; 95% CI: 0.97, 1.08) and artificially sweetened soft drink (HR per 100g/day=1.04; 95% CI: 0.98, 1.10) consumption were not associated with pancreatic cancer risk. Juice & nectar consumption was inversely associated with pancreatic cancer risk (HR per 100g/day=0.91;

25 95% CI: 0.84, 0.99); this association remained statistically significant after  
26 adjusting for body size, type 2 diabetes and energy intake.

27 **Conclusion:** Soft drink consumption does not appear to be associated with  
28 pancreatic cancer risk. Juice & nectar consumption might be associated with a  
29 modest decreased pancreatic cancer risk. Further studies with specific  
30 information on juice & nectar sub-type are warranted to clarify these results.

31 **Key words:** pancreatic cancer, soft drinks, sweet beverages, juice and nectar,  
32 risk factors, epidemiology, prevention; sugary drinks

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## Introduction

Pancreatic cancer was the 7th most common cancer and the 5th most common cause of cancer death in Europe in 2012 (1). Five year survival rates are among the lowest (<5%) of all cancer types in Europe (2). A screening test for early detection does not exist, and treatment is hardly effective. Avoiding exposure to modifiable risk factors is currently the most feasible approach to reduce pancreatic cancer incidence.

To date, no dietary factors have been consistently associated with pancreatic cancer (3). Type 2 diabetes and obesity, however, are established risk factors for pancreatic cancer (3,4). Studies have directly linked elevated pre-diagnostic blood glucose and insulin to increased pancreatic cancer risk (5-7). Because sweet beverage consumption (comprising soft drink and juice & nectar consumption) has been associated with greater risks of type 2 diabetes and obesity (8,9), it is conceivable that it is also associated with pancreatic cancer. If confirmed, such evidence could influence formulation of health policies and disease preventative strategies.

Previous studies on soft drink consumption and pancreatic cancer have shown inconsistent results (3,10,11). Although some individual studies have shown a significant positive association between soft drink consumption and pancreatic cancer (12, 13), a meta-analysis of seven prospective cohort studies and a pooled analysis of fourteen cohort studies showed an overall non-significant but positive association between high soft drink consumption and pancreatic cancer risk (3,10).

Evidence on the association among subgroups of soft drinks and fruit juice consumption and pancreatic cancer is also scarce, with a meta-analysis showing overall null findings (3).

The majority of the epidemiological studies that have explored the association of sweet beverages consumption and pancreatic cancer risk have been published in the United States, with only one European study (12) published on this issue. The consumption of sweetened beverages is lower in Europe compared to the United States, although it is on the rise (14). The European Prospective Investigation into Cancer and Nutrition (EPIC) cohort included over half a million participants from 10 European countries with a wide variety in dietary patterns. The aim of the present study was to examine the association between sweet beverage consumption (including total, sugar sweetened and artificially sweetened soft drink and juice & nectar consumption) and pancreatic cancer in the EPIC study, including European populations with diversity in dietary patterns, an asset in studies evaluating diet and disease risk; in addition, the large sample size allowed stratification by sub-groups of sugary drinks and evaluation of effect-modification with sufficient power.

## Methods

### *Population*

EPIC is a prospective study of over half a million participants from 23 centers in 10 European countries (Denmark, France, Germany, Greece, Italy, Norway, Spain, Sweden, the Netherlands and United Kingdom) established between 1992 and 2000. In some study centers, the participants were recruited from the general population residing in a given geographical area. However, the French cohort consisted of female members of a health insurance scheme for school and university employees; the Spanish and Italian cohorts mainly of local blood donors; the cohorts in Utrecht (the Netherlands) and Florence (Italy) of women invited for a breast cancer screening program; the Norwegian cohort of women participating in a nationwide cancer study; and the cohort in Oxford (UK) included mostly people who did not eat meat, and health conscious participants. In France, Norway, Utrecht (the Netherlands) and Naples (Italy), only women were recruited. All participants provided informed consent, and the study was approved by the Internal Review Board of the International Agency for Research on Cancer and the ethics committees of all centers. Recruitment and data collection were described in detail elsewhere (15).

Flowchart is shown in the Online Supplemental Material (**Supplemental Figure 1**). After exclusion of prevalent cancer cases at baseline other than non-melanoma skin cancer (n=23,785), participants with missing information on follow-up (n=4,383), **participants who did not complete dietary or non-dietary questionnaires** (n=6,253), participants with the ratio for energy intake vs estimated energy expenditure in the top or bottom 1% of the cohort distribution

(n=9,600), participants with pancreatic secondary tumors (n=67), endocrine tumors (n=40) and a benign tumor (n=1), a carcinoma in situ (n=1) and tumor with uncertain primary or metastatic origin (n=1), the analysis included a total of 477,199 participants (142,202 men and 334,997 women) with a mean age of 51.22 years at baseline.

### *Exposure and covariate assessment*

Usual diet over the previous 12 months was assessed using country-specific validated dietary questionnaires (16) at baseline. Individual energy, dietary folate intake and alcohol intake (g/day) were estimated through linkage with the standardized EPIC Nutrient Database (17). Sweet beverage consumption was derived from questionnaire data, summing total soft drink and juices & nectar consumption. Total soft drinks combines carbonate/isotonic drinks and diluted syrups. Juices & nectar refers to juices (obtained from either 100% fruit and vegetable or concentrates) and nectars (juices with up to 20% added sugar). Total soft drink consumption was subdivided into sugar sweetened and artificially sweetened soft drink consumption; however, these different types of soft drinks could not be distinguished in Italy, Spain and Sweden, hence these countries were excluded in analysis exploring subtypes of soft drinks. The available data did not allow distinguishing juice & nectar consumption into separate categories.

At baseline, questionnaires were administered to collect information on sociodemographic characteristics, lifestyle and previous illnesses (15). This included education level (no formal education, primary school, secondary school, technical school, university degree and missing); smoking status (never

smoker, former smoker and current smoker), intensity of smoking (i.e. never; former: quit smoking >20 y ago, quit 11–20 y ago, quit ≤10 y ago; smoker: 1–15 cigarettes/d, 16–25 cigarettes/d, >25 cigarettes/d; smoker, pipe or cigar) and duration of smoking (in years), physical activity (inactive, moderately inactive, moderately active, active and missing; using the Cambridge physical activity index) (18) and self-reported prevalent **type 2 diabetes** history.

Height (cm), weight (kg) and waist circumference (cm) were measured at baseline, except for France, Oxford and Norway where participants self-reported these data in questionnaires. For the health-conscious group from Oxford, sex- and age-specific anthropometric values were predicted by fitting linear regression models on a subset with measured and self-reported values (19). In France and Norway, self-reported values were used. In Norway, waist circumference was not assessed (20).

#### *Outcome assessment*

Incident cancer and mortality data were obtained from regional or national population-based cancer and mortality registers, except in Germany, Greece and France where they came from a combination of methods including active follow-up through study participants, next-of-kin information, the use of health insurance records, and cancer and pathology registries. Follow-up was considered completed up to the end of 2009 for Germany, France and Greece, mid-2008 for Cambridge; 2008 for Turin, Norway and Sweden; 2007 for Denmark, the Netherlands, Murcia, Navarra and Oxford; 2006 for Florence, Varese, Ragusa, Naples, Granada and San Sebastian, and 2004 for Asturias. This resulted in 11.6 years of median follow-up (interquartile range: 10.1, 12.6).

Pancreatic cancer cases were defined as first incident adenocarcinoma of the exocrine pancreas (International Classification of Diseases for Oncology, Third Edition [ICD-O-3], C25.0-C25.3, and C25.7-C25.9). All tumors self-reported by the study participants in Greece, Germany and France were confirmed by review of appropriate medical records. Of the 865 exocrine pancreatic cancer cases, 608 (70.3%) were microscopically confirmed, based on histology of the primary tumor (n=359), histology of metastasis (n=68), cytology (130) or autopsy (n=51). For the remaining 29.7%, the diagnosis was based on the clinical symptoms, physical examination or imaging results.

#### *Statistical analysis*

We estimated hazard ratios (HRs) and 95% confidence intervals (CI) using Cox proportional hazards regression. Time at entry was age at baseline and exit time was age at first pancreatic cancer diagnosis for cases and age at censoring for non-cases (death, loss to follow-up, or end of the follow-up, whichever came first). Models were stratified by center, sex and age at baseline in 1 year categories. The non-zero slope of the scaled Schoenfeld residuals on the time function suggested that the proportional hazard assumption was met.

Analyses were run separately for each country; and combined using random effects meta-analysis whilst calculating  $I^2$ , the percentage of variation between countries due to heterogeneity (21). **Statistical heterogeneity among the studies was assessed using the test Cochran's Q.**

We calculated HRs of pancreatic cancer associated with 100g/day and 12 oz (336g/day) increments in consumption of sweet beverages, total soft drinks, and juices & nectars; and when available, sugar sweetened soft drinks and

artificially sweetened soft drinks. We also modelled exposure variables categorized into non-consumers (consumption=0 g/day) and cohort-wide quintiles among consumers. To allow comparison with previous studies, we also used alternative categorizations of consumption (i.e. 0, 0.1-124.99, 125.00-249.99 and  $\geq 250$ g/day; or  $<1$  glass/month, 1-4 glasses/month,  $>1-6$  glasses/week,  $\geq 1$  glass/day). Because effect sizes and significance levels were comparable, we do not present these analyses.

Tests for linear trend were conducted among consumers only. The median consumption level within a quintile was assigned to all people within that quintile and entered as continuous term in the Cox models.

Restricted cubic splines with three knots (5th, 50th and 95th percentiles of the distribution of exposure variables) (22) showed that all associations could be assumed to be linear (see **Supplemental Figure 2** for the association with juice & nectar consumption; **other models are not shown**). Our interpretation therefore focuses on the continuous models.

We ran both minimally adjusted (stratified for sex, age, and center) and multivariable adjusted models, controlling for alcohol consumption as continuous variable and education level, physical activity, smoking status as categorical variables with an additional category for missing values. Models on total soft drink and juice & nectar consumption were mutually adjusted. Models on sugar sweetened and artificially sweetened soft drink consumption were mutually adjusted and adjusted for juice & nectar consumption. Models were additionally adjusted for energy intake (continuously, using the standard model for energy adjustment (23), self-reported **type 2 diabetes** and body mass index

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195 (BMI); these are shown separately because these factors could intermediate or  
 196 confound the association between sweet beverage consumption and pancreatic  
 197 cancer. Red meat, fruits and vegetables, dietary sugar, coffee and folate intake  
 198 did not materially alter the effect size of the associations and therefore were not  
 199 included in the final Cox models. Adjusting for weight and height or waist  
 200 circumference instead of BMI did not appreciably change the HRs. The same  
 201 applied after adjusting for the intensity and duration of smoking instead of  
 202 smoking status. These variables were therefore not used in the models.

203 In sensitivity analysis, we excluded the first two and five years of follow-up to  
 204 minimize any potential effect of subclinical pancreatic cancers on sweet  
 205 beverage consumption. **These were carried out as two different sensitivity**  
 206 **analyses.** We also focused on histologically confirmed pancreatic cancer as an  
 207 outcome (N= 608), and repeated our analyses in non-diabetics to minimize any  
 208 influence of possible dietary changes related **to type 2 diabetes** diagnosis. We  
 209 also examined the associations after excluding participants who were obese  
 210 (BMI>30 kg/m<sup>2</sup>) at baseline, to minimize reverse causation bias.

211 Effect modification by age (<62 years; ≥62 years; i.e. mean age in the study),  
 212 sex, BMI (<25 kg/m<sup>2</sup>; ≥ 25 kg/m<sup>2</sup>), waist circumference (normal/moderate:  
 213 <102cm in men and <88cm in women; large: ≥ 102cm in men, ≥88cm in  
 214 women), physical activity (combining inactive and moderately inactive in low  
 215 and moderately active and active in high) and smoking status (never, former  
 216 and current smokers) was examined by including **cross** product terms along



217 with the main effect terms in the adjusted plus BMI, type 2 diabetes and energy  
218 intake Cox models and using likelihood ratio tests.

219 All statistical analyses were performed with Stata 10.0 (StataCorp, College  
220 Station, TX, USA). P-values <0.05 were regarded as statistically significant.

## Results

Baseline characteristics according to categories of consumption are shown in **Table 1** (total soft drinks), **Supplemental Table 1** (sweet beverage consumption), **Supplemental Table 2** (juice & nectar consumption), **Supplemental Table 3** (sugar sweetened soft drinks) and **Supplemental Table 4** (artificially sweetened soft drinks). Fruit and vegetable intake decreased across the quintiles of soft drink consumption. On the contrary, total energy, total carbohydrates, sugar, total fat and coffee and tea intake increased across the quintiles of soft drinks consumption. Compared with the first quintile of soft drinks intake, participants in the fifth quintile had higher height and weight, but similar BMI, waist circumference and self-reported **type 2 diabetes**. Participants with high soft drink consumption were more likely to be men, less educated and less physically active. Comparable dietary patterns were seen across juice & nectar quintiles. However, BMI, waist circumference and the percentage self-reported **type 2 diabetes** appeared to be lower among high consumers of juices & nectars.

HRs (and 95% CI) for pancreatic cancer according to types and amount of sweet beverage consumption are shown in **Table 2**. Total soft drink consumption was not associated with pancreatic cancer risk. No consistent trend was seen for the association between total sweet beverage quintiles and pancreatic cancer. However, consumption of juices & nectars was inversely associated with pancreatic cancer. Adjustment for BMI, self-reported **type 2 diabetes** and total energy intake did not materially change HR estimates.

**Table 3** shows overall and stratified associations between 100g/day increment of sweet beverage consumption and pancreatic cancer. **Supplemental Table 5** expresses these associations per 336g/day (12 oz). As in Table 2, an inverse association between juice & nectar consumption and pancreatic cancer was observed. Soft drinks consumption, both sugar-sweetened soft drink and artificially sweetened soft drink consumption were not significantly associated with pancreatic cancer risk. HRs did not change after further adjustment for total energy intake, type 2 diabetes and BMI.

The association with artificially sweetened soft drink consumption was modified by sex ( $p=0.004$ ), and a positive statistically significant association was detected in women (HR: 1.09; 95% CI: 1.03, 1.15).

The association with sugar sweetened soft drink consumption was modified by waist circumference ( $p=0.035$ ). The HR was higher in those with normal/moderate than in those with large waist circumference, but these were not statistically significant within strata.

The HRs did not materially change after exclusion of the first two or five years of follow-up or participants with obesity ( $\text{BMI} \geq 30 \text{ kg/m}^2$ ). Considering only non-diabetics yielded almost the same HRs (data not shown).

**Supplemental Figures 3-7**, show HRs (95% CI) of pancreatic cancer associated with 100g/day increment of sweet beverage consumption types by country. There was no evidence of heterogeneity by country on the association of consumption of sweet beverages ( $I^2=0.0\%$ ,  $p$  heterogeneity=0.98), soft drinks ( $I^2=0.0\%$ ,  $p$  heterogeneity=0.95), sugar sweetened soft drinks ( $I^2=0.0\%$ ,  $p$  heterogeneity=0.65) and artificially sweetened soft drinks ( $I^2=0.0\%$ ,  $p$

268 heterogeneity=0.66) with pancreatic cancer, while the association with juice &  
269 nectar consumption was slightly heterogeneous ( $I^2=30.5\%$ ,  $p$   
270 heterogeneity=0.17).

## Discussion

This analysis conducted in the EPIC cohort, an European study of participants with diversity in dietary patterns and sweet beverage consumption, did not provide evidence that consumption of soft drinks is associated with pancreatic cancer. However, our findings suggest that consumption of juices & nectars might be associated with a modest decreased pancreatic cancer risk.

Prior evidence on the association between soft drink consumption and pancreatic cancer was inconsistent (3,10,11). In a pooled analysis of 14 cohort studies on 853,984 individuals including 2,185 incident pancreatic cancer cases, a modest positive association was reported between sugar sweetened carbonated soft drink consumption and pancreatic cancer risk (HR for every 177.5g/day increase =1.06; 95% CI: 1.00, 1.12) (10). A meta-analysis of six prospective cohorts (3) reported unexplained heterogeneous results on the continuous scale, although the summary RR suggested a positive non-significant association (RR for every 200ml/day increase in soft drink consumption: 1.22; 95 % CI: 0.98 , 1.51). The WCRF/AICR Continuous Update Panel judged the evidence for an association between soft drinks and pancreatic cancer as limited (3).

We observed a borderline inverse association for juice & nectar consumption with pancreatic cancer risk, which was of similar magnitude to that observed in a meta-analysis on fruit juice consumption and pancreatic cancer (3), including a total of 1,735 pancreatic cancer cases from two studies conducted in Europe, two in Asia and one in the United States, but this association did not reach statistical significance. The summary RR for every 200ml/day increase in fruit

juice was 0.89 (95% CI: 0.70, 1.13) in the meta-analysis (3), whereas we observed a HR per 200ml/day of 0.83 (95% CI: 0.70, 0.97; model stratified by center, sex and age and adjusted for education, physical activity, smoking status, alcohol consumption and soft drink consumption). Our findings were not mediated by energy intake, type 2 diabetes and BMI.

Juice & nectar consumption might prevent pancreatic cancer through their high content of antioxidants, minerals, fiber, flavonoids and polyphenols, which might reduce oxidative DNA damage and genetic mutations (24,25). In EPIC, plasma concentrations of  $\beta$ -carotene, zeaxanthin and  $\alpha$ -tocopherol were inversely associated with pancreatic cancer risk (26). The same applied to  $\alpha$ -tocopherol (27) and lycopene(28) in two other prospective cohort studies. However in EPIC, correlations of plasma levels of  $\alpha$ -carotene,  $\beta$ -carotene,  $\alpha$ -tocopherol, lutein, zeaxanthin,  $\beta$ -cryptoxanthin, lycopene, folate and vitamin C with juice & nectar and total soft drink consumption were virtually absent ( $r < 0.15$ ), hence it is unlikely that the antioxidant content of juices & nectars may explain the observed association.

The observed inverse association between juice & nectar consumption and pancreatic cancer should be interpreted with caution; juices & nectars are usually rich in added sugars and fructose, which could potentially increase pancreatic cancer risk (29). Yet the correlation between juice & nectar consumption and sugar of 0.29 in EPIC suggests that juice & nectar consumption represents mostly juice with no added sugars. We cannot elude our association may be due to chance, also because other studies (including EPIC) did not find an inverse association between fruit consumption and pancreatic cancer (3,22,30). Also, it might possible that the observed inverse

association between juice & nectar consumption and pancreatic cancer is due to residual confounding, given that high consumers of juices & nectars in this population tended to be slimmer and were less likely to be diabetic; nevertheless we adjusted for these variables measured at baseline with no considerable changes in the effect estimate. Studies with detailed information on different types of juices are needed to confirm their associations with pancreatic cancer.

Strengths of our study include its prospective design that minimizes recall and selection bias and the high number of histologically confirmed pancreatic cancers. We were able to evaluate the association between different types of sweet beverages and pancreatic cancer in a European population with a varied range of consumption and control for a large number of possible confounders. The study size allowed us to evaluate effect modification and perform sensitivity analyses.

Limitations of our study include the single assessment of diet and anthropometry, and our inability to differentiate between beverages with or without added sugars. Measurement error in self-reported dietary data may have biased estimated diet–disease relationships and reduced the statistical power to detect a dietary effect, despite the use of validated dietary questionnaires and adjusting of energy. As for any observational study, residual confounding cannot be totally ruled out.

In conclusion, in this large prospective cohort study, none of the soft drink categories was associated with pancreatic cancer. However, increased juice & nectar consumption was modestly associated with a decreased risk of

pancreatic cancer. Future studies that are sufficiently sampled should be conducted to confirm our findings, and to examine the association between juice consumption and pancreatic cancer by distinguishing juices with added sugar from those without.

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**Table 1. Baseline characteristic of the EPIC study participants (N=477,199) according to categories<sup>1</sup> of total soft drink consumption.**

<b>Total soft drinks (g/day)</b>	<b>Never drinkers 0</b>	<b>Quintile 1 0.1-13.1</b>	<b>Quintile 2 13.2-34.1</b>	<b>Quintile 3 34.2-85.7</b>	<b>Quintile 4 85.8-196.4</b>	<b>Quintile 5 &gt;196.4</b>
All (n, %)	187,176 (39.2)	58,110 (12.2)	57,107 (12.0)	52,633 (11.0)	64,127 (13.4)	58,046 (12.2)
Cases (n, %)	327 (37.8)	116 (13.4)	103 (11.9)	82 (9.5)	133 (15.4)	104 (12.0)
Age at recruitment (years; median, IQR)	52.8 (47.1, 58.9)	51.5 (44.1, 58.6)	51.6 (44.6, 58.9)	49.7 (42.8, 55.5)	50.5 (43.0, 57.1)	50.1 (40.2, 57.2)
Sex, % women	76.7	70.1	65.6	68.9	65.4	59.4
Level of education, % university	23.6	32.6	25.0	21.8	20.5	19.6
Smoking status, % current	20.8	19.2	21.9	23.7	25.2	27.2
Physical activity, % active <sup>2</sup>	23.5	21.3	21.8	16.4	16.5	18.2
Self-reported history of diabetes, %	3.3	2.0	2.2	1.8	2.1	3.0
Weight (kg; median, IQR)	66.0 (58.1, 76.0)	67.0 (59.1, 77.0)	69.5 (61.0, 79.5)	69.5 (61.5, 79.0)	70.7 (62.5, 80.8)	72.6 (63.5, 83.02)
Height (cm; median, IQR)	163.0 (158.0, 169.1)	165.5 (160.0, 172.0)	165.8 (160.0, 172.9)	167.0 (161.0, 173.0)	167.0 (161.5, 173.6)	168.0 (162.0, 175.0)
Body mass index (kg/m <sup>2</sup> ; median, IQR)	24.6 (22.2, 27.6)	24.3 (22.0, 27.1)	25.0 (22.6, 27.9)	24.8 (22.5, 27.6)	25.1 (22.7, 28.0)	25.4 (22.9, 28.5)
Waist circumference (cm; median, IQR)	85.0 (76.0, 94.5)	81.0 (73.0, 91.0)	84.0 (75.0, 94.0)	85.0 (75.0, 94.0)	85.0 (75.2, 95.0)	85.8 (75.0, 96.0)
Alcohol (g/day; median, IQR)	5.7 (0.6, 17.1)	6.1 (1.3, 15.3)	5.8 (1.2, 15.3)	3.7 (0.9, 11.0)	5.2 (1.1, 13.0)	5.2 (0.9, 13.6)
Total energy (kcal/day; median, IQR)	1980.7 (1617.1, 2409.4)	1921.9 (1574.7, 2331.4)	1996.1 (1627.1, 2430.3)	1936.2 (1590.2, 2365.9)	2018.3 (1657.1, 2460.6)	2169.0 (1759.3, 2652.3)
Total carbohydrates (g/day; median, IQR)	210.1 (168.3, 259.4)	212.1 (170.8, 260.7)	217.1 (175.5, 267.9)	215.3 (175.0, 263.5)	224.7 (183.4, 274.3)	250.4 (201.8, 308.4)
Sugar (g/day; median, IQR)	89.0 (67.7, 114.8)	94.4 (71.5, 122.8)	94.6 (72.4, 121.8)	92.8 (70.3, 120.4)	102.2 (78.8, 130.8)	122.8 (93.9, 157.9)
Total fat (g/day; median, IQR)	77.2 (60.4, 97.2)	74.2 (57.2, 94.1)	78.0 (60.5, 98.6)	75.6 (58.6, 96.1)	77.5 (60.2, 99.5)	80.9 (61.5, 104.0)
Dietary folate (mcg/day; median, IQR)	287.0 (226.7, 360.9)	303.1 (237.9, 389.1)	292.1 (213.5, 366.4)	265.6 (210.2, 339.3)	285.2 (224.3, 362.4)	301.2 (235.1, 385.6)
Fruits (g/day; median, IQR)	211.6 (115.5, 328.3)	196.5 (105.8, 324.8)	200.4 (111.7, 321.6)	174.3 (97.9, 285.7)	174.2 (98.7, 282.4)	171.7 (92.2, 288.8)
Vegetables (g/day; median, IQR)	189.9 (121.1, 288.4)	190.2 (116.3, 304.4)	176.9 (109.0, 280.1)	146.3 (93.8, 237.5)	158.1 (101.9, 251.0)	159.7 (99.4, 255.2)
Soft drinks (g/day; median, IQR)	0.0 (0.0, 0.0)	6.5 (3.3, 6.6)	21.3 (16.7, 25.6)	46.9 (42.9, 59.4)	114.3 (92.4, 150.0)	321.4 (234.0, 504.5)
Juices & nectars (g/day; median, IQR)	8.5 (0.0, 77.7)	27.9 (6.7, 103.6)	19.2 (5.8, 76.8)	35.7 (4.9, 94.3)	37.3 (3.8, 94.8)	28.6 (1.7, 107.1)
Red meat (g/day; median, IQR)	37.1 (18.0, 63.5)	28.7 (8.1, 56.3)	37.2 (16.1, 65.5)	29.1 (15.3, 54.0)	35.1 (17.5, 65.8)	36.9 (16.0, 68.6)
Coffee and tea (g/day; median, IQR)	398.7 (157.1, 735.1)	633.7 (301.6, 1000.0)	599.6 (216.4, 1000.0)	540.0 (258.9, 858.8)	625.0 (300.0, 985.7)	650.0 (314.8, 1000.0)

<sup>1</sup> Total soft drink consumption was categorized in non-drinkers (consumption=0 g/day) and cohort-wide quintiles among drinkers (consumption>0g/day); <sup>2</sup> Active means classified in the category with the highest physical activity level according to the ordered four-category index of physical activity (inactive, moderately inactive, moderately active, and active); Abbreviations: IQR, interquartile range

**Table 2.** HRs (and 95 CIs) for pancreatic cancer according to type and amount<sup>1</sup> of sweet beverage consumption in the EPIC study.

	Non-drinkers	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P <sup>5</sup>	Per 100 g/day increment
<b>Sweet beverages (g/day)</b>	0	0.1-24.6	24.7-66.7	66.8-131.9	132.0-246.3	>246.3		
Cases/person-years	114/724,386	169/949,727	147/935,787	163/934,646	141/940,526	131/930,201		
Minimally adjusted model <sup>2</sup>	1.18 (0.91, 1.53)	1.00	1.03 (0.82, 1.29)	1.12 (0.90, 1.40)	1.00 (0.79, 1.27)	0.94 (0.74, 1.20)	0.40	1.00 (0.97, 1.04)
Multivariable adjusted model <sup>3</sup>	1.15 (0.89, 1.50)	1.00	1.05 (0.84, 1.31)	1.14 (0.92, 1.43)	1.03 (0.81, 1.30)	0.96 (0.75, 1.21)	0.41	1.00 (0.97, 1.04)
Multivariable adjusted model <sup>3</sup> + EI+D+BMI	1.15 (0.88, 1.49)	1.00	1.05 (0.83, 1.31)	1.14 (0.91, 1.42)	1.01 (0.80, 1.28)	0.92 (0.72, 1.17)	0.17	0.99 (0.96, 1.03)
<b>Total soft drinks (g/day)</b>	0	0.1-13.1	13.2-34.1	34.2-85.7	58.8-196.4	>196.4		
Cases/person-years	327/2102,279	116/646,936	103/658,141	82/602,370	133/736,976	104/668,572		
Minimally adjusted model <sup>2</sup>	0.93 (0.73, 1.17)	1.00	0.87 (0.66, 1.14)	0.95 (0.71, 1.28)	1.12 (0.86, 1.45)	0.96 (0.73, 1.26)	0.68	1.03 (0.99, 1.07)
Multivariable adjusted model <sup>3</sup>	0.91 (0.71, 1.15)	1.00	0.87 (0.66, 1.14)	0.96 (0.71, 1.29)	1.12 (0.86, 1.46)	0.95 (0.72, 1.25)	0.71	1.03 (0.99, 1.07)
Multivariable adjusted model <sup>3</sup> + EI+D+BMI	0.90 (0.71, 1.14)	1.00	0.86 (0.65, 1.13)	0.94 (0.70, 1.27)	1.09 (0.84, 1.42)	0.90 (0.68, 1.19)	0.86	1.02 (0.98, 1.06)
<b>Juices &amp; nectars (g/day)</b>	0	0.1-8.3	8.4-26.2	26.3-57.1	57.2-123.1	>123.1		
Cases/person-years	188/1174,071	186/828,066	138/901,165	111/824,215	132/85,6613	110/831,142		
Minimally adjusted model <sup>2</sup>	0.99 (0.78, 1.25)	1.00	0.89 (0.70, 1.12)	0.87 (0.68, 1.12)	0.90 (0.71, 1.14)	0.74 (0.55, 0.96)	0.029	0.91 (0.84, 0.98)
Multivariable adjusted model <sup>3</sup>	0.97 (0.76, 1.23)	1.00	0.91 (0.72, 1.15)	0.89 (0.70, 1.14)	0.93 (0.73, 1.18)	0.75 (0.56, 0.98)	0.040	0.91 (0.84, 0.99)
Multivariable adjusted model <sup>3</sup> + EI+D+BMI	0.97 (0.76, 1.23)	1.00	0.91 (0.72, 1.14)	0.88 (0.69, 1.13)	0.92 (0.72, 1.16)	0.74 (0.57, 0.97)	0.030	0.91 (0.84, 0.98)
<b>Sugar- sweetened soft drinks (g/day)<sup>4</sup></b>	0	0.1-4.5	4.6-17.4	17.5-45.4	45.6-121.4	>121.4		
Cases/person-years	258/3163,993	85/492,862	62/343,382	45/445,442	75/473,733	61/495,861		
Minimally adjusted model <sup>2</sup>	0.87 (0.66, 1.15)	1.00	0.85 (0.66, 1.15)	0.69 (0.60, 1.20)	0.97 (0.70, 1.30)	0.94 (0.68, 1.30)	0.41	1.03 (0.97, 1.08)
Multivariable adjusted model <sup>3</sup>	0.85 (0.64, 1.12)	1.00	0.85 (0.60, 1.20)	0.70 (0.48, 1.01)	0.96 (0.70, 1.33)	0.92 (0.67, 1.28)	0.46	1.02 (0.97, 1.08)
Multivariable adjusted model <sup>3</sup> + EI+D+BMI	0.84 (0.63, 1.11)	1.00	0.85 (0.60, 1.20)	0.69 (0.48, 1.00)	0.95 (0.69, 1.32)	0.90 (0.65, 1.25)	0.70	1.02 (0.97, 1.08)
<b>Artificially sweetened soft drinks (g/day)<sup>4</sup></b>	0	0.1-2.0	2.1-9.9	9.9-28.6	28.7-92.2	>92.2		
Cases/person-years	340/3779,008	54/417,963	50/217,598	53/33,4323	42/329,076	47/337,305		
Minimally adjusted model <sup>2</sup>	0.93 (0.61, 1.42)	1.00	1.15 (0.70, 1.89)	1.16 (0.74, 1.82)	1.06 (0.66, 1.71)	1.12 (0.70, 1.79)	0.66	1.04 (0.98, 1.10)
Multivariable adjusted model <sup>3</sup>	0.88 (0.58, 1.35)	1.00	1.13 (0.69, 1.86)	1.12 (0.71, 1.77)	1.03 (0.64, 1.67)	1.07 (0.67, 1.73)	0.55	1.04 (0.98, 1.10)
Multivariable adjusted model <sup>3</sup> + EI+D+BMI	0.89 (0.58, 1.36)	1.00	1.12 (0.68, 1.84)	1.09 (0.69, 1.73)	0.99 (0.61, 1.60)	0.99 (0.61, 1.60)	0.81	1.02 (0.96, 1.08)

<sup>1</sup> Different types of sweet beverage consumption were categorized in non-drinkers (consumption=0 g/day) and cohort-wide quintiles among drinkers (consumption>0 g/day); <sup>2</sup> The model was stratified by center, sex and age at recruitment in 1-year categories; <sup>3</sup> The model was stratified by center, sex and age at recruitment in 1-year categories and adjusted for education level (no degree or primary school completed; technical or professional school completed; secondary school completed; university degree; not specified or missing), physical activity (active; moderately active; moderately inactive; inactive; missing), smoking status (never; former; current; missing) and alcohol consumption (g per day); juices and nectar and soft drinks in grams per day were mutually adjusted and sugar sweetened and artificially sweetened soft drinks were also mutually adjusted plus adjustment for juice consumption. <sup>4</sup> Excludes Italy, Spain and Umeå (Sweden) where information on type of soft drinks consumption was not collected. <sup>5</sup> P values obtained by trend test; Abbreviations: BMI: Body Mass Index; D: Diabetes; EI: energy intake; HR: Hazard Ratio



**Table 3.** HRs (and 95 CIs) for pancreatic cancer associated with 100 g/day increment in the consumption of different type of sweet beverage in the EPIC study, effect modification analyses

Per 100 g/day increment		No cases	Sweet beverages (g/day) HR (95% CI)	Soft drinks (g/day) HR (95% CI)	Juice and nectars (g/day) HR (95% CI)	No cases	Sugar- sweetened soft drinks (g/day) <sup>2</sup> HR (95% CI)	Artificially sweetened soft drinks (g/day) <sup>2</sup> HR (95% CI)
Multivariable adjusted model <sup>1</sup>		865	1.00 (0.97, 1.04)	1.03 (0.99, 1.07)	0.91 (0.84, 0.99)	686	1.02 (0.97, 1.08)	1.04 (0.98, 1.10)
Effect modification								
Sex	Women	469	1.02 (0.98, 1.07)	1.05 (1.00, 1.09)	0.89 (0.79, 1.01)	373	1.00 (0.94, 1.09)	1.09 (1.03, 1.15)
	Men	396	0.97 (0.91, 1.02)	0.98 (0.93, 1.05)	0.93 (0.84, 1.04)	313	1.04 (0.96, 1.13)	0.91 (0.80, 1.04)
<i>p for interaction</i>			0.12	0.12	0.85		0.55	0.004
Age of diagnosis	<62 years	294	0.99 (0.94, 1.05)	1.02 (0.96, 1.08)	0.91 (0.79, 1.04)	215	1.03 (0.94, 1.12)	1.00 (0.90, 1.10)
	≥62 years	571	1.00 (0.96, 1.04)	1.03 (0.98, 1.08)	0.91 (0.83, 1.01)	471	1.02 (0.95, 1.09)	1.05 (0.98, 1.12)
<i>p for interaction</i>			0.88	0.91	0.84		0.84	0.51
BMI	<25 kg/m <sup>2</sup>	358	0.99 (0.93, 1.06)	1.03 (0.97, 1.10)	0.89 (0.78, 1.01)	297	1.07 (0.99, 1.16)	0.95 (0.81, 1.11)
	≥25 kg/m <sup>2</sup>	507	1.00 (0.96, 1.05)	1.02 (0.98, 1.07)	0.93 (0.84, 1.03)	389	0.99 (0.92, 1.07)	1.05 (0.99, 1.12)
<i>p for interaction</i>			0.96	0.78	0.66		0.10	0.13
Waist circumference	Normal/moderate	522	1.01 (0.97, 1.06)	1.04 (1.00, 1.09)	0.91 (0.82, 1.00)	452	1.05 (0.99, 1.12)	1.05 (0.98, 1.13)
	Large <sup>3</sup>	237	0.97 (0.91, 1.04)	0.99 (0.92, 1.06)	0.91 (0.78, 1.06)	180	0.93 (0.81, 1.06)	1.02 (0.93, 1.11)
<i>p for interaction</i>			0.23	0.24	0.64		0.035	0.91
Physical activity	Low	505	1.02 (0.98, 1.07)	1.04 (1.00, 1.09)	0.94 (0.85, 1.04)	381	1.02 (0.95, 1.09)	1.07 (1.00, 1.15)
	High	323	0.97 (0.92, 1.03)	1.01 (0.95, 1.07)	0.84 (0.73, 0.97)	268	1.02 (0.94, 1.11)	1.02 (0.93, 1.12)
<i>p for interaction</i>			0.31	0.57	0.22		0.96	0.39
Smoking status	Never smoker	336	0.95 (0.88, 1.02)	1.00 (0.92, 1.08)	0.85 (0.74, 0.97)	257	0.99 (0.88, 1.12)	1.00 (0.88, 1.14)
	Former smoker	239	1.02 (0.96, 1.08)	1.03 (0.96, 1.10)	0.99 (0.87, 1.12)	201	1.04 (0.94, 1.14)	1.05 (0.96, 1.15)
	Current smoker	275	1.01 (0.96, 1.07)	1.04 (0.98, 1.10)	0.91 (0.79, 1.05)	213	1.04 (0.96, 1.12)	1.03 (0.93, 1.13)
<i>p for interaction</i>			0.17	0.43	0.50		0.34	0.86

<sup>1</sup> The model was stratified by center, sex and age at recruitment in 1-year categories and adjusted for education level (no degree or primary school completed; technical or professional school completed; secondary school completed; university degree; not specified or missing), physical activity (active, moderately active, moderately inactive, inactive, missing), smoking status (never, former, current, missing) and alcohol consumption (g per day); juices and nectar and soft drinks in grams per day were mutually adjusted and sugar sweetened and artificially sweetened soft drinks were also mutually adjusted plus adjustment for juice consumption; <sup>2</sup> Excludes Italy, Spain and Umeå (Sweden) where information on type of soft drinks consumption was not collected; <sup>3</sup> Large waist circumference : WC ≥102 cm in men; WC ≥88 cm in women; Abbreviations: BMI: Body Mass Index; HR: Hazard Ratio